The CRA's Guide
to Monitoring Clinical Research

FIFTH EDITION

Elizabeth Weeks-Rowe

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Editor	Susan Salomé
Cover and Interior Design	Paul Gualdoni
Design & Production Associate	Renee Breau

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DEDICATION

To my husband, Antony Rowe, for his unconditional support and honest feedback of my writing during this critical update: his wisdom has helped me progress as a person, and as a clinical researcher.
To Rusty Weeks, M.D. and Carol Weeks, the most unselfish parents and best unpaid medical editors a person could have. I would not have had the confidence to pursue my dream of writing without your love and guidance.
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INTRODUCTION

My greatest motivation in completing the updates to the 2018 release of *The CRA's Guide to Monitoring Clinical Research* was to continue the tradition of excellence set by Karen Woodin's pivotal work; a training guide that has so strongly impacted the field of clinical research and my own clinical research career. The book is highly relevant and resonates in today's changing industry.

Though it has only been two years since the last update, there have been relevant changes I wanted to include in this edition that further reflect how technology is driving and changing the way clinical trials are conducted, even influencing traditional monitoring roles and subject's participation.

I was honored to be part of the 2018 update process and strove to include the most relevant industry and regulatory information; technology and the evolving CRA role, and the emerging roles of the remote monitor and clinical trial educator; the prevalence of web-driven data collection and transmission; the broader scope of CRA responsibilities with site management; updates to the Common Rule, the updated platforms for regulatory submission, patient-reported outcomes and electronic informed consent, the process for CRA evaluation/confirmation of monitoring proficiency, as well as travel tips and apps that bring additional comfort and ease to the traveling monitor. Though the industry continues to change, the basic premise of the guide and contributing regulations that govern study conduct still serve as the integral foundation from which this industry has grown. *The CRA's Guide* still serves as the relevant industry reference to experienced and new clinical researchers, whether endeavoring to confirm established knowledge or progress their learning base with new information.

Karen was an outstanding researcher whose integral work will remain an endless reference for generations of CRAs to come. This process validates the importance of continuing education in clinical research and the importance of remaining aware and familiar with the changing regulations and industry practices.

We must remain vigilant in our pursuit of information and critical knowledge, for ourselves and for future generations.

Thank you, Karen, and John, for imparting your wisdom and experience, and for making everything so clear!

- *Elizabeth Weeks-Rowe*

CHAPTER ONE

What Is a CRA?

There is surprising diversity in what CRAs say their jobs and duties are. This is due to the great variation in their experience and in the organizations for which they work. There are also many people who are not CRAs who want to get a better feel for the clinical research process by understanding what CRAs do and how they do it.

The purpose of this chapter is twofold: to give the reader who is already a CRA a portrait of what a typical CRA "looks like," and to provide non-CRA readers with a quick, concise description of CRAs and an overview of what they do.

The CRA—An Overview

The acronym CRA (Clinical Research Associate) has evolved into a catchall title in the pharmaceutical industry and has become the universal term for anyone involved in monitoring clinical trials. Most CRAs have a bachelor's or master's degree in one of the health, natural or medical sciences; many of them are nurses. CRAs can be field monitors working regionally, or they can be based in-house. Some CRAs are employees of pharmaceutical companies developing a new drug or of contract research organizations (CROs) hired by pharmaceutical companies to help with drug development projects. Other CRAs work as independent contractors and may work on projects for one or more pharmaceutical companies and/or CROs concurrently.

Although CRAs perform a variety of clinical operations and monitoring activities, as shown in Table 1, traditionally they are the people who visit and work with study sites on behalf of a company sponsoring the research. The CRA's main role is to help ensure proper study conduct and the timely generation, review and retrieval of quality data.

Table 1: Overview of potential CRA activities

Study planning

- Write and edit protocols for clinical studies
- Assist/coordinate protocol review
- Write and review patient informed consent
- Identify and evaluate CROs that may assist in a development program
- Identify and evaluate central labs for a study
- Assist in overall drug development planning

Development

- Write or review sections of the design and develop case report forms (CRFs)
- Help write, assemble and distribute investigator brochures
- Write and assemble study/CRF instruction manuals
- Prepare and submit documents required to meet regulatory, GCP and SOP requirements
- Determine, order, ship and track investigational drug supplies
- Create feasibility questionnaires for site completion based on critical protocol elements
- Contact sites for feasibility purposes, provide feasibility questionnaires and follow up with interested sites to obtain completed questionnaires
- Evaluate and select investigators (sites)
- Conduct pre-study visits at investigative sites
- Help plan investigator meetings and/or present sessions
- Review investigator contracts
- Develop study budgets and grant payment schedules

In more recent years, the CRA's responsibilities—and in some cases title—have expanded to that of site manager; a fully dimensional role that encompasses the traditional monitoring activities of source data verification (SDV)/case report form (CRF) review, regulatory binder review and drug accountability, as well as expanded duties of handling investigational site relations, developing and assisting with patient recruitment plans, site blinding plans, corrective and preventative actions (CAPA), protocol deviation reporting oversight, and data management. CRAs truly manage all aspects of study activity and communication for their investigational site assignments.

Study conduct

- Write and review annual IND reports
- Update investigator brochures
- Conduct study initiation visits
- Conduct routine monitoring visits
- Maintain oversight of CRO activities
- Maintain and track study data (enrollment, CRF collection)
- Assist in data review and correction
- Review, assess and interpret study data
- Monitor and report adverse events
- Review regulatory documents
- Review and help manage site enrollment
- Assist in resolving site training and communication issues
- Monitor and report protocol deviations

Closeout

- Conduct study close-out visits
- Perform post-study follow-ups

Post study

- Write and review final study reports
- Archive study files
- Assist with writing and reviewing sections of the New Drug Application (NDA)
- Assist in response to any FDA site inspections

Miscellaneous

- Train and mentor new people
- Act as a project manager

With more emphasis placed on the CRA/site relationship as a partnership, as opposed to the previous CRA oversight dynamic, the trend of collaborative communication and problem solving between CRAs and investigational site staff will help promote data credibility, study transparency and patient safety.

As technology further influences the conduct of clinical trials and the role of the CRA, the emerging role of the remote monitor has added an additional layer of preparation and quality to the previously singular role of the CRA and monitoring visit conduct. Remote monitoring is a component of risk-based monitoring, as well as a stand-alone adjunct to traditional moni-

toring. It is a separate, specific role but can also be performed by a regional CRA.

The responsibilities of the remote monitor are very similar to the responsibilities of the CRA, but are performed remotely. No longer is SDV or CRF review limited to on-site monitoring visits. The prevalence of electronic CRF systems used in clinical trials, the opportunity for CRAs to review patient data almost immediately after entry via an EDC web-portal or internet database (as opposed to on-site), the means for site staff to upload source documents and even paper CRFs to a cloud-based shared drive, enables faster and more efficient (remote) data review, to prepare for on-site monitoring visits and to expedite data analysis in between monitoring visits. This has streamlined study conduct and added this critical dynamic to assist the CRA role.

The activities of the home- or office-based remote monitor include:

- Review of eCRF data entered by investigational sites to ensure data integrity and accuracy;
- Querying sites (via email and eCRF system tools) regarding data entry to question or confirm data completion;
- Conducting remote review of source documents/regulatory documents transmitted by sites (concomitant medication logs, adverse event logs, protocol deviation logs, enrollment logs, drug accountability logs, informed consent forms and various regulatory documents);
- Generating site payments for study patient visits and eCRF completion;
- Tracking and resolving data entry/queries during data analysis and as needed in between monitoring visits;
- Sending periodic study correspondence to sites with important study information/reminders/protocol amendments;
- Collaborating with sites on regulatory documents/activities for site activation prior to and during study conduct;
- Conducting weekly, biweekly or monthly site monitoring calls with investigational sites to discuss a variety of items, including regulatory activities, data entry, protocol deviations, serious adverse events (SAE), enrollment and any outstanding items from previous monitoring visits.

The remote monitor and CRA work collaboratively in a site management model; the remote monitor supplements/supports the CRA with various site management activities in between and during monitoring visits. He or she also helps the CRA prepare for site initiation/monitoring/close out visits by retrieving outstanding data, regulatory documents and SAE line listings for CRAs to utilize during monitoring visits. In some models, the remote monitor is solely responsible for regulatory activities, allowing the CRA to concen-

trate on drug accountability, source document review/CRF, site management and training and patient safety during monitoring visits. In other models, the role of the remote monitor and regional CRA overlap and they assist each other with completion of the above-referenced site monitoring and management tasks.

Today, an ever-increasing number of CRAs work successfully as independent contractors. This trend began in the 1980s when many companies made an effort to streamline business and improve bottom lines. Many experienced, knowledgeable people were dismissed, only to be rehired as independent contractors by both their former employers and their former employers' competitors. In uncertain economic times, financial climate dictates the demand for contract versus permanent CRAs. This trend is likely to continue and will make working as a CRA even more interesting and challenging in the years to come.

The CRA Personality

What type of person makes a good CRA? What skills are required to be successful?

A CRA should be someone who is detail-oriented, a self-starter with good interpersonal relationship skills and a good writer and speaker. A CRA must be self-confident, flexible and adaptable to a changing environment. He or she must also be focused, manage time well and follow through on problems and commitments.

As the role of technology influences and changes the CRA role, CRAs must be adept with the various computer and technology platforms emerging to manage clinical trials, such as regulatory and safety portals for electronic regulatory submissions and the provision of safety reports to investigators, operating systems to manage data review (electronic source and electronic informed consents), clinical trial management systems, electronic PROs (tablet diaries and questionnaires) and working remotely to review data and site management activities.

Above all else, a CRA must be professional. Respect is the cornerstone of the CRA/site relationship. The CRA must maintain a professional demeanor with site personnel, despite the potential for chaos or crisis on-site. A positive CRA/site dynamic is the primary driver of study success at the site level. Most CRAs spend a significant amount of time working away from the office without close supervision. It can be very easy to involve yourself in any number of diversions when your supervisor isn't around. Good CRAs maintain the same discipline and work habits on the road as they do in the office.

Years ago, almost all CRAs were ex regional sales managers. People in these positions were recruited and hired as CRAs because field experience and interpersonal relationship skills were considered of paramount importance. The assumption was that it would be much easier to teach the skills necessary to monitor clinical trials than to teach the personal skills necessary

to work and interact successfully with the variety of situations and personalities that a CRA encounters when monitoring clinical trials. These ex sales folks were some of the best CRAs in the industry. That same rationale applies to the current dynamic of medical professionals (physicians, nurses, health educators) being sought for entry-level CRA positions. Not only do these individuals have the medical terminology and clinical training critical to this role, they are skilled in the most fundamental elements of human interaction and can relate to investigational site staff on a variety of levels due to similar backgrounds.

Some people are simply never able to develop excellent people skills. You can have all the training and knowledge in the world regarding the conduct and monitoring of clinical trials, but if you cannot work or communicate with the people involved, you won't be a successful CRA.

If you're considering this profession, or if you are already a CRA and hope to improve your performance, you must ask yourself:

- Am I a team player?
- Do I get along with most everyone?
- Do speaking and writing come easily to me?
- Am I comfortable working remotely?
- Am I comfortable with various operating systems and computer platforms?
- Do I conduct an honest day's work, in or out of the office?
- Do I meet deadlines?
- Do I pay attention to details?
- Do I listen?
- Do I like to travel?
- Do my personal commitments allow me to travel with a clear conscience?

Be honest with yourself. If you answer "no" to any of these questions, take action to improve.

The dynamics of the working relationships between the CRA, the sponsor/CRO and the investigative sites are complex. A CRA must maintain current information on each site that he or she is monitoring, including data on site performance, current enrollment status, problem resolution and corrections that must be made during the next visit. To maintain this information, the CRA must depend on other sponsor personnel—people who may be stressed, busy and working to meet deadlines.

At an investigative site there are similar problems, including the fact that your study may not enjoy the same priority at the site that it does at your company. Consequently, the CRA must be able to act as a cheerleader and

coach, as well as an enforcer. These are difficult roles to perform at the same time. Whether working with colleagues at the home office or site personnel, the CRA needs to employ all the skills mentioned above to avoid problems and get the job done.

A CRA must be a "Jack or Jill of all trades" if they plan to be involved in this line of work for any length of time because there are so many activities and tasks he or she will be a part of.

The mindset of a concierge

During a recent teaching assignment, I stopped by the concierge desk at the hotel to inquire about activities and restaurants in the area. The concierge was a delightful person who was able to tell me everything I wanted to know and who obviously enjoyed her work. Not only did the experience leave me with the knowledge I sought, but I also felt good as a result of my interaction with this personable individual. As I walked out the door with all the maps and instructions I had been given, I pondered my experience with the concierge and thought, "that is what a good CRA should be."

As you prepare for your site visits, try putting yourself in the mindset of a concierge, providing investigators and their staffs with the information and knowledge needed to do an efficient clinical study, while leaving them feeling good about you and the sponsor, both throughout and after the trial. Having a site's satisfaction extend after the completion of a study makes it easier for a CRA to enlist the site for future studies, just as a good concierge generates repeat business for a hotel.

—JC

CRA Tasks

CRAs are involved in a variety of research-related activities. Some of these are listed in Table 1. You may be able to add other activities to the list. This table shows that a good, experienced CRA has a wealth of knowledge and skills.

CRAs must also be able to work under adverse conditions, think on their feet and be away from home for days at a time. Travel today is strenuous, time-consuming, frustrating and stressful. Being alone under these conditions and in places unfamiliar to you may be unsettling.

In addition to the stress of travel and working conditions at sites that are often less than ideal, medical institutions and private-practice facilities rarely have enough room, because clinical studies usually don't enjoy a very high priority with regard to space. Consequently, you might well be doing various monitoring tasks in some pretty uncomfortable places. It's hard to work when you're balancing everything on your knees or leaning over an exam table between patient visits. However, as detailed in the travel scenarios

noted above, the positives far outweigh the negatives for the brave individual who wants to tread the exciting and demanding, but extremely gratifying, CRA career path.

The two sides of being a CRA

I thoroughly enjoyed working as a regional CRA. The sites with whom I worked were experienced, hard-working and professional, located in large cities with easily accessible hotels and transportation. I consider myself fortunate to be able to count the number of travel debacles on one hand, with countless outstanding travel experiences as the "norm."

The smart CRA recognizes that extremely negative/inconvenient travel experiences are the exception, and best endured with patience and humor. The CRA will exponentially increase travel comfort and ease by accumulating frequent flier miles and hotel points across a variety of programs.

One of the most frustrating travel experiences of my monitoring career resulted in the cancellation of two monitoring visits in one week, a collective five hours of sleep in three days and a thirteen-hour travel day home with nothing to show for my efforts but stress and sleep deprivation. I was scheduled to conduct two monitoring visits in Northeast Canada and was excited to visit the investigational sites for divergent reasons. One site was in Montreal, and the other was in Newfoundland, a beautiful, northern island in Canada that I had always wanted to visit. The first night of my journey I never made it out of the U.S. due to lightning storms in Minneapolis. After a three-hour delay, the airline ultimately rescheduled the flight to the next morning, due to an airport-imposed ground stop. The new flight schedule would have had me arrive in Montreal three hours after my morning meeting, so I had to reschedule the first monitoring visit. After spending an hour on the phone with the airline representative re-booking my flight to go directly to Newfoundland, I found last-minute accommodations at an airport hotel, but had only two hours of sleep due to the early flight the next day. I traveled most of the next day to Ontario, and then took the final flight to Newfoundland. As we approached our initial descent to Newfoundland, we were unexpectedly diverted to Nova Scotia due to high winds. The airline did not know if we would even be able to make it to Newfoundland the following day. After sitting in the Nova Scotia airport for what seemed an eternity, I made the decision to reschedule the second monitoring visit, as I had a sinking feeling that we were never going to get to Newfoundland. I found another airport hotel that looked to have a small vacancy and implored the kind-hearted front desk clerk for the most meager accommodation. I spent an additional two hours on the phone with the airline representative (they could not find me in their system), and they finally rebooked my journey home; Nova Scotia to Calgary to Seattle to San Diego. This was a thirteen-

hour travel journey that I completed on two hours of sleep, again due to an early departure. The only thing achieved for my exhausting efforts; zero monitoring visits conducted, and almost five hours speaking to hotel and airline representatives on the telephone.

One of my most outstanding travel experiences as a monitor was when I went to New York City the evening before Halloween, for a monitoring visit on the holiday itself. I was upgraded to first class on every flight. Upon my arrival in the city, I was upgraded to a five-room suite at a beautiful hotel, which included a spectacular view of the Hudson River and the city skyline. The pre-study monitoring visit was for a retrospective data collection study that was simple in design; the meeting at the site took two hours, and after I finished my remaining work, I spent the rest of the afternoon sight-seeing and enjoying the outrageous Halloween display by New Yorkers. What a way to work!

—Karen

Career Preparation

How does someone prepare for this complex, challenging career? Today, most CRAs have a bachelor's degree in nursing or in one of the health, natural or medical sciences. Many universities offer post-graduate courses in clinical research (some web-based). There are courses taught by professional societies such as the Drug Information Association (DIA) and the Association of Clinical Research Professionals (ACRP).

The ratio of open CRA positions vs. CRAs to fill them ebbs and flows with the economic climate, disease treatment trends and other critical factors. And while there are plenty of experienced investigational site staff desiring to transition to the industry side as a CRA, the current "industry standard" requirement of at least two years of clinical monitoring experience to become a CRA has virtually delayed or even halted this career progression. Extensively experienced study coordinators and data managers, with advanced degrees or nursing degrees, who have worked for more than 5 years coordinating or managing investigational sites, struggle for years to cross over to the pharma or CRO side as they are missing key monitoring experience. People trying to get that first CRA position often feel as though they're caught in a catch-22. Employers want to hire someone with experience, but how can experience be gained without landing a job? Unfortunately, there is no easy answer, but more solutions are emerging to help with this problem. Web- and classroom-based accelerated CRA courses, taught by working CRAs and industry professionals, teach the fundamentals of the CRA position and provide internships and job placement assistance for a nominal fee.

More pharmaceutical and CRO companies are recruiting for new CRAs at universities and offer college internships with prospective positioning for qualified candidates. Some CROs offer specialized oncology monitoring training for oncology nurses looking to transition to the CRA role and/or

formal CRA training programs for qualified candidates (experienced study coordinators, new graduates, nurses, project assistants). An individual is hired externally or promoted internally to learn the CRA role and then offered an entry-level CRA position within the company upon successful completion of the training.

Another option is to take an entry-level position at a CRO or pharmaceutical company as a project or clinical trials assistant, to work toward a CRA position. This is a longer route that requires willingness to take a pay cut and a proverbial step backward to ultimately move forward, but it does work.

Generally speaking, CROs tend to hire more first-timers than large pharmaceutical companies. However, don't exclude the pharmaceutical companies from your list when sending out résumés. Once you get your first CRA position, give it everything you have. A good track record is the greatest asset to furthering your career.

As you gain more experience, you will be able to register with a job listing service. CenterWatch's JobWatch service has job listings available online. New positions are posted at centerwatch.com/jobwatch. A résumé can be submitted online for free, which is then visible to employers and recruiters. Monitorforhire.com, another job listing service, places blinded profiles of monitors on its site at monitorforhire.com.

Monitors need at least two years of field monitoring experience and must go through a qualification and verification process to be listed. DIA and ACRP also list job postings on their websites.

Most sponsor companies have from two-to-four levels of available CRA positions. The differences are primarily related to experience. One key difference is the CRA's ability to evaluate a potential study site and determine whether that site has the expertise, experience, resources and patients to do a particular study well. A CRA who can consistently find good investigators and who can generate accurate, timely data with a minimum of enrollment problems, is a valuable asset to a sponsor company or CRO.

As noted earlier in this chapter, with the advent of electronic clinical trials (eClinical trials), the role of the CRA has changed to include a greater computer component. CRAs work with computer/internet-based programs, such as electronic data capture (EDC) or electronic

(eCRF) systems and clinical trial management systems, to review and manage data, queries, enrollment, adverse events and protocol deviations. As a result of internet-driven data analysis/collection, remote monitoring is now an essential element of site management.

Experienced CRAs should have a good understanding of the scientific method, which enables them to recognize actions and procedures that could bias a study and invalidate the data. Expertise in these key areas is developed only over time, which is why experience and proven performance are of such high value. Generic job descriptions for two levels of CRAs, plus a job summary comparing tasks for entry level and advanced CRAs, are included in Appendix D.

Once on the job, knowledge, networking and common sense are your

best weapons. You never outgrow your need to learn. Be prepared to read quite a bit. At the top of your reading list should be the federal regulations that govern the conduct of clinical research. These are included in Appendix G. All CRAs should read the regulations periodically and be aware of possible regulatory updates. Don't rely too heavily on the advice of colleagues because they may not have read the regulations recently. The ICH Guidelines and the Belmont Report should also be on your list of required reading.

CRAs must constantly educate themselves on different diseases and medical conditions, and on new drugs and devices. You need to have enough of an understanding to be able to recognize things that are problematic as you monitor sites. You won't be offering medical opinions or advice, but knowledge of basic information in each therapeutic area you monitor is necessary.

Standard operating procedures (SOPs) are an important tool for CRAs and should be used to help manage work and as an overall guidance. This means that the CRA does not always have to rely on intuition or ethical standards; SOPs will provide a basic level from which to approach tasks and problems. Sponsors and CROs should have a complete set of SOPs to govern monitoring activities, including:

- Investigator selection.
- Clinical trial agreements.
- Collection and maintenance of study documents.
- Initiation of a clinical trial.
- Routine monitoring of a clinical trial.
- Remote monitoring of a clinical trial.
- Source data verification.
- Investigational product handling and accountability.
- Site visit monitoring reports.
- Reporting noncompliance.
- Study closeout.
- Audits of clinical sites.
- Serious adverse event (SAE) reporting.
- Protocol deviation reporting.

CROs and pharmaceutical companies rely on quality assurance measures to ensure the integrity and accuracy of data collected, and this extends to monitoring proficiency and accuracy of the CRAs they employ. CRAs are evaluated in the on-site conduct of all monitoring visit types (evaluation, initiation, interim monitoring and closeout visits), at periodic intervals, by qualified clinical management/senior CRA staff, to ensure regulatory and

study compliance. This evaluation, by the individual assessing the CRA, includes specific assessment of all elements of each visit type. Specific interim monitoring visit evaluations include additional review of source/CRF data, drug accountability logs and regulatory documents by the CRA evaluator to ensure the accuracy of data previously reviewed by the CRA currently being assessed. The individual evaluating the CRA will also observe site staff relations and investigator discussions to ensure professionalism and diligence.

The CRA should develop a large network of peers and colleagues. One of the best ways to do this is through membership in professional associations. ACRP (acrpnet.org), the Society of Clinical Research Associates (SOCRA) (socra.org) and DIA (diahome.org) are three of the largest associations. It's a good idea to join at least one of these groups. All above noted associations have journals, provide training and offer information and sponsor meetings and workshops. Each also has an annual conference, with continuing education sessions, panels on industry trends and issues and opening sessions with well-known industry influencers/speakers. Try to attend at least one professional meeting each year, as these are great learning opportunities, as well as perfect networking events. There are also speaking opportunities for CRAs at the above conferences; they require abstract submission and acceptance on the proposed speaking topic, but help develop critical speaking and leadership skills important to the CRA role. Check out their websites and talk with current members to get a feel for which organization best meets your particular needs. You will want to maintain a list of colleagues you feel comfortable calling when you have a problem or to seek advice.

There are emerging clinical research education and networking groups such as GCP Café, and clinical research podcasts (clinicaltrialsguru.com) that provide clips, vlogs and interviews about the industry and relevant CRA training items as a means of educating CRAs/clinical researchers.

Finally, rely on your common sense as well as your business sense. The people participating in your studies are your customers; without them you are out of work. Treat them accordingly. Be polite, courteous and kind. Return calls and emails promptly. Before visiting a site, contact the staff and tell them what you will be doing during the visit, who you wish to have available and how long you plan to be there. A detailed discussion of the business approach to monitoring is covered in the chapter on monitoring.

In the Future

What's coming in the future? Though the economy and clinical trials landscape are recovering from the 2009 recession, changes resulting from the economic impact still cause uncertainty within the industry, and a potential desire to change positions.

The more movement there is within a job category, the more opportunity it brings. The CRA job has always had a high turnover rate, primarily because it involves a lot of travel and many people reach a point at which their fam-

ily responsibilities limit their travel availabilities. CRAs who are well-versed in their jobs and complete their responsibilities in a professional manner should have no trouble finding and maintaining good positions.

The 2015 CenterWatch-ACRP Career and Salary Survey was conducted online from September through November 2014. A total of 2,508 clinical research professionals from pharmaceutical and biotechnology companies, CROs, medical device companies, academic medical centers (AMCs), investigative sites and private practice sites (affiliated with hospitals or office practices) responded. The largest number of responses came from clinical research coordinators (CRCs), clinical research associates (CRAs), clinical research nurses (CRNs) and managers.

Since the 2008-2009 financial crisis, when clinical research professionals shared generally pessimistic attitudes about their workplace environments, job satisfaction levels have gradually increased. A total of 46% of respondents were either "extremely satisfied" or "very satisfied" with their current positions in 2014, compared to 40% in 2012 and 36% in 2010.

More than 40% of respondents said their company expects them to take on more responsibility in their current role and 26% reported an "informal" morphing of job functions. Many have been given more responsibility for training and supervising new hires, for example, and are expected to do non-clinical activities usually supported by other functional areas, such as business development, regulatory affairs and medical writing.

As the CRA role evolves, so do those of some other closely aligned positions in clinical research, primarily the data manager and the project manager. Since these positions need to work closely together for successful research projects, people holding these positions tend to become knowledgeable about each of them. Frequently, the project manager position is a step up for a CRA, especially when the CRA may reach the time when significant travel becomes problematic. The CRA job, on the other hand, is often seen as a step up the career ladder for a data manager. As people become more experienced and more familiar with the details of how research projects function, they are more apt to obtain new positions that might integrate all three of these functions.

Another role gaining traction in clinical research is that of the clinical trial educator (CTE). The need for the CTE has increased exponentially in the highly competitive research landscape, which is focusing more on investigator, staff and sponsor collaboration, study training and education and patient-centric clinical trials. The CTE has the therapeutic expertise to better train and facilitate investigational staff understanding of protocol design, endpoints, eligibility criteria and investigational product modalities. There is a science to patient recruitment that involves strategic collaboration between investigators, study staff and physician/facility referrals, as well as a specific understanding to successfully utilize electronic medical records (EMRs) and laboratory databases in the search for potential research subjects.

The CTE is a strategic role with therapeutic and clinical operations expertise to bridge the gap between site/patient education/awareness of clinical

studies and patient recruitment. The CTE can ease the investigational site burden by answering site questions, proposing recruitment strategies and serve as a reminder of study importance to investigational sites with frequent communication and support techniques. The CTE builds investigator networks that identify study sites and solicit interest from physicians in study conduct. They have even employed compliance and retention training to study patients.

CTEs are most often RNs, but the position can also be fulfilled by other clinical specialists with expertise in a specific therapeutic area (respiratory therapists, dieticians, pharmacists).

Nearly three-quarters of survey respondents said their workload has increased by more than 10% in the past three-to-five years. The volume of studies a typical study coordinator manages has nearly doubled in the past decade while, at the same time, clinical trials have become more complex and demand more procedures, which has increased administrative work and makes it harder to recruit patients. Regulatory requirements, particularly paperwork associated with GCP-ICH compliance, have intensified. About 60% of respondents said the two top job challenges they faced were an increase in their workload and the complexity of their responsibilities.

Compared to 2009, when the industry had just experienced massive layoffs as a result of the global economic downturn and widespread consolidation, survey respondents in 2014 were more optimistic about the overall economic outlook for pharma and biotech companies. Nearly 90% of respondents expected that the economic situation for their companies and the industry would either improve or stay the same. Only 12% believed the overall economy would worsen during the next year, compared to more than 25% of respondents in the 2010 survey.

Overall, survey respondents reported only modest growth in salaries. The mean salary increase for clinical research professionals was 3.3% from 2012 to 2013, comparable to national levels during that time period.

There is a trend toward certification for CRAs—certification will be helpful for differentiating yourself professionally. Currently, both ACRP and SOCRA offer certification programs for CRAs. Both programs require previous experience and passing a written examination. Although it is not necessary at this point for a CRA to be certified, it does add to a person's credentials and credibility. At some point in his or her career, the CRA should investigate and work toward achieving certification. A certified CRA may have an edge when it comes to being hired or promoted. In the future, it may well become standard practice for CRAs to be certified.

Ambition is integral for career progression and to prevent career stagnation. As a CRA grows within their position, so does the desire for increased responsibilities and commensurate pay. Some CRAs feel they can advance internally and will work with their line managers for a promotion/pay increase, while some CRAs feel they need to move to another CRO/company for a dramatic increase in salary/position. The prospect of a promotion and change in climate that accompany a move are appealing, however there are

also benefits to staying and growing with a company, such as consistent work history on a CV. Recruiters expect some degree of "jumping" from position to position, but a CV with inconsistent or historically short work histories is a red flag to hiring managers.

Salaries have increased the most for CRAs, project managers and directors—6% from 2012 to 2013. Median salaries in 2013 were $85,000 for CRAs and project managers, and $102,392 for directors. Median salaries for CRCs increased 5%during the same period, reaching $50,000 in 2013, while the median salary for CRNs increased 3% to $67,000.

There are many opportunities for successful CRAs to expand their careers into new, yet related, opportunities. Be ready and prepared for change, as change always occurs over time.

Your Value

The importance of the CRA role in clinical research cannot be over-emphasized. CRAs are on the front line and play a major role in study conduct and quality. Bad studies are not usually the fault of site personnel; they result from poor planning and study design and from improper selection, preparation and training of the study site. A CRA may not be involved in planning and study design, but selection, preparation and training are usually CRA responsibilities. Few people on the drug development team have as much direct impact on study quality and timeliness as the CRA.

The CRA also has an influence on the bottom line for a drug program. The CRA is the main defense against data errors during clinical trials, which can cost millions of dollars to correct. In addition, according to a Boston Globe (bostonglobe.com) article from November 18, 2014, "Drug makers can expect to spend more than $2.5 billion during more than a decade before winning approval to sell a new prescription medicine." The article also details the staggering costs surrounding delays to market: "Joseph A. DiMasi, director of economic analysis for the Tufts center and principal investigator for the study, said the two main components of the $2.558 billion cost per approved drug are average out-of-pocket outlays of $1.395 billion and 'time costs' of $1.163 billion, reflecting returns investors forgo while a drug is in development."[1] The CRA has a major impact on the timely completion of trials, assuring that company development timelines are realistic and are met or exceeded. It's not hard to understand the value of a good CRA in terms of program quality and cost.

Key Takeaways

- CRAs are paramedical personnel who perform a variety of clinical research monitoring activities in support of a drug development program.
- CRAs must be self-starters with excellent interpersonal relationship skills, detail-oriented and have excellent written and oral communication skills.
- CRAs must possess a breadth of clinical knowledge that enables them to provide investigative site personnel with the information they need to perform good clinical trials.
- CRAs need to be adaptable and be able to work under a wide variety of conditions.
- CRAs should stay abreast of technology and innovations that impact clinical trials and the monitoring role.
- CRAs should develop a large network of peers and colleagues.
- CRAs play a major role in the conduct, quality and timeliness of clinical trials.
- Industry trends and technology serve as the impetus for new CRA/education positions.

References

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CHAPTER TWO

The History Behind the Regulations

Good Clinical Practices (GCPs) are the accepted procedures for conducting clinical trials.

GCP is defined as an international, ethical and scientific-quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki and that the clinical trial data are credible.

GCPs are derived from federal regulations, ethical codes, ICH guidelines and official guidance documents. They evolved because of concerns about the treatment of human research subjects around the world and about the reliability of the data and conclusions from trials. Concern about data and conclusions goes beyond the need to protect subjects in clinical trials, extending to the greater goal of protecting all patients who use pharmaceutical products. There are serious consequences for not following the GCPs, including loss of revenue and loss of reputation. Also, not following GCPs can expose sponsors and investigative sites to legal liability, not only from study subjects, but also from future users of a medication (class action suits, for example).

Understanding why the regulations were developed, and some of the factors that will undoubtedly lead to additional regulations in the future, will help you become a better CRA.

Over the course of the past few years, several large institutional review boards (IRBs) have had their activities curtailed by the U.S. Food and Drug Administration (FDA) and the Office for Human Research Protection (OHRP) because of serious problems and deficiencies found during inspections. Because of these findings, clinical trials at some of these institutions had enrollment halted or were closed completely. Sponsor companies suf-

fered because they were counting on the data to support their new drug applications (NDAs), and the respective institutions suffered because of the loss of study revenues and the intangible loss of their status in the clinical trials community. The discovery of serious problems at a handful of IRBs has already resulted in increased government surveillance, primarily by increasing the number of IRB inspections, and a reorganization within the U.S. Department of Health and Human Services (HHS) to better handle the need for this increased surveillance.

There have also been concerns raised about potential problems inherent in genomics research, both from an ethical viewpoint and because genomics involves new and untried research techniques. It is likely that changes in federal regulations will further tighten research requirements. CRAs should be aware of these changes and be prepared to make appropriate adjustments in the way they work with investigative sites and clinical trials. It is wise to be cognizant of the current research environment and be prepared for impending changes. You will be a better CRA by having an understanding of why the pharmaceutical industry is so highly regulated and why the primary vehicles for human subject protection, IRBs and informed consent are so important.

Crisis is an impetus for change. Crises breed controversy, which leads to the involvement of Congress, which then enacts legislation. Some of the major milestones in regulations and in human subject protection, and the crises that spurred them, where appropriate, are discussed below.

Regulation and Human Subject Protection Milestones

1848: Drug Importation Act

The first regulatory action regarding drugs came in 1848, when Congress enacted a law that required the U.S. Customs Service to stop the import of adulterated drugs.

1862: Bureau of Chemistry

In 1862, President Abraham Lincoln appointed Dr. Charles M. Wetherill, a chemist, to serve in the new Department of Agriculture. This was the beginning of the Bureau of Chemistry, which in 1927 became the Food, Drug and Insecticide Administration. The name was changed to the Food and Drug Administration (FDA) in 1930.

1906: Food and Drugs Act

Until the Food and Drugs Act was signed by President Theodore Roosevelt in 1906, there was no comprehensive statute regulating drugs. Before this, standard medical practice consisted of activities such as purges and bloodletting. There were very few effective drugs on the market. All products could

be freely advertised and sold and were readily available without need for any prescription. Then came Dr. Wiley.

Dr. Harvey W. Wiley was the Chief Chemist at the Department of Agriculture from 1883 to 1912. He had a driving interest in the adulteration of food and drugs and set up a plan to investigate food preservatives. In 1902, Dr. Wiley set up his "poison squad"—a group of young, unmarried men who had volunteered to test foods Dr. Wiley thought might contain unhealthy preservatives or coloring agents. The squad lunched together, trying the various substances Dr. Wiley wanted to test. Judgment on the degree of harm the substances caused was based on how sick the men got after eating them. The experiments were carried out over the course of five years, and proved conclusively that many preservatives found in food were harmful.

It was, at least in part, because of Dr. Wiley's work that Congress passed the 1906 Pure Food and Drugs Act, which prohibited the interstate transportation of adulterated and misbranded foods, drinks and drugs. It didn't limit companies from producing the items, but it cut down on their ability to widely market them, as these items could not be taken across state lines.

1938: Food, Drug and Cosmetic Act

The next major crisis was precipitated by the use of Elixir of Sulfanilamide. Sulfanilamide was a tablet—a very large tablet—used to treat infections. The manufacturer wanted to market it for children, but the tablet was too big for them to swallow. The company decided to make it into a liquid by adding diethylene glycol, the principal ingredient in antifreeze. The company was able to get a liquid form and tested it for flavor—it tasted just fine. Unfortunately, the company never tested the resulting elixir for toxicity. It was very toxic, causing the deaths of more than a hundred people, many of them children.

The FDA had no authority to withdraw the product from the market for safety reasons, because there were no regulations regarding safety. The agency could, however, remove it for mislabeling. It was called an elixir, and elixirs had to contain alcohol, which Elixir of Sulfanilamide did not. Based solely on this finding, the FDA was able to have the unsafe product removed from the market.

As a direct result of this tragedy, Congress passed the 1938 Food, Drug and Cosmetic Act. For the first time, a premarket approval of "new drugs" was required for safety. "New drugs" meant new chemical entities or combinations. Drugs marketed prior to 1938 were specifically exempted (grandfathered in) as long as their labeling didn't change. There was no definition of safety in the act; however, the general understanding was that the benefits must outweigh the risk. The act also did not require active approval by the FDA. Unless the FDA objected within 60 days of the New Drug Application (NDA) being filed, the manufacturer could automatically begin marketing. No proof of efficacy was required. Between 1938 and 1962, most NDAs that were filed were essentially just testimonials from physicians.

1947: Nuremberg Code

After the Nuremberg Trials of Nazi leaders during 1945-1946, a series of supplemental trials were held. One trial, officially known as United States v. Karl Brandt et al. and commonly referred to as the Doctors' Trial, was held from Dec. 9, 1946 to August 20, 1947. The judges and prosecutors in this court trial were all from the U.S. The 23 defendants (including 20 physicians)—all members of the Nazi Party—were charged with murder, torture and other atrocities committed in the name of medical science.

When the final judgment in the Doctors' Trial was delivered, 15 of the 23 defendants were found guilty. Seven were sentenced to death. Four presiding American judges issued a 10-point code that described basic principles of ethical behavior in the conduct of human experimentation. This 10-point code is known as the Nuremberg Code. Although the Code focuses on the ethical treatment of humans in non-therapeutic research (research not intended to result in a cure for a condition), the elements described formed the cornerstone for the guidelines and regulations we have today and reflect that:

- Informed consent should be obtained without coercion.
- The experiment should be useful and necessary.
- Human experiments should be based on previous experiments with animals.
- Physical and mental suffering should be avoided.
- Death and disability should not be expected outcomes of an experiment.
- The degree of risk taken should not exceed the humanitarian importance of solving the problem.
- Human subjects should be protected against even remote possibilities of harm.
- Only qualified scientists should conduct medical research.
- Human subjects should be free to end an experiment at any time.
- The scientist in charge must be prepared to end an experiment at any stage.

1962: Kefauver-Harris Amendments (Drug Amendments of 1962)

In the late 1950s, thalidomide was being tested extensively in Europe, and to some degree in the U.S. It was a sleeping pill, and pregnant women were included in the testing groups. Unfortunately, it had a terrible effect on the fetus when taken during the first trimester, and many children born to women who had taken thalidomide suffered from phocomelia, a shortening of the limbs which resulted in arms that looked like flippers. Dr. Francis Kelsey at

the FDA was responsible for much of the research that defined the link between phocomelia and thalidomide use in pregnancy.

The Kefauver-Harris amendments, passed in part due to the aroused public support for stronger drug regulation because of the thalidomide tragedy, formed the basis of the current Investigational New Drug (IND) application regulations. For the first time, drugs were required to have proven efficacy, as well as safety. Also for the first time, an active FDA approval was required, beyond the review and 60-day waiting time. In addition, this law required mandated reporting of adverse events and disclosure of risks in advertisements.

Much to the chagrin of pharmaceutical manufacturers, as part of this regulation the FDA also had to re-review all the NDAs submitted between 1938 and 1962 to see if products met the new efficacy standard. There were numerous lawsuits over the definition of substantial evidence of efficacy, including the Pharmaceutical Manufacturers Association vs. FDA, and suits by almost all major pharmaceutical manufacturers. This controversy led to the definition of the "adequate and well-controlled" clinical investigations required today.

1964: Declaration of Helsinki

The World Health Organization (WHO) spent more than 10 years working on the statement of ethical principles that became known as the Declaration of Helsinki. This document defined rules for therapeutic and non-therapeutic research. It repeated the Nuremberg Code requirement for consent for non-therapeutic research but allowed for enrolling certain patients in therapeutic research without consent. The Declaration of Helsinki also allowed legal guardians to grant permission to enroll subjects in research, both therapeutic and non-therapeutic, and recommended written consent—an issue not addressed in the Nuremberg Code. In addition, the Declaration of Helsinki required review and prior approval of a protocol by an IRB. Several revisions have been made to this document, including a Clarification.

1979: The Belmont Report

The National Research Act, passed by Congress in 1974, created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. This commission wrote a document entitled Ethical Principles and Guidelines for the Protection of Human Subjects of Research, which became known as the Belmont Report when it was published in 1979. The three basic principles of the Belmont Report are respect for persons, beneficence and justice.

1. Respect for persons is manifested by the informed consent process, as well as in safeguards for vulnerable populations such as children, pregnant women, mentally disabled adults and prisoners. Other important concerns of respect for persons include privacy and confidentiality.

2. Beneficence has two general characteristics: do no harm and maximize benefit while minimizing risk. Beneficence is manifested in the use of good research design, competent investigators and a favorable risk/benefit ratio.
3. Justice implies fairness and is manifested in the equitable selection of subjects for research, ensuring that no group of people is "selected in" or "selected out" unfairly based on factors unrelated to the research. This means that there must be appropriate inclusion/exclusion criteria and a fair system of recruitment.

The Belmont Report formed the cornerstone for the ethical treatment of human subjects in research.

1987: IND Rewrite Regulations

Additional regulations were enacted after three extreme examples of abuse illustrated the need for further protection of human subjects.

Tuskegee Syphilis Study[1]

In this study, which began in 1932 and extended for more than 40 years, several hundred black males with syphilis were enrolled. They were not informed about the purpose of the study, but were told that government doctors were examining people for "bad blood." Even after penicillin became available and was known to be effective for syphilis (1943), the males in this study were not treated with it. This study was not stopped until 1973, when treatment was given as needed. In 1997, President Clinton made a formal apology to study subjects and their families.

Jewish Chronic Disease Hospital Study[2]

In 1963, physicians at this hospital were interested in studying the nature of human transplant rejection. To do this, they injected live cancer cells into indigent, elderly patients suffering from a variety of chronic debilitating diseases, without their consent. The subjects were not told about the live cancer cells because the physicians thought the cells would be rejected anyway, and they didn't want to alarm the subjects.

Acres of Skin[3]

This book, by Allen M. Hornblum, revealed some of the abuses of testing in the Holmesburg Prison in Philadelphia, where subjects underwent extensive and painful testing of numerous chemicals to see their effect on the skin. Paying the prisoners $100 to be in a study, compared to the 10 cents a day they were paid for prison jobs, undoubtedly influenced their willingness to participate in these trials.

These studies were carried out from the mid-1950s through the mid-1970s. There were three principal objectives of the 1987 IND Rewrite Regulations: protecting the safety of subjects in clinical trials, ensuring the ad-

equacy of clinical trial designs to support marketing approvals and assuring the quality, integrity and validity of the data that form the bases of FDA approval decisions. Not only was patient/subject safety covered by aspects of these regulations, but the regulations were the impetus for greatly expanded statistical sections in protocols; from relatively short, basic descriptions of the analyses to be done, they became full-blown, detailed plans. For the first time, the FDA became a real partner in ensuring both adequate trial design and the generation of data that would stand rigorous inspection.

1988: Expedited NDA Approval Process for Life-Threatening Illnesses

Primarily as a result of the AIDS crisis, Congress enacted the 1988 Expedited NDA regulations. The purpose of these regulations was to establish procedures to expedite the development, evaluation and marketing of new therapies intended to treat people with life-threatening and severely debilitating illnesses, especially where no satisfactory alternative therapy existed. These regulations provide for consultation with the FDA early in the development process to review and agree on the design of non-clinical and clinical studies. They also provide for treatment protocols under which an investigational drug can be provided to patients throughout the clinical development program and review period, prior to marketing. (These studies are known as expanded access or named patient trials.) Because nothing else is available to treat these illnesses, and people are dying from them, the risk/benefit assessment is more lenient than for other investigational drugs.

In consultation with the FDA, companies may be allowed to collapse phase II and III studies together (see Chapter 5 for an explanation of the phases of drug testing); however, in this case, phase IV post-marketing surveillance studies are often a condition of approval. If post-marketing studies are required, the company is given a time period (usually two to three years) within which the studies must be completed, and these studies must be submitted, reviewed and approved, or marketing approval may be withdrawn.

1992: Prescription Drug User Fee Act (PDUFA)

In the years preceding the PDUFA, the FDA was under fire because it took so much longer to review and approve drugs in the U.S. than it did in Europe. Congress asked why. The FDA replied that the agency didn't have enough people available to do the job any faster. In response, Congress enacted the Prescription Drug User Fee Act of 1992, which provided the FDA with more people to review human drug applications. The funds for acquiring additional people came from fees collected from the firms developing drugs and biologics. The goal was to reduce the time required to review and evaluate certain drug applications without compromising the quality of the review.

The industry was, and is, willing to pay. The fees associated with this program have sped up the review time for NDAs. It is estimated that for 2019, the fee a sponsor will have to pay for submitting an application requiring

clinical data is $2,588,478, while the fee for an application not requiring clinical data, or for a supplement requiring clinical data, is $1,294,239. Sponsors must also pay a program fee of $309,915.

These fees are actually a small price to pay for accelerating NDA approval, when you consider that every day saved is worth about $1.4 million (based on a good, but average, drug that brings in about $500 million in annual sales.)

1997: FDA Modernization Act (FDAMA)

The PDUFA was considered a success. The problem with the PDUFA, however, was that the period for collecting fees expired after five years. In 1997, Congress reauthorized the PDUFA for an additional five years by enacting the FDA Modernization Act. Not only did this act extend the PDUFA, but it also increased patient access to investigational drugs and mandated an expanded database on clinical trials that was accessible to patients. It also accelerated the review of important new drugs, like those used to treat conditions with high morbidity and mortality where no treatment already existed, in part by allowing one pivotal trial rather than two in certain circumstances. FDAMA also requires child testing in certain categories of drugs for which pediatric use is expected. FDAMA mandates the most wide-ranging agency reforms since 1938, including not only the provisions listed above, but also others designed to accelerate the review of devices, regulate advertising of unapproved uses for approved drugs and devices, and regulate health claims for foods.

Summary

The regulations and the ethics documents are in place to ensure the safety and well-being of human subjects involved in research. The government has made tremendous strides to ensure not only that subject protections are in place, but also that safe drugs reach the market. A list of readings is included in the appendices, in case you'd like more history and background about why the business of clinical trials is as regulated as it is today.

Key Takeaways

- Regulations are often a result in response to abuse of human research subjects and of concerns about the validity of data and conclusions from clinical trials.
- The primary vehicles for human subject protection are IRBs and informed consent.
- The Declaration of Helsinki and the Belmont Report are critical documents for the protection of human subjects in research.
- The FDA, by means of PDUFA and FDAMA, has made significant gains in accelerating the process of making new drugs available for patients who need them.
- Problems with clinical trials and trial oversights may well lead to increased regulation.

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CHAPTER THREE

Regulations and GCPs

This chapter discusses the regulations and guidelines a CRA must be familiar with and understand.

An informal survey of a few large investigative sites showed that many CRAs exhibit a lack of knowledge of the regulations. This is especially true of those new to the business. Unfortunately, many of these same CRAs think they have a good working knowledge of the regulations. How can this happen? Very easily. Instead of reading the regulations for themselves, too many people rely on information by asking someone else who may not have actually read them either. This leads to misinformation, self-perpetuating myths and misinformation.

It is a good practice for CRAs to carry pocket-sized copies of the FDA regulations and International Council on Harmonization (ICH) Good Clinical Practice (GCP) guidelines (or have access to the internet links) to monitoring visits, to ensure they can be referenced during discussions with study staff to explain or support a questioned directive.

FDA Regulations for Clinical Trials

As a CRA, you will want to make sure you have a thorough understanding of the regulations. This will help to keep your sites in compliance. The regulations CRAs should be familiar with are:

- 21 CFR Part 11—Electronic Records and Electronic Signatures
- 21 CFR Part 50—Protection of Human Subjects (Appendix G)
- 21 CFR Part 54—Financial Disclosure by Clinical Investigators (Appendix G)

- 21 CFR Part 56—Institutional Review Boards (Appendix G)
- 21 CFR Part 312—Investigational New Drug Application (Appendix G)
- 21 CFR Part 314—Applications for FDA Approval to Market a New Drug

If you are working with devices, you should be familiar with:

- 21 CFR Part 812—Investigational Device Exemptions
- 21 CFR Part 814—Premarket Approval of Medical Devices

If you are working with biologics, you also want to be familiar with:

- 21 CFR Part 600—Biological Products; General
- 21 CFR Part 601—Licensing of Biological Products
- 21 CFR Part 610—General Biological Products Standards

The first six parts listed above encompass the Good Clinical Practice (GCP) sections of the Code of Federal Regulations, and they form the basis of the regulations pertinent to conducting clinical trials in the U.S.

Since the job of a CRA is to monitor clinical trials, it follows that the CRA must have a good working knowledge of these regulations. The regulations tell us what is actually required by the FDA when involved in conducting clinical studies. They cover the responsibilities of sponsors, investigators and IRBs for conducting trials involving human subjects.

Exploring the FDA's website, www.fda.gov, is a great way to find all kinds of information about conducting trials. Taking some time to look around and delve into different topics on the web will be time well spent for a CRA. From this site, you can branch off into information about drugs, biologics and devices.

ICH Guidelines for Good Clinical Practice

In addition to FDA regulations, CRAs must be familiar with the ICH Guideline for Good Clinical Practice. Although not yet required by regulation in the U.S., this guideline has been published in the Federal Register and represents the current thinking of the FDA on good clinical practices. Many sponsor companies require their studies to follow the ICH Guideline as well as FDA regulations.

The ICH was organized to provide opportunities for standardized regulatory initiatives to be developed with input from both governmental bodies and industry representatives. There are three regions involved in the ICH: the European Union, Japan and the U.S. The ICH guideline from 1997 defines Good Clinical Practice and provides a unified standard for designing, conducting, recording and reporting on clinical trials involving human subjects.

Compliance with good clinical practice ensures that the rights, well-being and confidentiality of human subjects are protected and that trial data are credible. This guideline may also be found in Appendix F.

FDA Guidelines and Information Sheets

The FDA also publishes a number of guidelines and information sheets that are very useful in the conduct of clinical trials. These give further explanation to the regulations, including current interpretations and thought processes of the FDA. They often include questions and answers for items that are of particular interest. Although the guidelines do not carry the weight of regulations, it is highly recommended that they be followed, as they are the FDA's expectations for the conduct of trials.

Links to specific guidelines can be found on the FDA website. Some of the more useful guidelines are:

- FDA Information Sheets for IRBs and Investigators—1998 Update
- Good Clinical Practice in FDA-Regulated Clinical Trials
- Monitoring of Clinical Investigations
- A Guide to Informed Consent
- Exception from Informed Consent Requirements for Emergency Research
- Recruiting Study Subjects
- Disqualified/Restricted/Assurance List for Clinical Investigators
- Using a Centralized IRB Review Process in Multicenter Clinical Trials
- FDA Inspections of Clinical Investigators (June 2010)
- Investigator Responsibilities – Protecting the Rights, Safety and Welfare of Study Subjects
- Statement of Investigator (Form FDA 1572) - Frequently Asked Questions – Information Sheet (2010)
- Waiver of IRB Requirements for Drug and Biological Product Studies – Information Sheet (2017)
- Medical Devices, Frequently Asked Questions About – Information Sheet (2006)
- Significant Risk and Nonsignificant Risk Medical Device Studies – Information Sheet (2006)
- Guidance for Industry: Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring (August 2013)

- Guidance for Industry and Investigators Safety Reporting Requirements for INDs and BA/BE Studies (December 2012)
- Electronic Informed Consent in Clinical Investigations, use of – Questions and Answers (2016)
- Electronic Source Data in Clinical Investigations (2013)
- Payment and Reimbursement to Research Subjects – Information Sheet (January, 2018)

CRAs should familiarize themselves with these guidelines as well as with the regulations. Exceptions from informed consent are discussed in detail in Chapter 9. Risk-based monitoring practices are detailed in Chapter 14.

FDA Compliance Program Guidance Manuals

There are also a number of FDA Compliance Program Guidance Manuals (CPGMs) that can be helpful to a CRA. These are the manuals FDA personnel use when they conduct inspections of clinical investigators, sponsors or IRBs. All of these manuals can be found at www.fda.gov/oc/gcp/compliance.html. Those of particular interest include:

- CPGM for Clinical Investigators
- CPGM for Sponsors, Monitors and Contract Research Organizations
- CPGM for IRBs

These manuals will tell you exactly what the FDA will focus on during inspections.

NIH-Regulated Research

CRAs are not generally involved in monitoring trials conducted under the auspices of the Department of Health and Human Services (DHHS or HHS). There are occasions, however, when a sponsor may run a joint trial with an NIH (National Institutes of Health) group, such as the National Cancer Institute (NCI). In this case, the trial must be conducted by HHS regulations, which differ somewhat from FDA regulations. For example, HHS regulations contain specific sections on working with vulnerable subjects, such as pregnant women, children and prisoners, which are not found in FDA regulations. There is an online document that compares the regulations for the two groups called "Comparison of FDA and HHS Human Subject Protection Regulations," which can be found by searching for this title on the FDA website.

FDA Bioresearch Monitoring Program (BIMO)

The FDA requires that the biomedical research it regulates conform to GCP standards as found in FDA regulations. To help ensure that GCP standards are followed, the agency inspects clinical trials. (Note that what the FDA calls inspections are commonly called audits by others.) The FDA's program of inspections/audits is called the Bioresearch Monitoring (BIMO) program and covers all of the parties involved in regulated clinical trials, including clinical investigators, IRBs, sponsors, monitors and CROs. FDA audits are covered in Chapter 19.

Good Clinical Practice (GCP)

Good Clinical Practice (GCP) is not a single document that can be referenced, printed or read. The phrase Good Clinical Practice was, in fact, coined by the industry and is a standard for the design, conduct, performance, monitoring, recording, analysis and reporting of clinical trials. The purpose of GCP is to protect human subjects in trials, as well as the general population who will use the products being tested once they are available on the market. GCPs comprise the FDA regulations and guidance documents, the ICH guidelines for good clinical practice and codes of ethical conduct, such as the Declaration of Helsinki and the Belmont Report. They are recognized as overall standard operating procedures for the conduct of clinical research and encompass the informed consent process, accurate collection of data, maintaining audit trails, reporting adverse events, investigator oversight and record retention. All of these items are covered in this book. Compliance with GCPs ensures not only that the rights and safety of study subjects are not compromised, but that the integrity of the data collected is maintained.

Common Rule Updates

A major component of GCP in the United States is the Federal Policy for the Protection of Human Research Subjects, which is enforced by a number of federal agencies that support clinical research. Known as the Common Rule, the policy puts forth requirements for informed consent and IRB review, among other issues.

The Common Rule, established in 1991, applies any time human subjects research is conducted using federal funding; therefore, federal agencies, academic institutions and healthcare research institutes are among the top qualifying institutions. The rule grew out of prior HHS regulations as well as a number of international developments in bioethics, including the Nuremberg Code, the Declaration of Helsinki and the Belmont Report. In 2011, the federal agencies began a regulatory overhaul of the rule to bring it up to date with current research practices and issues.

The revised rule, scheduled for implementation in January 2019, includes

new requirements for informed consent, the delineation of several new and expanded exempt categories of research, the creation of a new classification of "broad consent," the introduction of limited IRB review, the discontinuation of IRB continuing review and an update to the description of vulnerable populations.

The touchstone of the requirements is new language that states that informed consent must begin with "a concise and focused presentation of the key information that is most likely to assist a prospective subject or legally authorized representative in understanding why one might or might not want to participate in the research." This statement, according to the revised language, must be "organized and presented in a way that facilitates comprehension." The informed consent document should be readable, engaging and clear. Patients also must be given the chance to ask questions and discuss anything they might not understand.

The revised Common Rule suggests that prospective study subjects be provided a description of five "factors" at the beginning of the informed consent process, as well as at the beginning of the informed consent form:

1. Consent is being sought and participation is voluntary.
2. The purposes of the research, expected duration of participation and procedures to be followed.
3. The reasonably foreseeable risks and discomforts.
4. The benefits to the prospective subjects, or others, that may reasonably be expected from the research.
5. Appropriate alternative procedures or courses of treatment that may be advantageous to the prospective subject.

The rule also requires that informed consent forms be published online—to a federal website—within 60 days of the close of enrollment of the clinical study. Most likely that posting will be done by the sponsor.

Contacting the FDA

The FDA invites contact from sponsors, investigators and IRBs with respect to questions about proper procedures or interpretation of regulations. Most companies have a specific procedure to follow for calling the FDA. If a CRA has a question for the FDA, he or she should check with the sponsor company's regulatory department to be sure that it is acceptable to call. Company procedures may require that the regulatory department make all FDA contact. The main telephone number for the FDA is 1-888-INFO-FDA (1-888-463-6332). Contact numbers for all FDA offices are available on the FDA website.

In conclusion, there are many sources of information available to CRAs that will help them ensure compliance when working with investigative sites on clinical trials. CRAs should utilize these resources when doing their jobs.

Key Takeaways

- The FDA regulations pertaining to clinical trials are found in 21 CFR Parts 11, 50, 54, 56, 312 and 314.
- The ICH Guidelines for Good Clinical Practice should be followed in clinical trials.
- The FDA publishes many guidelines and information sheets pertaining to the appropriate conduct of clinical trials.
- Good clinical practices are the ethical and clinical standard for designing, conducting, analyzing, monitoring and reporting on clinical trials.
- There are differences between FDA and HHS rules for doing research in human subjects.
- CRAs should read and be familiar with the regulations that pertain to clinical trials and the ICH guidelines.

CHAPTER FOUR

Roles and Responsibilities in Clinical Trials

A clinical trial is a study done in human subjects to investigate a potential new drug, device or biologic product. There are three primary groups involved in the conduct of clinical trials: sponsors, clinical investigators and IRBs. This chapter looks at the specific regulatory responsibilities each of these three has when it comes to conducting clinical trials. Also involved are regulatory agencies (FDA, HHS), and the human subjects who participate in trials. Although many of these responsibilities are discussed in more detail in other chapters, this chapter will give you a summary of responsibilities as they appear in FDA regulations.

Sponsors

In the regulations (21 CFR 312.3(b)), a sponsor is defined as "a person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or a pharmaceutical company." For this book, a sponsor is the pharmaceutical or device company that initiates a clinical trial for one of its products. The regulatory responsibilities of sponsors are found primarily in 21 CFR 312, subpart D (Responsibilities of Sponsors and Investigators).

Sponsors are responsible for:

- Selecting qualified investigators.
- Providing investigators with the information they need to conduct an investigation properly.
- Ensuring proper monitoring of the investigation.
- Ensuring that the investigation is conducted in accordance with the general investigational plan and protocols contained in the IND.

- Maintaining an effective IND with respect to the investigations.
- Ensuring that the FDA and all participating investigators are promptly informed of significant new adverse effects or risks with respect to the drug.
- Additional specific responsibilities of sponsors are:
- Selecting only investigators who are qualified by training and experience as experts to investigate the drug.
- Shipping investigational new drugs only to investigators who are participating in the investigation.
- Obtaining appropriate information from the investigator.
- Selecting monitors who are qualified by training and experience to monitor the progress of the investigation.
- Monitoring the progress of all investigations involving an exception from informed consent.
- Giving each participating clinical investigator an investigator brochure.
- Keeping each participating investigator informed of new observations discovered by or reported to the sponsor on the drug, particularly with respect to adverse effects and safe use.
- Monitoring the progress of all clinical investigations being conducted under the sponsor's IND.
- Upon discovering that an investigator is not complying with the Form FDA-1572, the general investigational plan or the regulations, will promptly either secure compliance or discontinue shipments of the investigational new drug to the investigator and end the investigator's participation in the investigation.
- Reviewing and evaluating the evidence relating to the safety and effectiveness of the drug as it is obtained from the investigator. If determining that its investigational drug presents an unreasonable and significant risk to subjects, the sponsor will discontinue those investigations that present the risk. The FDA, all institutional review boards and all investigators who have at any time participated in the investigation of the discontinuance must be notified.
- Maintaining and retaining adequate records and reports.
- Permitting the FDA to inspect records and reports relating to clinical investigations.
- Maintaining written records of the disposition of the investigational drug.

This means that the sponsor is essentially responsible for all operational aspects of the clinical trials it sponsors.

Sponsor delegation of duties to a Contract Research Organization (CRO)

ICH defines a CRO as "A person or an organization (commercial, academic or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions."

In many instances, the sponsor will delegate a portion of clinical trial-related responsibilities to a CRO. This is dependent on sponsor capabilities, logistics, location, finances, company size and personnel. Some CROs are delegated a small portion of responsibilities such as central lab, or monitoring responsibilities. Other CROs serve as a "one stop shop" and provide a variety of services such as central lab, IVRS, project management, data management, safety, medical writing, investigator selection, study startup and monitoring responsibilities for a study.

The regulations describe the transfer of responsibilities in detail:

> *Section. 312.52—Transfer of obligations to a contract research organization:*
>
> *(a) A sponsor may transfer responsibility for any or all of the obligations set forth in this part to a CRO. Any such transfer shall be described in writing. If not all obligations are transferred, the writing is required to describe each of the obligations being assumed by the CRO. If all obligations are transferred, a general statement that all obligations have been transferred is acceptable. Any obligation not covered by the written description shall be deemed not to have been transferred.*
>
> *(b) A CRO that assumes any obligation of a sponsor shall comply with the specific regulations in this chapter applicable to this obligation and shall be subject to the same regulatory action as a sponsor for failure to comply with any obligation assumed under these regulations. Thus, all references to "sponsor" in this part apply to a CRO to the extent that it assumes one or more obligations of the sponsor.*

Institutional Review Boards (IRBs)

In the regulations (21 CFR 56.102(g)), an IRB is defined as "any board, committee or other group formally designated by an institution to review, approve the initiation of and conduct periodic review of biomedical research involving human subjects. The primary purpose of such review is to assure the protection of the rights and welfare of the human subjects." As a side note, institution means any public or private entity or agency (including

federal, state and other agencies), to include hospitals, universities, private medical clinics and so forth.

For our purposes, an IRB is a committee that formally reviews and approves a trial before it can start with the primary goal of protecting human subjects of research. There is an entire chapter devoted to IRBs in this book, but their responsibilities will be summarized here in order to compare and contrast them with those of sponsors and investigators.

The regulatory responsibilities of IRBs are found primarily in 21 CFR 56 (Institutional Review Boards). 21 CFR 56 requires that IRBs:

- Follow regulations regarding an IRB organization and personnel.
- Follow written procedures, including those for:
- Conducting initial and continuing review of research and reporting those findings to the investigators.
- Determining which projects require review more than once annually.
- Ensuring prompt reporting to the IRB of changes in the research.
- Ensuring that changes are not implemented before IRB review, except where necessary to eliminate apparent immediate hazards to human subjects.
- Promptly report to the IRB, institution and the FDA any:
- Unanticipated problems involving risk to human subjects.
- Any instance of serious or continuing noncompliance with regulations or IRB requirements.
- Any suspension or termination of IRB approval.
- Review proposed research at convened meetings with a majority of members present, including at least one member whose primary concerns are non-scientific.
- Require that information given to subjects as part of informed consent meets the regulations.
- Notify investigators in writing of its decision to approve or disapprove the proposed research, or of any modifications required to secure approval.
- Conduct continuing review of the research at least annually, or more often, depending on the degree of risk.

The IRB is primarily responsible for the ethical aspects of the clinical trial.

Clinical Investigator

In the regulations (21 CFR 312.3(b)), an investigator is defined as "an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the drug is administered or dispensed to a subject). In the event the investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. "Sub-Investigator" includes any other individual member of that team. Investigators are discussed in detail in another chapter of this book.

The regulatory responsibilities of investigators are found primarily in 21 CFR 312, subpart D (Responsibilities of Sponsors and Investigators). Under 21 CFR 312.60, an investigator is responsible for:

- Ensuring that an investigation is conducted according to the signed investigator statement (Form FDA 1572), the investigational plan (protocol) and the applicable regulations.
- Protecting the rights, safety and welfare of subjects under his or her care.
- Controlling the drugs under investigation.
- For FDA-regulated drug studies, the investigator must sign a 1572 (Statement of Investigator) form. By signing this form, the investigator agrees to:
- Conduct the study in accordance with the protocol.
- Personally conduct or supervise the investigation.
- Inform study subjects that the study drugs are being used for investigational purposes.
- Ensure that the requirements for obtaining informed consent (21 CFR 50) and for obtaining IRB review (21 CFR 56) are met.
- Report adverse experiences that occur during the course of the investigation to the sponsor, in accordance with 21 CFR 312.64.
- Have read and understood the material in the investigator's brochure, including the potential risks and side effects of the drug.
- Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations.
- Maintain adequate and accurate records as per 21 CFR 312.62 and make those records available for inspection in accordance with 21 CFR 312.68.
- Ensure that an IRB compliant with 21 CFR 56 will be responsible for the initial and continuing review and approval of the clinical investigation, and will:

- Promptly report all changes in research activity to the IRB.
- Promptly report all unanticipated problems involving risk to human subjects or others.
- Will not make changes to the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

Additional investigator responsibilities under 21 CFR 312.60 include:

- Maintaining adequate records of drug disposition.
- Preparing and maintaining accurate subject case histories that record all observations and other data pertinent to the investigation, including case report forms, signed and dated consent forms, medical records, progress notes, etc.
- Retaining all records appropriately and for the required time periods.
- Furnishing progress and final reports to the sponsor.
- Providing financial disclosure information to the sponsor as required.

The investigator, then, is primarily responsible for the conduct of the trial.

Other Research Partners

The FDA, the Department of Health and Human Services (HHS) and regulatory agencies around the world also have a major role in clinical research. These agencies regulate clinical research conducted in their countries by maintaining and enforcing the regulations covering research, and issuing guidance and other documents detailing acceptable research practices. They interact with sponsors throughout a sponsor's development program, dispensing advice and working with the sponsor on the initiation and continuation of the program. The FDA also performs inspections of sponsors, investigative sites and IRBs to ensure both the safety and well-being of study subjects and the integrity of the data. When the research program is complete, the FDA reviews the studies and the data, and makes a decision about whether the sponsor can proceed with marketing of the new product. In effect, regulatory agencies act as overseers to ensure clinical research is done properly and new medications are safe and effective to be used in the general population.

There is one more major contributor to the research process—the subjects who actually volunteer and participate in research studies. They are the unsung heroes without whom new drugs and devices could not be tested and brought to market. Study subjects deserve a big round of applause from all of us.

Occasionally, there is also a role for an institution in clinical research.

This often occurs in large teaching hospitals, for example, where a separate department within the institution handles some matters, such as grants and contracts, for all investigators affiliated with the institution.

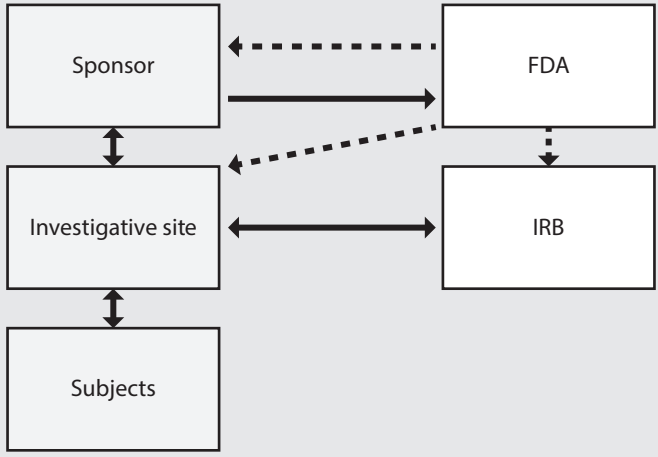
The diagram below shows the interactions between the different entities involved in clinical trials. The solid lines designate primary interactions, while the dotted lines show secondary interactions.

The sponsor interacts primarily with investigators (sites) and the FDA. In the past, sponsors rarely had contact with IRBs. This has changed somewhat with multi-center trials, as sponsors often submit the protocol and consent to a central IRB that will review the study for all, or most, of the individual sites. In this case, however, the sites still communicate directly with the IRB with regard to other documentation that is site specific.

The clinical investigators are the primary link to both the IRB and, of course, the study subjects. It is rare for anyone other than the investigator and his or her staff to interact with study subjects, although upon occasion, a subject may contact an IRB with concerns about the study. If an institution is involved, there will be interactions between the appropriate institution departments and the investigators involved in research at the institution.

The FDA, although interacting primarily with the sponsor, may also interact with sites (and the institution), and conducts inspections of sponsors, investigative sites and IRBs.

Figure 1: Primary communications



- Solid lines denote primary communications.
- Dotted lines denote secondary communications.
- The boxes contain the entities charged with conducting the study.

Managing Relationships

With so many groups involved in a clinical trial, there are a lot of relationships to manage. Not only are there relationships between the groups mentioned above, but there are those within each group to think about as well. Many of these associations appear in other chapters.

As with all relationships, respect for the other people and their problems and situations can go a long way to smoothing out a rocky relationship. Think about "working with people" rather than "working for me"—if you can maintain this attitude, it will go a long way toward ensuring a good relationship.

Key Takeaways

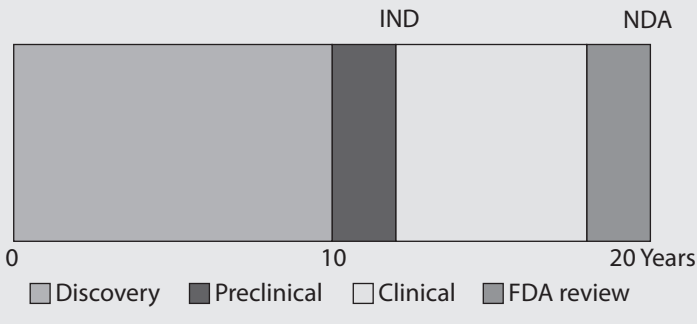
- Regulations contain the key responsibilities for the primary groups involved in clinical trials.
- In general, the sponsor is responsible for the operational aspects of the clinical trials it sponsors. The sponsor can choose to delegate a few, or all of these responsibilities, to a CRO.
- The IRB is primarily responsible for the ethical aspects of the clinical trial.
- The investigator is primarily responsible for the conduct of the trial.
- Other research partners are the study subjects and regulatory agencies.
- Maintaining good relationships among study partners is critical to a successful clinical trial.

CHAPTER FIVE

The Research Process

This chapter presents an overview of the research process for new pharmaceutical compounds, looking first at preclinical work, then at clinical development. Also briefly discussed are the two main documents that must be filed with the FDA. One of these is the Investigational New Drug (IND) application, which is filed before studies can begin in humans. The other is the New Drug Application (NDA), which is the formal request for permission to market a new product. It is important that CRAs comprehend the entire drug development process, even though they will not be involved in every step. This will help the CRA understand why things happen as they do and to participate knowledgeably in the process.

Figure 1: The research process



Source: FDA, Tufts CSDD

Preclinical Research

This section looks at drug discovery and the preclinical work that must be done before phase I studies in humans can begin. Preclinical refers to studies that do not involve human subjects. Clinical studies are studies conducted with human subjects. Note that sometimes people refer to research as preclinical, even though non-human work can continue after clinical studies have begun. Also, the terms preclinical and non-clinical can be used interchangeably.

The purpose of preclinical studies is to provide information on safety and, if possible, efficacy, in order to begin conducting clinical studies in humans. The information gathered from preclinical studies provides the pharmaceutical company, the FDA and the IRB with enough evidence to make reasonable decisions about exposing humans to the compound. The information from preclinical studies includes: data on acute toxicity, the kinetics and metabolism of the drug, and organ sensitivity. Most importantly, these studies determine a starting dose with an acceptable margin of safety so that there is minimal chance of endangerment to human study subjects.

Drug Discovery

The discovery of new substances, which subsequently become marketed drugs or biologics, occurs in a number of ways. There is direct research, during which medicinal chemists create compounds with structures likely to evoke the kind of physiological effect they are looking for. Another approach is to change the molecular structure of known compounds in the hope of improving safety or efficacy, while creating a new chemical entity that is sufficiently different from the parent compound to allow for the filing of a new patent.

In addition to classical chemistry, there are many new laboratory tools for developing viable drug substances. Computer technology provides many methods for molecular structuring. There are also computer-readable chemical libraries, which may contain several hundred thousand molecular structures. Many pharmaceutical companies have contracts with firms that provide these libraries; the companies take these chemical structures from the database and perform structure/function/activity computations and computer modeling to look for a hit on a potential compound. Pharmaceutical companies can also perform high throughput screening and other computer-related inquiries to look for hits. Other methods include gene sequencing, gene vector delivery and recombinant DNA.

Naturally occurring compounds are another source of potential pharmaceuticals. A number of drugs originated from soil samples (antibiotics), plants (digitalis) and other natural materials such as coral (prostaglandins).

Serendipity plays a role in any research program. Some very exciting compounds have been discovered by accident. Many drugs are marketed for an indication that was discovered by accident during studies for the primary

indication. One example is Rogaine®. This compound, minoxidil, was originally developed as an antihypertensive (Loniten®). Its hair-growing capability wasn't known until subjects enrolled in the hypertension studies began exhibiting accelerated hair growth—in all the wrong places. Women weren't thrilled with new mustaches and bushy eyebrows. Based on this unwanted side effect, the company eventually developed a topical formulation of minoxidil as a hair-growth product.

Preclinical Studies of Product Candidates

Once a compound appears to be a viable product candidate, it must be determined if the compound is reasonably safe for initial testing in humans and exhibits pharmacological activity that might justify developing it commercially. The preclinical work will focus on collecting data and information to establish that humans will not be exposed to unreasonable risks in early-phase clinical studies. This evidence will be presented to the FDA in an IND application.

The first step is to determine the basic physical, chemical and biological characteristics of a new compound:

- Preliminary analytical methods and release criteria must be defined prior to beginning toxicology studies. Methodology and release criteria will change and become better defined as more work is completed and additional information becomes available.
- Data must be developed that will provide evidence of the stability of the compound for the duration of the toxicology studies and clinical trials.
- A formulation of the compound for use in animals and humans must be developed.
- Bioavailability studies must be done to demonstrate equivalence each time the formulation is changed.
- For biologics (monoclonal antibodies, vaccines, etc.), steps such as the identification of adventitious agents and the characterization of cell lines must be completed. (Adventitious agents are impurities or contaminates; for example, all vaccines that are bovine-based must now be checked for mad cow disease.)

The outcomes for these parameters change as the preclinical studies progress. They may even change as phase I and phase II studies in humans are carried out. This ongoing process will result in a final formulation by the time phase III studies begin.

There will be a final collection of analytical methods, release criteria and formulation prior to beginning phase III studies, and all excipients must be identified both quantitatively and qualitatively. (An excipient is an inert substance that forms part of the vehicle for delivering a drug, e.g., gum arabic or starch.)

Once a compound is characterized and satisfactory stability data are in hand, preclinical studies can be initiated. The type of studies and their design will vary depending on the intended use of the drug or biologic being developed. The purpose of preclinical studies is to characterize the toxic effects of the compound with respect to target organs, dose dependence and relationship to exposure. The studies must normally be conducted using two routes of administration: the route intended for human administration—oral, nasal, topical, etc.—and intravenous (IV). If the IV route will solely be used in humans, then no other route needs to be studied in preclinical investigations.

These preclinical studies will establish a number of different things, including:

- The highest dose of the compound that can be tolerated, as well as a low dose that evokes no overt toxicity, in order to determine initial dosing in humans and to characterize potential organ-specific adverse events.
- Proposed dosing, route of administration and duration of treatment for phase I studies.
- Whether the observed adverse effects are reversible.

The recommended preclinical safety studies necessary to obtain marketing approval for a pharmaceutical include: genotoxicity studies, single and multiple (repeated) dose toxicology studies, local tolerance studies and teratology or reproductive studies.

Other preclinical studies that must be completed are pharmacology studies for safety and pharmacokinetic studies that identify absorption, distribution, metabolism and excretion of the compound (ADME studies).

The following are brief descriptions of the different types of preclinical studies that are required to support clinical trials for a pharmaceutical product.

Single-Dose Toxicity Studies

Often referred to as acute toxicity studies, single-dose toxicity studies should be done in at least two non-human mammalian species. An acceptable alternative is dose-escalation studies. Acute toxicology studies examine the toxicity produced by one or more doses of the compound during a period of 24 hours or less, followed by a 14-day non-treatment observation period. The observation period is used to look for delayed toxicity and recovery from overt toxicity. Information from these studies is useful in choosing the doses for repeated dose studies.

Repeated-Dose Studies

Sometimes referred to as sub-chronic and chronic toxicology studies, repeated-dose studies should be conducted for a period of time consistent with the therapeutic indication and the length of the proposed clinical program. In general, the duration of these studies, which must be conducted in two non-

human mammalian species (one rodent and one non-rodent species), should equal or exceed the length of the clinical trials. The longest chronic toxicity study duration is nine to 12 months.

Safety Pharmacology Studies
These studies assess the effect of the drug on vital functions, such as respiratory, central nervous and cardiovascular systems in animals. Safety pharmacology studies may be conducted separately or with toxicology studies. In general, these studies look at what the drug does to the body at pharmacological (intended) doses and should be completed prior to human exposure in phase I.

Pharmacokinetic Studies
Pharmacokinetic studies (PK studies) look at what the body does to the drug in animals. They are also known as ADME studies because they answer questions related to the absorption, distribution, metabolism and excretion of the test substance. Note that the PK studies in animals are the counterpart to phase I clinical trials in humans.

Genotoxicity Studies
Genotoxicity studies are done to determine if mutations or chromosomal damage occur when exposed to the drug. These *in vitro* tests *(in vitro* means "in glass," as opposed to *in vivo*, which means in living organisms) must be completed prior to human exposure. Positive findings dictate additional testing and may be an indication for carcinogenicity testing.

Carcinogenicity Studies
These studies in animals are required for compounds that are expected to be used continuously for six months or longer, or intermittently for periods that, when combined, equal six or more months of continuous use. These studies do not need to be done in advance of clinical trials unless there is cause for concern. Carcinogenicity studies are generally not required for drugs intended to treat subjects with a life expectancy of less than two to three years (e.g., anti-cancer drugs) or if treatment is for a short duration (e.g., anesthetics). These studies are typically performed in rats and mice and involve daily dosing of the animals for two consecutive years (approximately 90% of the rodent's life span) to determine if the drugs, when used for a lifetime, elicit cancer in the animals.

Reproductive Toxicity Studies
Reproductive toxicology studies involve the administration of multiple doses of the drug before, during and after the gestational period in animals to assess the drug's effect on fertility, reproduction and fetal toxicity. There are three segments in this testing.

- Segment I is the general study of fertility and reproductive perfor-

mance in one non-human species, usually the rat.

- Segment II evaluates the effect on the fetus (teratology) and is done in two non-human species, usually the rat and rabbit.
- Segment III is the peri- and post-natal portion, assessing the effect on the unborn or litters. This testing is also done in two non-human species.

Male fertility studies in animals should be done prior to initiation of phase III trials. Women who are unable to bear children (permanently sterilized or post-menopausal) may be enrolled in clinical trials without any reproductive toxicity studies as long as repeated-dose studies have been completed, since the repeated-dose studies include an evaluation of female reproductive organs.

All three segments of the teratology work must be completed prior to submitting the NDA.

Data Collected in Animal Studies

Lastly, just a bit will be covered about the data collected in the animal studies listed above. Here are the items that are evaluated in animals in preclinical studies:

- Daily clinical observations with palpation, body weight and food consumption measurements
- Hematology, clinical chemistry and urinalysis
- Electrocardiograms
- Ophthalmic examinations
- Neurobehavioral testing

Post-mortem evaluations are carried out, which include organ weights (absolute and relative to body and brain weights) and a complete histopathological (microscopic) examination of some 56 tissues.

These studies are all conducted in compliance with regulatory guidelines, which are typically harmonized between the U.S., Europe and Japan, thus accepted globally. In addition, Good Laboratory Practices (GLPs) are strictly followed for documentation and to ensure the integrity of the data. The GLPs are the toxicology counterpart to the GCPs.

To ensure the ethical treatment of animals during these studies and to guarantee that the animals do not suffer any unnecessary pain or distress, there is an independent group called the Institutional Animal Care and Use Committee (IACUC), which must review and approve all animal studies before they begin. It also monitors the progress of these studies through real-time reporting from the attending veterinarian. The IACUC reports directly to the highest official at the facility and is independent from any scientific or management influence. Guidelines for animal studies are covered under the

Animal Welfare Act, which is law; infractions are punishable by fine and/or imprisonment.

The IND Application

The FDA becomes involved in a drug development program when the sponsor has completed enough preclinical work with the compound to determine it is safe enough to begin human trials, and files an IND with the FDA. This is when the compound changes in legal status under the Federal Food, Drug and Cosmetic Act. It becomes an investigational drug and is subject to specific regulatory requirements.

Approval of INDs is passive. The sponsor may begin clinical trials 30 days after submission of the IND unless the FDA indicates there is a problem. Most companies will contact the FDA a few days prior to the 30-day expiration period just to be sure they will be able to proceed with the trials.

The IND contains all known information about the compound. In general, the IND includes:

1. Animal pharmacology and toxicology studies. These are the preclinical data that allow the FDA to make an assessment about whether the compound is reasonably safe for initial testing in humans.
2. Any previous experience with the compound in humans from non-U.S. studies.
3. Chemistry, Manufacturing and Control information.
4. The protocol and investigator information. This includes a complete protocol so the FDA can assess whether the risk for the initial trials (phase I) is acceptable as well as information about the qualifications of the investigator(s).
5. Assurance that a duly-formed IRB will be responsible for initial and continuing review of the trial.
6. If involved, what responsibilities have been delegated to the CRO?
7. The general development plan for the drug.

The IND must be updated on an annual basis. In the update, the sponsor includes any new information about the drug, as well as the results of any studies that are still active or were completed during the year. This information will include current enrollment numbers, adverse events information and the overall study status. The update also includes the clinical plan for the next year. This information keeps the FDA abreast of what is happening with the compound over time. Amendments to the IND may be filed at any time.

Amendments are filed for any changes in protocols, medicine strength, investigators or the development program. The regulations pertaining to INDs are found in 21 CFR 312.

A CRA will rarely have any involvement with the IND; however, when it is time for the annual update, the CRA may be asked to contact sites for current information needed for the update. When this happens, there are often critical timelines involved, so the CRA will need to collect the information in a timely manner.

Clinical Trials

In this section we will discuss the clinical development of a compound. The term clinical implies human studies, as opposed to animal studies. Clinical trials are research studies that involve the active participation of people (trial subjects) to test the safety and efficacy of new medical treatments. Clinical studies are not begun until a reasonable amount of preclinical work has been completed and there is evidence that the compound is potentially safe for use in humans.

Clinical trials are divided into phases: I, II, III and IV. Many companies also use the designation of phase IIIb, which will also be defined in this chapter. (Note that you may also see the phases numbered using Arabic numerals: 1, 2, 3 and 4.) The phases simply serve as markers or milestones in the drug development process and are not necessarily distinct, consecutive periods. For example, in some cases phases II and III can be combined, and phase II may start before phase I is complete. However, each phase does have distinct characteristics and purposes, and each is important to the development program.

Phase I Clinical Trials

During phase I, the investigational drug or biologic is given to humans for the first time.

Phase I studies, frequently referred to as safety studies, enroll a small number of subjects. The total number of subjects in phase I is usually between 20 and 100. Subjects are usually healthy volunteers although, in some cases, patients with the target disease are studied. The type of subject depends on the nature of the disease and the expected toxicity of the investigational drug. It would not be ethical, for example, to give healthy subjects a toxic investigational drug meant to treat one of the cancers.

The purpose of phase I studies is to determine the metabolic and pharmacologic action of the investigational drug in humans, assess the adverse effects associated with different doses and to, perhaps, get an indication of whether or not there is any evidence of efficacy. Subjects are usually given increasing doses of the test product until the side effects reach the point that they are no longer tolerable; this is part of establishing the maximum dose that can be used in humans. Because of the lack of knowledge about the drug, phase I studies are often done in special testing. Since this is the first time humans are exposed to the investigational drug, these studies are very closely

monitored by medical personnel. Phase I studies are often done in special testing facilities designed for this work. Frequently, subjects may be required to stay several nights, so phase I facilities are set up with sleeping, dining and recreational facilities.

Essentially, phase I should provide the researcher with sufficient information about the investigational drug's pharmacokinetics and pharmacological effects (safe dose range and adverse effects) to permit designing safe, well-controlled, scientifically sound phase II studies. The primary concern of phase I is subject safety.

A lot of preclinical work must be done before phase I studies can begin. This is reviewed in Table 1.

Table 1

The following preclinical studies must be completed before phase I studies can begin in the U.S.

- Single-dose toxicity in two mammalian species
- Safety pharmacology studies to include assessment of effects on vital functions
- Pharmacokinetic studies (ADME)
- Repeated-dose toxicity studies in two species (one non-rodent) for two to four weeks, providing phase I studies will not exceed two weeks
- Local tolerance studies using route of administration relative to proposed clinical administration
- In vitro tests for evaluation of mutations and chromosomal damage (genotoxicity)
- Carcinogenicity studies (only if there is cause for concern)

Source: Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals, U.S. Department of Health and Human Services and the FDA (CDER and CBER), July 1997, ICH

Phase II Clinical Trials

When the appropriate phase I studies have been completed and sufficient safety data are in hand, phase II studies are initiated. Phase II studies are rigid, well-controlled studies in a relatively small homogeneous patient population, usually no more than a few hundred subjects in total. These subjects have the target disease, but no other confounding illnesses. Phase II usually consists of double-blind, well-controlled studies using a placebo or comparator drug, or both. Their purpose is to determine whether or not the investigational drug demonstrates efficacy for the proposed indication within the safe dose range established in phase I. Short-term adverse effects and risks are also assessed. While the focus of phase II studies is primarily efficacy, they also assess safety. Dose-range finding, e.g., establishing a minimum and maximum effective dose, and PK data correlating blood levels of the inves-

tigational drug with pharmacological effect (also known as the pharmacokinetic/pharmacodynamic relationship) are also studied during phase II.

Near the end of phase II, most sponsors will meet with the FDA to review the results obtained to date and present their plans for phase III. This is called the end-of-phase II meeting. The FDA views these meetings as being of considerable assistance (to both the FDA and the sponsor) for planning later studies of the compound. Pursuant to the provisions of PDUFA, agreements reached at these meetings are binding on the FDA and the sponsor.

Remember, there are preclinical studies that may have been active during phase I but must be completed before phase II can start. This requirement is shown in Table 2.

Table 2

Preclinical requirements before initiating phase II studies in the U.S.:

- Repeated-dose toxicity studies in two species (one non-rodent) for a period of time equivalent to the length of the phase II studies. Six-month rodent and chronic non-rodent studies will support clinical trials of six months' duration in the U.S. Studies of longer treatment duration are supported by nine-to-12-month-long preclinical studies.

Source: Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals, U.S. Department of Health and Human Services and the FDA (CDER and CBER), July 1997, ICH

Phase III Clinical Trials

Phase III studies are initiated only if the data generated in phase I and II have a satisfactory safety profile and there is sufficient evidence of efficacy. The purpose of phase III studies is to demonstrate the safety and efficacy needed to assess the risk/benefit relationship for the intended use of the investigational drug and to provide adequate data for the product package insert.

Phase III studies are expanded, controlled studies in large patient populations (often thousands of patients) that represent the types of patients the compound is intended to treat after it is marketed. They may extend over several years. The development plan for the compound usually includes many different studies, including more than one multicenter study using the same or similar protocols. Multicenter studies are those for which multiple investigative sites all follow the same protocol, and for which the data are pooled together in one group for analysis.

The FDA requirement for registration of a drug is two "adequate and well-controlled" (primary efficacy) studies. However, under the FDAMA legislation of 1997, the FDA may allow one study instead of two for a product for which it is determined (by the FDA) that "data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness."

The decision to do one, rather than two, adequate and well-controlled studies is not one that a sponsor will make on its own. This decision will be made after consultation with and support of the FDA.

As is the case for phases I and II, there are a number of preclinical studies that must be completed before or during the phase III program. The completion of these studies is required before a sponsor can file the NDA with the FDA (See Table 3). We will discuss the NDA in more detail later in the chapter.

Table 3

Preclinical requirements for initiation of phase III studies in the U.S.:

- Repeated-dose toxicity studies in two species (one non-rodent) for a period of time equivalent to the length of the phase III studies. Six-month rodent and chronic non-rodent studies would support clinical trials not exceeding six months.
- Carcinogenicity studies if the duration of treatment of the drug is expected to be six months or longer or if intermittent exposure is equal to six months of continuous exposure, or if there is cause for concern. Carcinogenicity studies are not required if the patients receiving the drug have a life expectancy of less than two years.
- Fertility studies in males.
- Repeated-dose toxicology studies that include an evaluation of female reproductive organs must be done if women of non-childbearing potential are used.
- Assessment of female fertility and embryo-fetal development if women of childbearing potential will be included.
- All reproduction toxicity studies and the standard genotoxicity tests should be completed if pregnant women will be included.

Source: Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals, U.S. Department of Health and Human Services and the FDA (CDER and CBER), July 1997, ICH

The NDA (New Drug Application)

The NDA is a formal request to be allowed to market a drug. The sponsor submits the NDA to the FDA at the time the primary efficacy studies (phase III) are complete. The company is essentially telling the FDA that it has completed the necessary safety and efficacy requirements needed for approval. This signals the end of phase III, although there are likely to be some studies still in progress.

In the NDA, as in the IND, the sponsor is informing the FDA of everything that is known about the drug to date. This includes copies of all protocols and case report forms from studies. (These applications can be enormous.) The regulations for NDAs are found in 21 CFR 314. They delineate

the particular information that must be included.

Field-based CRAs are unlikely to be involved in helping put together an NDA submission. However, CRAs who are based in-house may well be involved in helping to assemble the clinical section. Often CRAs are involved in a last-minute push to retrieve and/or clean up data needed for the NDA. CRAs also may be asked to re-verify information from sites when questions arise during the NDA writing process.

Part of the NDA is the proposed package insert that the sponsor would like to use with the drug. This is the information that goes with the drug that

Table 4: Notes on Studies in Women and Children

Recently there has been a greater emphasis on studying new compounds in women and children. These populations were previously understudied and many compounds do not work the same way in women or children as they do in men. Consequently, the FDA determined that studies should include women and children if the compounds would be used to treat them after marketing. The rationale is that it is preferable to determine the effects of the compound under the controlled conditions in clinical trials as opposed to uncontrolled use of the drug after marketing.

CRAs should have basic knowledge about the testing of compounds in women of childbearing potential, pregnant women and children.

Women of childbearing potential are a major concern in clinical trials because of the possibility of unintentional exposure of an embryo/fetus before data are available relative to potential risk. Some teratology work (segments I and II) is usually done before entering women of childbearing potential into a clinical trial, although this is not essential.

In the U.S., women of childbearing potential may be included in early studies prior to completion of reproductive toxicology studies, providing that the studies are carefully monitored and all precautions are taken to minimize exposure in utero. This generally involves pregnancy testing and establishment of highly effective methods of birth control. Monitoring and testing should continue throughout the trial to ensure compliance with all measures intended to prevent pregnancy.

If women of childbearing potential participate in a clinical trial prior to completion of the teratology studies, the informed consent process should clearly indicate the possible risk associated with taking the investigational drug since effects on the embryo/fetus are unknown.

If pregnant women are to be enrolled in clinical trials, all reproductive toxicity studies and genotoxicity tests must be completed. Data from any previous experience in humans will also be needed.

If children are to be included in clinical trials, repeated-dose toxicity studies and all reproductive toxicity and genotoxicity studies should have been completed. In addition, safety data from previous studies in human adult populations should be available.

tells physicians about the drug and how it should be used. The package insert negotiations between the sponsor and the FDA can be extensive.

There is an active approval process for an NDA (as opposed to the passive 30-day wait for an IND). The sponsor must receive a formal approval letter from the FDA before marketing of the drug can begin.

Phase IIIb Clinical Studies

A sponsor will frequently have some studies that are still active at the time it files the NDA for a new compound. There are also studies that may be initiated and conducted while the NDA is pending approval. These studies are known as phase IIIb studies. The purpose of these studies may be to gather additional safety data, to gather information on additional indications for the drug, or to assess its use in special patient populations such as geriatric patients.

Phase IV Clinical Studies

Phase IV studies are those conducted after the approval of the NDA, often to determine additional information about the safety or efficacy profile of the compound. They consist of studies:

- Required as a condition of approval by the FDA
- Required as long-term safety studies by the FDA
- Conducted to study the compound in comparison with other marketed products
- Designed to familiarize physicians with the compound

If the sponsor was allowed to file the NDA with one, rather than two, adequate and well-controlled studies, the FDA may require that one or more additional confirmatory studies be completed within a certain time period of the approval. This is a condition of the approval; if it is not met, the approval may be withdrawn.

The FDA may also require that a sponsor do a long-term safety study as a condition of approval. These studies are often referred to as epidemiologic or post-marketing surveillance studies. These may be required because the FDA has seen problems with similar compounds, or because the compound is novel and the FDA thinks additional safety information will be beneficial.

During the development time for the compound, other drugs may have been approved by the FDA and become the new standard of care for the disease or condition. In this case, the sponsor may want to do additional studies comparing its drug to these new compounds. The sponsor may also wish to look at different formulations, dosages, durations of treatments or medical interactions with other compounds commonly used by people with the disease targeted by the drug. Note that if the sponsor wants to evaluate

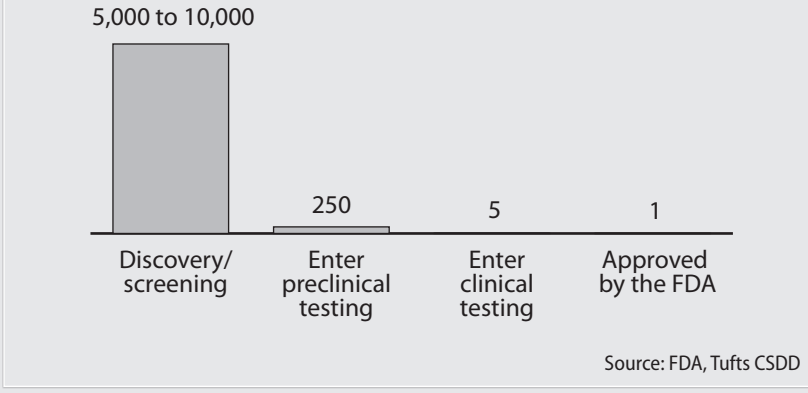
the compound for a new (additional) indication, a new NDA will need to be filed for the new indication(s), but it will not require repeating studies. Studies designed to familiarize physicians with the new drug are sometimes referred to as marketing studies. Physicians may be given a relatively small amount of the new drug to use in an open-label manner with appropriate patients and will be required to collect some data, usually only safety data, on these patients. The goal of the sponsor of these studies is to have the physician become familiar with the product.

There are other types of "studies" that do not actively involve treating patients with investigational devices or products, such as "registry studies" and "retrospective chart review" studies.

According to the Virginia Commonwealth University Office of Research and Innovation, "A registry is an **organized system that uses observational study methods to collect uniform data** (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition or exposure, and that serves one or more predetermined scientific, clinical or policy purposes."

Retrospective chart review studies involve review/analysis of pre-existing

Figure 2: Investigational drug success rates by stage



data, such as based on data already collected in a medical record.

Summary

It is important to understand that most of the new compounds discovered by pharmaceutical scientists and chemists never make it through the entire process to become marketed products. In fact, only a small fraction of these "interesting" compounds actually enter the human testing phases. Of

the compounds tested in phase I studies from 1998 to 2008, 70.6% went on to phase II trials but only 45.4% went into phase III trials. Of these, 63.3% were submitted for regulatory approval, with 93.2% being approved. Thus, the overall approval rate for compounds entering phase I was only 19%. If you started with all of the compounds of interest that never made it to phase I, the overall success rate is far less than 0.01%.

The following diagram shows the progression of activities in drug research, as well as some of the important milestones covered in this chapter. Drug discovery and development is a long process; the time between a compound entering preclinical testing and the NDA approval averages about 10 years, and the attrition rate is very high. For every 5,000 to 10,000 compounds screened, only 250 enter non-clinical testing; of the 250, only five go into clinical testing, and only one makes it all the way to approval by the FDA.

Key Takeaways

Preclinical

- Preclinical trials do not involve human subjects.
- Clinical trials involve human subjects.
- Before clinical trials begin, the sponsor must file an IND with the FDA.
- The IND must include results from the preclinical studies.
- Animal studies are monitored to ensure ethical treatment.
- The IND is filed after significant preclinical testing has been done on a compound, and it appears to be reasonably safe for use in humans.
- There is no formal FDA approval for an IND. A sponsor must wait 30 days after filing the IND before starting studies in humans.
- INDs must be updated annually. The update contains what was learned about the compound during the year and the clinical plan for the following year.

Clinical

- Phase I studies are small safety studies usually done in healthy volunteers.
- Phase II studies are usually the first studies in patients with the disease or condition of interest.
- Phase III studies are large, comprehensive safety and efficacy studies.

- Phase IIIb studies are those being conducted during the time the compound is in the FDA review cycle.
- Phase IV studies are conducted after approval of the compound.
- There is an increased emphasis on conducting studies in women and children.

NDA

- The NDA is the sponsor's formal application to market a new drug.
- The NDA is filed when the primary safety and efficacy studies are complete.
- The FDA must formally approve a drug before it can be marketed.

CHAPTER SIX

Devices and Biologics

The FDA is responsible for protecting public health by assuring the safety and effectiveness of a variety of medical products, including drugs, devices and biological products. It also has responsibility for advancing public health by helping to speed innovations that make treatments more effective, safer and more affordable. Although much of the information in this book is geared toward the study of drugs, many CRAs will also be involved in clinical trials of devices and biological products. The precepts of conducting good research (GCPs, etc.) are the same in any clinical trial, but there are some differences in the regulations when the potential product is a device. This section discusses some of the differences. The Center for Devices and Radiological Health (CDRH) in the FDA is responsible for both the premarket and post-market regulation of medical devices. The CDRH page can be found on the FDA website. A medical device is a product used for diagnosis, therapy or surgery purposes in patients, and that acts by physical, mechanical or physico-chemical (drug/device combination) means. Medical devices include a wide range of products that vary in complexity from tongue depressors to artificial hearts and X-ray machines.

There are different types of marketing applications a medical device manufacturer may submit to CDRH. Most medical devices reach the market through either the premarket approval (PMA) process or the premarket notification process (510(k)). The great majority are approved through the 501(k) process.

The FDA recognizes different classes of medical devices, based on their design's complexity, their use characteristics and their potential for harm if misused. "Class" refers to the level of regulatory control attached to the device. The definitions pertaining to the classification of devices are found in 21 CFR 860 (Medical Device Classification procedures).

Class I devices are subject only to the general controls authorized by or under sections 501 (adulteration), 502 (misbranding), 510 (registration), 516 (banned devices), 518 (notification and other remedies), 519 (records and reports) and 520 (general provisions) of 21 CFR 860. A device is in class I if these general controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device, if the device is not life-supporting or life-sustaining or for a use that is of substantial importance in preventing impairment of human health, and that does not present a potential unreasonable risk of illness or injury. Examples of Class I devices are examination gloves and elastic bandages.

Class II devices are subject to special controls because general controls alone are insufficient to provide reasonable assurance of its safety and effectiveness. Special controls can include the need for performance standards, post-market surveillance, patient registries, the development and dissemination of guidance documents and other appropriate actions that the FDA deems necessary to provide this assurance. Examples of Class II devices are powered wheelchairs and infusion pumps.

Class III devices, which are usually novel devices, require the submission of PMAs. These devices tend to have a higher risk or raise new safety and effectiveness questions that must be answered before they are approved for marketing. Data in a PMA application must demonstrate a "reasonable assurance" of safety and effectiveness. Examples of Class III devices include implantable pacemakers and automated external defibrillators.

Manufacturers submit 510(k)s for devices similar to those already on the market. Data in a 510(k) submission must demonstrate that the new device is substantially equivalent in safety and effectiveness to a Class II device already on the market. Most device applications cleared under the 510(k) program are based on non-clinical testing with no clinical data, while the majority of PMA applications contain clinical data.

Many devices are designed and developed as tools to accomplish a specific task that is already an established practice, so the intended patient population and anticipated effects of the device are known before testing begins. This is different than the drug development process, where a new molecular entity may be identified before determining any potential clinical applications.

Another major difference between device and drug development is the interpretation of safety events seen in a clinical trial. A control group is almost always necessary to interpret safety information from a drug trial, while a control group may not be needed to identify adverse events related to the use of a device.

Premarket trials tend to be simpler than drug trials when demonstrating safety with regard to intended use, and compliance is usually easier to measure in device trials. There are a number of other differences between device and drug trials. For example, it may not be possible to "blind" the device, so many device trials are done with the investigator and subject both being aware of the device being used. It also may not be possible to have a

direct comparison with a competitor device, either because there may not be a comparable device or because of the logistics involved.

When studying a drug, the dosage may be an issue; with a device, the size of the device may be an issue, especially in implantable devices. Implanting a device may carry a greater risk than prescribing a drug, especially in later-phase trials when more is known about a drug. Depending on the device, there may be more precise endpoint determination (especially when there is electronic information storage on the device). Many endpoints in drug trials, on the other hand, are quite subjective (think of a depression rating scale versus a "hard" measurement such as blood pressure).

There are also some differences in the collection and reporting of medical events between device and drug trials. These are discussed in more detail in the adverse events chapter.

If you will be monitoring device trials, it is recommended that you read the device regulations found in 21 CFR Part 812 (Investigational Device Exemptions) and 21 CFR Part 814 (Premarket Approval of Medical Devices). 21 CFR Part 860 (Medical Device Classification Procedures) and 21 CFR Part 803 (Medical Device Reporting), which covers adverse event reporting, will also be helpful.

Biologics and Vaccines

The Center for Biologics Evaluation and Research (CBER) is the organization within the FDA responsible for ensuring the safety and efficacy of vaccines, blood and blood products, and cells, tissues and gene therapies designed for the prevention, diagnosis and treatment of human diseases, conditions or injury. The CBER page can be found on the FDA website.

The Biologics License Application (BLA) is a request for permission to introduce a biologic product into interstate commerce (21 CFR 601.2). (This means approval for marketing.) The BLA is regulated under 21 CFR 600-680. The application, which shows the clinical efficacy and safety of a biologic product in humans and requests marketing approval in the U.S., is usually submitted to the FDA after completion of the phase III trials.

The regulations that apply to drugs also apply to biologics. In addition to these, the regulations in the preceding paragraph regulate the BLA.

Vaccine clinical development follows the same general pathway as drugs and other biologics. A sponsor that wishes to begin clinical trials with a vaccine must submit an IND to the FDA. The IND describes the vaccine, its method of manufacture and quality-control tests for release. Also included is information about the vaccine's safety and ability to elicit a protective immune response (immunogenicity) in animal testing as well as the proposed clinical protocol for studies in humans.

The NIH has guidelines for "Research Involving Recombinant or Synthetic Nucleic Acid Molecules (November 2013)," that state:

> **Section I-A-1-a.** *For experiments involving the deliberate transfer of recombinant or synthetic nucleic acid molecules, or DNA or RNA derived from recombinant or synthetic nucleic acid molecules, into human research participants (human gene transfer), no research participant shall be enrolled (see definition of enrollment in Section I-E-7) until the RAC review process has been completed (see Appendix M-I-B, RAC Review Requirements); Institutional Biosafety Committee (IBC) approval (from the clinical trial site) has been obtained; Institutional Review Board approval has been obtained; and all applicable regulatory authorization(s) have been obtained."*[1]

According to the U.S. Department of Health and Human Services website, "Institutional Biosafety Committees are the cornerstone of institutional oversight of recombinant DNA research."

It is important for CRAs to be aware that institutions that conduct this type of research (including some investigational vaccine treatments) are subject to additional oversight/review/approval by Institutional Biosafety Committees (IBCs). The IBC oversight includes additional requirements for drug containment, storage, preparation and dispensation practices at the institution performing the research, among many other things. There are specific IBC requirements that institutions have to meet before they can conduct these types of trials. CRAs need to ensure they are aware of IBC oversight and institutional requirements for trial conduct when monitoring these types of studies at their investigational sites.

Clinical trials for vaccines are typically done in three phases, just like drugs and biologics. Initial human studies, referred to as phase I, are safety and immunogenicity studies performed in a small number of closely monitored subjects. Phase II studies are dose-ranging studies and may enroll hundreds of subjects. Finally, phase III trials typically enroll thousands of individuals and provide the proof of effectiveness and safety required for licensing.

After the successful completion of all three phases of clinical development, the sponsor can submit a BLA. To be considered, the application must provide the FDA reviewer team (medical officers, microbiologists, chemists, biostatisticians, etc.) with the efficacy and safety information necessary to make a risk/benefit assessment and to recommend or oppose approval of the vaccine.

As is the case for drugs, vaccine approval also requires the provision of adequate product labeling to allow healthcare providers to understand the vaccine's proper use, including its potential benefits and risks, to be able to communicate with patients (and parents if the vaccine is for use in children) and to safely deliver the vaccine to the public. The FDA continues to oversee production of vaccines after the vaccine and the manufacturing processes are approved, in order to ensure continuing safety.

Until a vaccine is given to the general population, all potential adverse events cannot be anticipated. Thus, many vaccines are required to undergo

phase IV studies after they are on the market. There is also a Vaccine Adverse Event Reporting System (VAERS) to help identify any problems with a vaccine after marketing begins.

Many large pharmaceutical companies are adding vaccines to their portfolios because of growth opportunities. Vaccine area growth means that more CRAs will have the opportunity to work on vaccine trials. Although vaccines and drugs fall under the same regulations, there are some significant differences in vaccine trials. One fundamental difference in the trials is that vaccines are typically given to healthy individuals in the hope that the vaccine will keep them from contracting the disease of interest (e.g. flu). Since these trials take healthy people and expose them to an investigational product (the vaccine), there is very little tolerance for risk.

Vaccine trials tend to be extremely large, and recruiting large numbers of healthy people can be very resource-intensive. There is also an issue of retaining subjects for the duration of the trial, as the site does not normally see the subjects again after the administration of the vaccine until the very end of the trial. Enrollment time also may be very short, especially if you need to "catch the season," as with the flu. When a new strain of flu is expected to become endemic, for example, studies on a vaccine to prevent it must be done before the flu season commences.

This is another interesting area in which CRAs may have the opportunity to be involved. If you will be working with biologics, including vaccines, you may want to become familiar—along with the drug regulations—with 21 CFR Part 600 (Biological Products: General), 21 CFR 601 (Licensing) 21 CFR Part 610 (General Biological Products Standards) and NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH GUIDELINES) November 2013.

Key Takeaways

- CDRH is responsible for both the premarket and post-market regulation of medical devices.
- There are a number of differences between device and drug trials.
- CBER is responsible for vaccines, blood and blood products, and cells, tissues and gene therapies.
- The regulations that apply to drugs also apply to biologics and vaccines.
- There are other regulations and institutional requirements that apply specifically to devices and to biologics.
- One of the main differences in vaccine studies is that the vaccines are normally given to healthy study subjects.
- The vaccine area is growing very rapidly.

References

1. "Research Involving Recombinant or Synthetic Nucleic Acid Molecules." The National Institutes of Health (NIH). November 2013.

CHAPTER SEVEN

Globalization of Clinical Trials

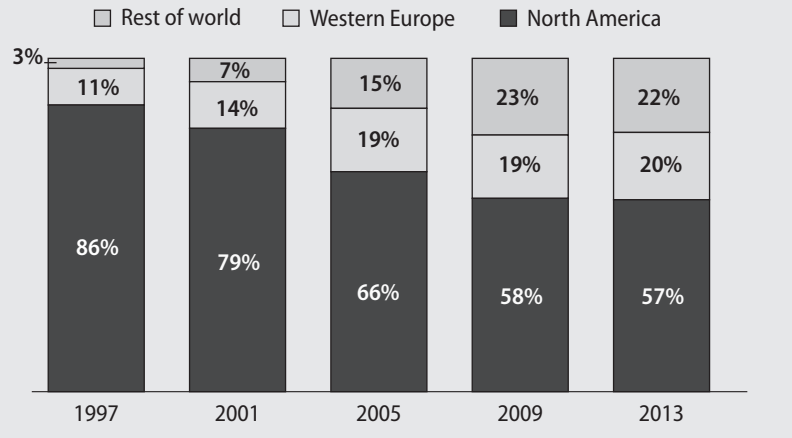
Many diseases, such as diabetes, hypertension and HIV/AIDS, have now become global in scope. Instead of being confined to a small geographic area or one group of people, diseases have become more prevalent among many different cultural groups. In part because of these new global markets, there is a growing interest in conducting clinical trials.

Sponsors are conducting clinical trials in countries that would hardly have been considered in the past, for many reasons. Some populations around the world have used considerably fewer medications than in more developed countries, making it easier to assess the effects of a study medication. Also, some diseases have an extremely low incidence in developed countries (e.g. malaria), but there is still a need for new medications; these medications could not be developed without conducting trials in countries where the disease is still prevalent. Another reason for the increase in the number of global trials is that some developing nations require local clinical trial data for product registration (e.g. India and China).

There has been a large increase in the number of clinical trials conducted in countries outside the U.S. over the past decade, especially in later-phase studies that enroll large numbers of subjects and have higher per-subject costs. In fact, many multicenter trials currently being conducted have a mixture of both U.S. and non-U.S. sites. By 2009, the average phase III trial was taking place in 34 countries.

According to Ken Getz at the Tufts Center for the Study of Drug Development (CSDD), in 1997, 86% of FDA-regulated investigators were located in the U.S., with most of the rest (9%) in Western Europe and only 5% in the rest of the world. By 2009, however, only 53% of FDA-regulated investigators were in the U.S., with 14% located in Western Europe and 33% located in the rest of the world.

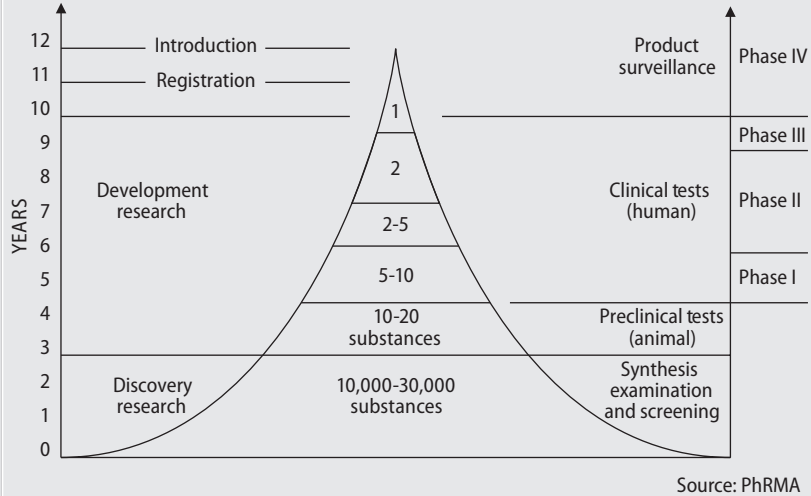
Figure 1: Global distribution of unique investigators filing form 1572



Source: Tufts CSDD analysis of FDA's Bioresearch Monitoring Information System File

Using sites in emerging markets such as Central and Eastern Europe, China, India and Latin America in later-stage trials often enables sponsors to increase subject recruitment and cut costs, while establishing a presence in these emerging markets. With the huge increase in global trials, sponsors have had to broaden their procedures and processes to handle the varying regulatory and cultural requirements of many counties. Note that if these trials are to be used for registration in the U.S., they must follow FDA regula-

Figure 2: Development of a successful new drug



Source: PhRMA

tions, as well as those of the country that is conducting the trial.

Completing trials in other countries may help the sponsor register the product more quickly in these countries and in the U.S., as well as reduce its overall development time and cost. In 2008, the industry and government spent over $35 billion on drug and device clinical trials, of which $8.3 billion was for investigator grants. Cutting costs has become a critical aspect of research and development programs, so as long as costs continue to be lower in emerging markets, the trend toward conducting studies in these areas of the world will undoubtedly continue to rise.

Managing Multinational Trials

Many CRAs are working on trials in which some, if not all, of the investigative sites are in other countries. Some CRAs actually travel to other countries to monitor non-U.S. sites. Even if the CRA is not actually monitoring non-U.S. sites, activities often involve the U.S.

There are some inherent difficulties when studies involve sites in different countries. Language, cultural differences and time zone differences can make working together a challenge. Translating study materials into other languages can be expensive and time consuming. Working with a translator makes meetings awkward, and misunderstanding cultural differences can cause embarrassment. Differences in standard medical practice are important to recognize, as are differing attitudes toward medical care. For example, in some countries patients would never think to complain about an issue that would be seen in the U.S. as an adverse event. Projects can go awry simply because of misunderstandings and difficult personal interactions due to cultural differences.

The distribution and storage of study products can be difficult in terms of time, cost, the environment and accountability. Storage can be an issue, especially if the product needs to be temperature controlled, refrigerated or frozen. Conditions can vary considerably in some countries, especially where basic utility services are not available on a regular basis.

It can also be difficult to transfer data from the site to the sponsor in a timely manner. If electronic data transfers are being used, the required connections may not always be reliable or available. If relying on mail services, it may take a much longer time for the transfer. These issues need to be recognized and addressed before the trial begins.

Global trials should be conducted with the same ethical principles as trials run in the U.S. They should follow all national and international regulatory requirements, as well as ICH guidelines. There are certainly some ethical issues to consider. For example, in Europe as well as other non-U.S. countries, there is a bias against using placebo controls in clinical trials. It is felt that it is not ethical to withhold active medication from someone suffering from a medical condition that could be treated. Informed consent may not mean the same thing in another country that it does in the U.S. Written consent may

not be possible, so one might have to work with a witness who can explain and interpret what will happen in the study. Payments to subjects and to investigators can be an issue, and should be appropriate to the local economy.

These issues need to be considered and managed. To help with ethical issues, some companies have an IRB in the U.S. review the study and related issues, as well as a local IRB in the trial country.

If a sponsor is large, more resources may be available to facilitate global trials. Many large sponsors have offices in multiple countries, so people are available who speak both English and the local language, understand the cultural climate and can assist colleagues coming from the U.S. to work at investigative sites. Some sponsors also use CROs based in foreign countries to monitor trials, which is another good resource. Even when an in-country CRO is used, however, it is likely that sponsor personnel from the U.S. will need to visit non-U.S. sites periodically.

As a CRA, if you have involvement with non-U.S. sites, there are some basic things you will want to keep in mind that will make for smoother interactions when working with them:

- Time differences are significant. You may need to adjust your working hours to be available earlier or later in the day to talk to your non-U.S. colleagues. You cannot expect others to always adhere to your most convenient times. This is especially true when contacting study site personnel, who are not sponsor employees.
- Although many other people around the world speak English, it is often not their first language. You may need to speak more slowly to be understood. Try not to use slang, abbreviations, colloquialisms, etc., that may not be familiar to others. Check to be sure what you said is clear to the other person. If you are speaking in person, watch the other person's body language for clues. It's easier to confirm that everyone is on the same page than it is to fix misunderstandings later.
- Cultural differences can be landmines. We've all heard stories about gaffes made because of these differences, from using the wrong word in a situation to making a gesture that has a completely different meaning to giving an inappropriate gift. Go slowly, ask people with more experience, watch others—be aware. Books have been written about appropriate etiquette in other countries; check your local library or bookstore.
- When in large meetings or teleconferences with non-U.S. investigational or sponsor personnel, be sure to avoid uncomfortable or controversial topics such as politics, religion or world events. Individuals on the same study team may hold dramatically different views on these topics. Discussing them can be unprofessional and cause discord within a study team.
- Remember that some people are better with spoken English than

written English, or vice-versa. Think as much about what you write as what you say.

- Ensure that your passport is renewed and current, as you may have to travel internationally at the last minute.
- Large meetings, such as investigator or study startup meetings, with many speakers and long sessions are tiring, especially when English is not your first language. Take time at these meetings to speak individually with people to see if they have questions. Note: It is important to build in more breaks—longer breaks—into meetings with participants from multiple countries or who speak multiple languages.
- Allow more time for monitoring visits. You may need extra time to develop trust and cooperative relationships, as well as for study-related activities that need to be carried out. When you are traveling long distances, it would be counter-productive to cut your visit short without accomplishing everything that needs to be done.
- Be nice. Be pleasant. Be friendly. This will go a long way toward good, professional working relationships.

Did you know?

The following advice came from Sue Fox, author of Business Etiquette for Dummies.

- In Argentina, it is rude to ask people what they do for a living. Wait until they offer the information.
- In China and most Asian cultures, you should avoid waving or pointing chopsticks, putting them vertically in a rice bowl or tapping them on the bowl. These actions are considered extremely rude.
- In Greece, if you need to signal a taxi, holding up five fingers is considered an offensive gesture if the palm faces outward. You should face your palm inward with closed fingers.
- In Egypt, showing the sole of your foot or crossing your legs when sitting is an insult. Never use the thumbs-up sign, because it is considered an obscene gesture.
- In Japan, never write on a business card or shove the card into your back pocket when you are with the giver. This is considered disrespectful. Hold the card with both hands and read it carefully. It's also considered polite to make frequent apologies in general conversation.
- In Spain, always request your check when dining out. It is considered rude for wait staff to bring your bill beforehand.
- In Vietnam, shake hands only with someone of the same sex who initiates it. Physical contact between men and women in public is frowned upon.

Source: Stoller, Gary. Doing business abroad? Simple faux pas can sink you. USA Today. August 24, 2007.

If you are lucky enough to be involved in non-U.S. studies, enjoy the opportunities afforded by travel to other countries and working with people from other cultures; you may never have this wonderful good fortune again.

Key Takeaways

Many multicenter trials being conducted today have a mixture of both U.S. and non-U.S. sites:

- Working with multinational sites presents numerous challenges, including logistical problems due to travel and different time zones.
- Cultural and language differences need to be carefully considered when working in other countries.
- Global trials should be conducted with the same ethical principles as trials run in the U.S.

CHAPTER EIGHT

Institutional Review Boards and Data Safety Monitoring Boards

When conducting clinical trials, the safety of human subjects comes first. The two main safeguards for human subjects are Institutional Review Boards (IRBs) and the informed consent process. This chapters cover IRBs—what they are, their purpose and how they function. Another entity frequently used to enhance safety in clinical trials is a Data Safety Monitoring Board, which will also be discussed later in this chapter.

The regulatory definition of an IRB is "any board, committee or group formally designated by an institution to review, approve the initiation of and conduct periodic review of biomedical research involving human subjects. The primary purpose of such review is to assure the protection of the rights and welfare of the human subjects." Notice that an IRB must approve a study before it can start. All research done in humans in the U.S. must be approved by an IRB. (21 CFR Part 56 contains the regulations that pertain to IRBs.)

Since many companies do research globally, a CRA should be aware that ethical reviews of protocols are conducted outside the U.S. The Independent Ethics Committee (IEC) is the body analogous to an IRB in countries outside the U.S. The IEC is an independent body, the responsibility of which is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial by reviewing and approving/providing a favorable opinion on the trial protocol and informed consent. Both IRBs and IECs have one fundamental purpose: to protect the rights, safety and welfare of human subjects in research. In general, IECs give a favorable opinion about the research, rather than an actual approval; this difference in wording is the main difference between the two groups. For all purposes, the favorable opinion of an IEC carries the same weight and is just as binding as the approval of an IRB; it is especially viewed as such for any studies that will be submitted to the FDA for registration purposes.

Our discussion, however, will focus on IRBs and the U.S. regulations for IRBs and investigators.

An investigator who is planning to conduct a trial must contact an IRB, submit the appropriate materials, including the proposed protocol and consent form, and wait for formal approval from the IRB before he or she may initiate the trial. Interacting with and asking an IRB for approval are the responsibilities of the clinical investigator, not the pharmaceutical company sponsoring the research. (Note: Occasionally a sponsor may submit documents to the IRB on behalf of investigators.) However, the CRA will verify the investigator's IRB approval for the sponsor.

Types of IRBs

There are two types of IRBs: those that are affiliated with an institution and those that are not. Unaffiliated IRBs are called independent, central or national IRBs. They can be used by any researcher who is not constrained by institutional policy to the use of a particular institutional review board.

If an investigator is affiliated with an institution (hospital or university, etc.) that has an IRB, and if that investigator is conducting the trial or any part of the trial at the institution, then he or she would normally use the institution's IRB (also known as the local IRB). If the trial is being conducted at the investigator's private practice and is not affiliated in any way with an institution, then he or she is not normally required to use the institution's IRB. However, a few institutions have policies that require any person affiliated with the institution to use its IRB, even for research conducted outside the institution. If an investigator is conducting a study at more than one institution (e.g., two hospitals), IRB approval is required from each institution where the study will be conducted.

Independent IRBs (also known as commercial, or central IRBs), those not affiliated with a particular institution, are available to any investigator who is not affiliated with an institution, who will not be conducting clinical trials at an institution or whose institution does not have its own IRB. Independent IRBs are frequently used for multi-center studies in non-hospitalized patients. Study sponsors prefer to use independent IRBs when possible because, in general, they tend to review studies more quickly (turnaround time). The IRBs at some teaching hospitals, for example, can take three to six months to review a protocol, while most independent IRBs have a review time of less than one month. Sometimes sponsors or investigators may express concerns about having research reviewed by an IRB that is not local and may not be as familiar with the investigative site, the investigator or the community. To counteract concerns, the better independent IRBs visit investigative sites and have methods of determining community attitudes and other local issues in order to appropriately approve or disapprove research.

A more common trend to mitigate the long approval timeframes of large institutional/academic health site IRBs is the practice of deferring the local

IRB responsibilities to a central IRB. These large institutions enlist the assistance of well-established central IRBs to complete study review and approval; they essentially delegate the institutional IRB responsibility to a central IRB (the central IRB will essentially serve as the local IRB). The basic process is that the institutional IRB will complete review of the study and accompanying materials, and if contingently approving the study, will send the study materials on to the central IRB for final verification and approval. This is usually done in cases where the institutional local IRB is backlogged with internal study review, or fraught with excruciatingly long review timeframes. Delegating study review responsibilities to a central IRB expedites the study submission and approval process, which allows institutions to stay competitive with their counterpart institutions, as well as local private physicians and research sites that use central IRBs.

IRB Responsibilities

Whether or not the IRB is affiliated with a particular institution, its primary responsibility is to protect the rights and welfare of human subjects participating in clinical research. To fulfill this responsibility, the IRB must answer two basic questions:

1. Should the study be done at all? Do the benefits outweigh the risks? If so,
2. What constitutes adequate informed consent?

Should the Study be Done at All? (The Benefit vs. Risk Assessments)

When determining whether or not the study should be conducted, the IRB must consider several items. The IRB members must have assurance that the study is scientifically valid; in other words, that there is a properly designed protocol. However, it is not the responsibility of an IRB to judge the scientific merit or worth of the trial. For example, it is not the function of an IRB to decide whether we need another drug for hypertension, but rather to determine if the research methods being used to study that potential antihypertensive are valid.

Risks to the subjects must be minimized, so the IRB will look for a sound research design that does not expose human subjects to unnecessary risk. It will also ascertain if the protocol uses procedures that would be performed on these patients, both diagnostically and treatment-wise, even if they were not in the study, when appropriate.

The IRB must determine whether the anticipated benefit to subjects, and the overall knowledge to be gained from the research, compares favorably to the risks. In this evaluation, the IRB considers only those risks and benefits that may result directly from the research, excluding the risks and benefits the subjects would have encountered even if they had not been involved in

the research (just in the standard treatment for the condition). Remember, there are always risks involved in doing research. The IRB also will want to know what the subject selection process is, in order to ensure that the selection is equitable and that no groups of potential subjects are routinely excluded or included based on non-study related characteristics. Depending on the particular study, some of these characteristics might include sex, race, ethnic background, weight, smoking, educational background, etc. In making this assessment, the IRB will consider the particular setting in which the research will be conducted, as well as the purposes of the research.

What Constitutes Adequate Informed Consent?

If the IRB determines that the answer to the first question (Do the benefits outweigh the risks?) is yes, then it will consider the consent form submitted by the investigator. It is a regulatory requirement that informed consent is sought from each subject, or the subject's legally authorized representative, before that person may be enrolled in the research project. By regulation, informed consent must be documented, which is usually done by having the subject sign a written copy of the consent document. (Consents are discussed in detail in the next chapter.)

There is a specific process to the development and finalization of the informed consent form for a study, relative to the sponsor, and the institutional and independent IRBs used by sites. The sponsor/CRO is responsible for developing an appropriate informed consent form template. It is submitted to the independent IRB for review/approval. The investigative sites using institutional IRBs have to change sponsor language, and or/include specific institutional language into the informed consent template, which are then submitted to their respective institutional IRBs for review/approval. The sponsor also has to approve the informed consent template changes made by sites using institutional IRBs. The back and forth review process of the informed consent template between sites and sponsors can extensively delay site activation if the parties cannot agree in a timely manner.

Along with written consent, there must be provisions in the research plan for ongoing safety monitoring of the data, with the goal of ensuring the safety of subjects during the research. It's not sufficient, for example, to have all adverse event data reviewed only at the completion of a trial—data must be regularly reviewed throughout the study period in case problems arise as more is learned about the drug, device or procedure under investigation.

The IRB will also determine whether or not there are adequate provisions in the research to protect the privacy of the research subjects, as well as to maintain the confidentiality of the data, where appropriate.

Payments to study patients and advertising are considered by the FDA and IRBs as part of the consent process, as both might encourage a subject to enroll in a trial. If subjects are to be paid for their participation in the research, the IRB will review the planned compensation to ensure that it does not constitute an undue influence, or coercion, which could influence the

subject's decision to participate. Ideally, subjects would not take the risks involved in study participation simply because of compensation. The IRB's decision will be based not only on the amount subjects may receive for being in the study, but also on the setting in which the study will take place. An amount that may be coercive in one setting may not be in another.

The IRB will also review any proposed advertising to ensure it does not make misleading or untruthful claims and does not constitute undue influence. Glowing claims of success for a new treatment, for example, can also influence subjects to participate in a trial they might otherwise not want to be involved in. (See Chapter 16 for more on advertising.)

Vulnerable Subjects

Sometimes special, vulnerable populations are studied in research trials. Vulnerable subjects include children, pregnant women, prisoners, people with physical or mental disabilities, people with acute or severe mental illness and people who are economically or educationally disadvantaged. If any of these categories of people are going to be included in the research, the IRB needs to determine whether or not there are sufficient additional safeguards to protect them from coercion or undue influence. There are a number of NIH regulations (45 CFR 46) regarding research in various vulnerable populations. IRB members, investigators and others involved in these types of research, including CRAs, should familiarize themselves with this information.

State and Local Regulations

The IRB must determine that the research does not violate any existing state or local laws or regulations, or any applicable institutional policies or practices. Some states, for example, California and Massachusetts, have regulations that may exceed federal regulations. People working in these states, and others, should be familiar with their state requirements for conducting research.

As an example, California requires that an experimental subject bill of rights be provided to every study subject in a trial. For an example of a subject's bill of rights based on California's experimental subjects' bill of rights, see Table 1. Another example is a 2017 Pennsylvania Supreme Court decision that rules that physicians, not their delegates, should obtain consent for medical procedures. The ruling has more restriction than the current federal clinical research regulations, and mandates that clinical investigators in Pennsylvania should be obtaining informed consent themselves from research subjects until this decision goes through further court proceedings.

IRB Review of Proposed Research

An IRB considers each research project submitted for review separately. In order to determine if the research meets all the criteria discussed above, the

Table 1: Example of a California patient's Bill of Rights for study subjects

Any person who is requested to consent to participate as a subject in a research study involving a medical experiment, or who is requested to consent on behalf of another, has the right to:

- Be informed of the nature and purpose of the experiment.
- Be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be used.
- Be given a description of any attendant discomforts and risks reasonably to be expected from the experiment, if applicable.
- Be given an explanation of any benefits to the subject reasonably to be expected from the experiment, if applicable.
- Be given a disclosure of any appropriate alternative procedures, drugs or devices that might be advantageous to the subject, and their relative risks and benefits.
- Be informed of the avenues of medical treatment, if any, available to the subject after the experiment or if complications should arise.
- Be given an opportunity to ask any questions concerning the experiment or other procedures involved.
- Be instructed that consent to participate in the medical experiment maybe withdrawn at any time, and the subject may discontinue in the medical experiment without prejudice.
- Be given a copy of a signed and dated written informed consent form when one is required.
- Be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion or undue influence on the subject's decision.

IRB will review:

- Investigator qualifications
- Study protocol and supporting documents
- Proposed consent form
- Subject compensation, if applicable
- Advertising, if applicable

Materials Submitted to the IRB by an Investigator

To ensure an adequate review, the investigator submits a number of materials to the IRB for review, including the following:

- A current curriculum vitae (CV) that includes his or her qualifications

for conducting the research, including education, training and experience.

- The study protocol, which includes or addresses the following items, as applicable:
  - Title of the study
  - Purpose of the study, including any expected benefits
  - Sponsor of the study
  - Results from previous related research
  - Subject inclusion/exclusion criteria
  - Study design, including a discussion of the appropriateness of the research methods
  - Description and schedule of the procedures to be performed
  - Provisions for managing adverse events
  - Payment to subjects for their participation
  - Compensation for injuries to research subjects
  - Provisions for protecting subject privacy
  - Extra costs to subjects for participation in the study, if applicable
  - Extra costs to third-party payers because of a subject's participation, if applicable.
- The investigator brochure or package insert, if applicable.
- The proposed informed consent document, containing all appropriate elements.
- All subject advertisements and recruitment procedures. In general, advertising includes anything that is directed toward potential research subjects and is designed for recruitment.
- Statement of Investigator (Form 1572), if applicable. This form is required for all FDA-regulated studies conducted under an IND. (Some IRBs do not require this, but many do.)
- Grant application for federally-funded research, if applicable.
- Any other specific forms or materials required by the IRB, such as an application form.

IRB Deliberations

After documents are received from an investigator, an IRB will schedule the protocol review. For the initial review of a protocol, the committee will meet

to decide whether or not to approve the proposed research. In order to make this decision, the group will review all the submitted materials and discuss the proposed research, followed by a vote. The IRB may approve the project or request changes or additional information in order to approve it or disapprove it. Please note that an investigator can sit on an IRB, but he or she cannot participate in the discussion leading to the vote or the voting for his or her own research, as this would constitute a conflict of interest. The IRB will usually provide documentation of the investigator's abstinence from voting on the study in which he or she is participating; this is usually documented in IRB meeting minutes, the IRB membership roster for the committee that reviewed the trial, the IRB approval letter or separate IRB documentation. This does not solely involve investigators. Site research pharmacists, study coordinators, i.e. any investigative research staff that sit on the IRB, must abstain from voting on the study in which he or she may be involved. It is not only the responsibility of the CRA to ask the critical question when conducting the site evaluation visit, it is just as much the responsibility of the investigational site staff to disclose which site members sit on the IRB, during the initial study discussions/site evaluation visits. CRAs are also obligated to collect a copy of the documentation verifying that the investigator and/or staff in question did abstain from voting on the study, for the internal study file.

The IRB must notify the investigator in writing that the study is approved. If a study is rejected, the IRB will also notify the investigator in writing of its action and must allow the investigator to address the IRB concerning the decision either in writing or in person.

Any planned advertising must be approved before use, although this does not have to be approved before the study begins. Advertising is often started after study initiation, especially when subject recruitment has not been as rapid as anticipated.

Most importantly, IRB approval of the study and the consent form must be obtained prior to patient enrollment.

As detailed throughout this book, CRAs must be diligent and proactive in the conduct of their job responsibilities and with the many tasks that require collaboration with sites to complete. I once had a CRA friend who was assigned to a site with an overworked but well-meaning study coordinator. The site was close to activation. All that was pending was the IRB approval letter, which the study coordinator had not gotten around to requesting. The CRA did not want to miss the (Site Initiation Visit) SIV schedule deadline and took it upon herself to contact the IRB and request the letter. She obtained the approval letter almost immediately and sent it to the harried SC, who appreciated the gesture and the thoughtfulness of the CRA.

Investigator Reporting Responsibilities

Throughout the study, the investigator must report any protocol changes or amendments to the IRB. Any change that would increase risk to subjects must be approved by the IRB prior to implementation. The only exception

to this is when the change is necessary to eliminate an apparent immediate hazard to the safety and well-being of the subjects, in which case it should be implemented immediately, followed by a timely notification and submission to the IRB. For example, if it is determined during a trial that taking a particular concomitant medication is unsafe, investigative sites would be notified by the sponsor to immediately stop giving that particular medication to study patients. Sites would do this immediately, then notify their IRBs. These exceptions are quite rare.

The investigator must also promptly report "immediately reportable" adverse events to the IRB. These usually include deaths and other serious adverse events that are unexpected during the study. Occasionally deaths may be the expected outcome in a study; in this case, the reporting rules may change, and deaths will not be reported as immediately reportable adverse events. This exception is also quite rare. (Adverse event reporting is discussed in detail in Chapter 15.)

The investigator must promptly report any unanticipated problems that arise during the research that involve risk to the study subjects or others to the IRB.

The investigator is required to submit periodic reports to the IRB detailing the progress of the study. This will be submitted at least annually and may be required on a more frequent basis.

Continuing Review of a Research Study

The IRB will review each research project at least annually, although the IRB may require updates on a more frequent basis, such as quarterly, based on the degree of risk to which subjects are exposed. At the continuing review, the IRB will ensure that the risk/benefit relationship remains acceptable, that the consent and study documents being used are still appropriate and that the selection of subjects has been equitable.

To help make these determinations, most IRBs will require the investigator to submit an IRB-specific form about the progress of the study, including enrollment figures, withdrawals, adverse events and unanticipated problems, protocol violations, etc., at each review period. The IRB will also want to see a copy of the consent form currently in use, advertising and any other appropriate documents. The IRB will ask for any protocol amendments that were made during the time period, especially if they were not previously reviewed by the IRB. This information allows the IRB to determine whether or not the research can continue.

All research must be re-approved at least annually. The investigator will receive written notification of each formal re-approval. Re-review and re-approval continue throughout the entire research project, until such time as all subjects have completed their participation and the project is closed.

If an investigator is not submitting the required study updates to the IRB for review, the IRB has several options. The IRB may send the investigator a reminder that he or she is required to submit the update, with a deadline for

receipt of the requested materials. If the reminder does not work, the IRB may put enrollment on hold until the updates are received and reviewed. In the worst case scenario, the IRB may withdraw approval of the study. It is important to remember that each approval is good only for a specified time period. If re-approval is not received prior to the expiration date of the previous approval, the study is out of compliance with the regulations.

Expedited Review

Upon occasion, an IRB may utilize an expedited review process for minor changes in previously approved research; this may be done only during the time period for which the approval was authorized. Expedited review may be done by the IRB chairperson or by experienced members who are designated as expedited reviewers. Items may be approved by expedited review, but they cannot be rejected. If the expedited reviewer(s) thinks something should be rejected, it must go to the full board for review. The board also must be made aware of all expedited review decisions, which is usually done at the first regular meeting following the review.

Expedited review is never used in circumstances in which the risk to human subjects increases. It cannot, in general, be used for the initial review of a research study. There are a few exceptions by which initial review of a project can be done using expedited review, but these are not the kinds of studies in which CRAs would normally be involved; these exceptions are published in the Federal Register. If you are interested in reading more about this, there is an FDA guidance document called Categories of Research That May Be Reviewed by the Institutional Review Board (IRB) Through an Expedited Review Procedure.

IRB Membership

An IRB must have at least five members; a quorum. IRB membership should be selected to assure appropriate diversity, including representation by multiple professions, multiple ethnic backgrounds and both genders, and must include both scientific and non-scientific members. The members must possess the appropriate professional competence to review the diverse types of protocols received. Most IRBs also have alternate members to ensure a quorum if a regular member is unable to be present.

There must be at least one member who is not affiliated with the institution (and who has no immediate family member affiliated with the institution) other than his or her IRB membership. There must also be one member whose interests and background are non-scientific (lay person). It is acceptable for one IRB member to fulfill both of these criteria. In addition, an IRB that reviews FDA-regulated products (drugs, biologics and devices) should have at least one member who is a physician.

IRB Operations

IRBs are required by regulation to follow written procedures. IRBs are audited by regulatory authorities, and they will be held responsible for having the appropriate written procedures and for following them. They must also carefully document their decisions and retain this documentation appropriately.

Conflict of Interest

No IRB member may participate in the initial or continuing review of any project in which he or she has a conflicting interest in the research. A person whose research is being reviewed may be present at the IRB meeting to answer questions and provide information about the project, but he or she should not be present for the discussion leading to the vote, or during actual voting. The minutes of the meeting or IRB documentation need to reflect that the person was not present to alleviate any claim of conflict of interest.

IRB Registration

In 2009, the FDA began requiring the registration of IRBs that review FDA-regulated studies. Registration gives the FDA more complete information about the IRBs that review these studies and will:

- Facilitate sharing educational and other information with the IRBs
- Assist the FDA in scheduling and conducting IRB inspections
- Help the FDA prioritize IRB inspections.

Once registered, IRBs are required to review and submit current information every three years, although some information, such as a change in the IRB chairperson, is required to be submitted within a certain amount of time after the change occurs.

IRB registration is not accreditation or certification by the FDA, nor does it address issues of the IRB's competence, expertise or ability to conduct reviews.

FDA Guidance Documents for IRBs

There are a number of FDA guidance documents that discuss topics relevant to IRBs. Some of the more useful ones include:

- FDA Institutional Review Board Inspections—April 2018
- IRB Information Sheets—Research and Review (Updated 9/98) – Cooperative Research

- Non-local IRB Review
- Significant Risk and Nonsignificant Risk Medical Device Studies-2006
- Sponsor - Investigator - IRB Interrelationship

Scientific Review Committee

Some medical and academic institutions have an additional scientific panel or committee required to review and approve a potential study, in addition to IRB review, known as a "scientific review committee." This is usually to confirm study science or medical merit, or design, and represents an additional layer of institutional oversight of potential studies. Therapeutic indications that usually require additional scientific review include oncology studies, pediatric studies and radiology studies. These are just basic examples and are not all inclusive. Institutional requirements for scientific review committees vary.

Scientific review is usually completed in conjunction with IRB review. However, some institutions require scientific review committee approval of a study before it can be submitted to the IRB. This can add additional time to the submission and approval process for the study and needs to be considered when evaluating sites for studies.

Data Safety Monitoring Boards (DSMBs)

A Data Safety Monitoring Board (DSMB), sometimes known as a Data Safety Monitoring Committee (DSMC) or Data Monitoring Committee (DMC), is a group of expert advisors, usually appointed by a sponsor, to periodically review the accumulating data from a clinical trial, primarily to assess the continuing safety of trial subjects. The purpose of this committee is to advise the sponsor, after review of the data to date, whether or not the trial should continue in its present form, be modified or perhaps even be discontinued.

DSMBs were used in some clinical trials as early as the 1960s, mainly in large, randomized multi-center trials sponsored by the NIH and the Department of Veterans Affairs (VA), in which mortality and morbidity were the primary outcome measures. The establishment of these committees was based not only on the premise that monitoring of the accumulating study data is essential to ensure the ongoing safety of trial subjects, but also on the premise that sponsor representatives closely involved in the design and conduct of a trial might not be fully objective in reviewing the interim data for any emerging concerns.

FDA regulations do not require the use of DSMBs in trials except under 21 CFR 50.24(a)(7)(iv) for research studies in emergency settings in which the informed consent requirement is excepted.

A DSMB consists of people who are external to the trial organizers, spon-

sors and investigators, in order to minimize bias. They must have the appropriate expertise to evaluate the data, and members usually include one or more medical people, a statistician and others, as appropriate. They may meet on a regular schedule based on time, such as every six months, or they may meet based on enrollment, e.g., after every increment of 50 enrolled subjects, or on some other "trigger" appropriate for the trial. The DSMB will receive the data from the study up to the cut-off date for that review.

During its review, it will look at the data, have the DSMB statistician run some appropriate programs for looking at aggregate data, discuss the findings and inform the sponsor of its recommendation. This review usually results in one of three possible recommendations: Continue the trial as is, continue with modifications (or more frequent DSMB review) or stop the trial because of safety concerns. Although the DSMB recommendation is not binding, sponsors take these recommendations very seriously and usually abide by them.

All clinical trials require safety monitoring, but not all trials require monitoring by a DSMB. DSMBs have usually been used for large, randomized, multi-center studies that evaluate treatments intended to prolong life or reduce risk of a major adverse health outcome, such as cancer or cardiovascular events. They are recommended in controlled trials in which mortality or major morbidity is the outcome measured, or in trials that have a high risk of severe outcomes. They are not usually needed for trials looking at less serious outcomes or for early-stage trials.

Adding a DSMB to a trial adds cost and resources, as well as additional administrative complexity, so the FDA does not recommend using a DSMB unless the trial meets particular criteria related to safety, practicality and scientific validity. The FDA has a guidance document, Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees, which provides additional information and the FDA's current thinking on the use of DSMBs, as well as practical information relating to the establishment and function of such groups.

A CRA usually will not have any reason to interact with a DSMB. However, there can be situations in which an upcoming DSMB review will necessitate the rapid collection and cleaning of data from study sites. In this case, the CRA may be expected to retrieve data for the subjects included in the DSMB review without regard to the normal monitoring schedule. The CRA may need to spend significant time on the phone with study coordinators, or may have to make additional monitoring visits, to ensure that the necessary information is available for the DSMB.

Applicable early phase studies will use a safety committee to review available safety and dosing data to determine if dose escalation is safe, or if the current dose needs extra evaluation with additional subjects, or if a stop is required due to dose-limiting toxicities. This can also help determine a recommended phase II dose.

Some studies may involve committees to assure appropriate study oversight as well as committees for the adjudication of specific medical events.

Key Takeaways

IRBs

- IRBs are one of the primary safeguards for the protection of human subjects in research.
- CFR Part 56 contains the regulations that pertain to IRBs.
- An IRB must approve a study and the informed consent document before the study can begin.
- There are two types of IRBs: those that are affiliated with an institution and those that are independent, i.e., not affiliated with an institution.
- The IRB must make a risk/benefit assessment for each proposed project.
- There are special regulations concerning research in vulnerable subjects (children, pregnant women, prisoners, etc.)
- State and local research regulations must be followed.
- IRBs must approve advertising and subject compensation.
- An investigator must report adverse events and study progress to the IRB at least annually.
- Continuing review of a study must be done at least annually.
- Expedited review may not be used for the initial review of a project, except in particular instances published in the Federal Register.
- IRB members may not vote if they have a conflict of interest.
- IRBs reviewing FDA-regulated research must register with the FDA.

DSMBs

- DSMBs are appointed by the sponsor to review study safety on a periodic basis.
- DSMBs are used primarily for clinical trials in which high morbidity or mortality is anticipated.
- FDA regulations do not require the use of a DSMB except for research studies in emergency settings in which informed consent is accepted.
- After review, a DSMB makes a recommendation to the sponsor concerning whether the study should continue as it is, continue with modifications or be discontinued.

CHAPTER NINE

Informed Consent

One of the main safeguards for the protection of human subjects in research is informed consent. This chapter discusses informed consent, including governing regulations, how a consent form is written, CRA review and administration and the emergence of electronic informed consent.

The decision whether or not to participate in a study is not an easy one. There is the hope of help and the desire to please the physician investigator, as well as apprehension and fear of the unknown. To help a potential subject make a decision that is not based purely on emotions such as fear and hope, everything possible must be done to provide complete information in a format that is accessible and easy to read, along with sufficient time to make an informed decision.

Informed Consent is defined by the ICH E6(R2) - Guidelines for Good Clinical Practice as:

> *"A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form."*

The two key words in this definition are "voluntarily" and "informed." These words form the cornerstone of ethical conduct in clinical research and are in place to protect the rights and safety of the subjects who participate in research. Potential subjects of clinical research must understand what they are getting into and must be free to decline to participate. The freedom to say "no" with a clear conscience and no fear of repercussion is an aspect of the consent process that must be considered. Many people have a certain reverence for their personal physicians; they want to please their physicians and

will do as they direct. This carries over into the informed consent process and needs to be understood by physicians involved in research. CRAs should advise investigators to be conscious of this phenomenon. Investigators must make every effort to help potential study subjects understand that it is entirely acceptable if they choose not to participate. It is also important for subjects to understand that during a trial, as per ICH E6(R2) 4.8.10(m), "the subject's participation in the trial is voluntary and the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled."

Monitoring Informed Consent

Informed consent should be one of the primary areas of concentration during a CRA's monitoring visits, both because it is so important ethically and because it is a frequent deficiency found during clinical investigator inspections conducted by the FDA. The problem is not that the consent process is not being done, but that it is not being done correctly. Common problems are:

- The timing of the administration of consent may not be correct, meaning that the consent is not always obtained before any study-related procedures take place.
- Proper signatures are not always obtained.
- The consent form is poorly written.
- There are missing required elements.
- The amended informed consent is not signed
- Re-consenting of study subjects with an amended informed consent does not occur in a timely manner.
- Inappropriate staff (not medically trained or qualified) are conducting the informed consent process/obtaining informed consent.

The first step in monitoring informed consent is to be familiar with the requirements, both for the document itself and the process. There are three basic requirements that a consent form must meet:

- It must completely and accurately describe all of the activities required by the protocol and what the subject's participation will involve.
- It must be able to be read and understood by the study subjects.
- It must contain all the elements required by regulation (21 CFR Part 50, see Appendix G).

In other words, consents must inform, be comprehensible and comply with regulations. Here is a closer look at each of these requirements.

Activities and Participation

Potential study subjects need to be told about the study and their involvement in detail to be able to make an informed decision regarding their participation. Subjects need to know they will be participating in research, what is required of them, their rights as research subjects, and the potential benefits and risks they will face. The required elements of consent will be discussed later in this chapter. All the requirements (tests, procedures, activities, etc.) of the protocol must be described, including how these various activities will have an impact on the subjects, both in terms of personal discomfort and any lifestyle changes. Subjects also need to know when each activity must be done and how long it will take for each activity and study visit.

Readability and Comprehension

It is difficult to adequately inform potential subjects about a study without overwhelming them. A consent form may contain a very detailed description of protocol activities and consequences, but if it is a long, multiple-page document, a subject may not have a good feel for what will happen because the document is simply too long and presents too much information to comprehend. Writing a consent that properly informs without overwhelming is mostly the result of common sense and experience. It is important to keep this balance in mind if you are writing or reviewing a consent form.

Writing a comprehensible consent is as difficult as making it informative without being overwhelming. The consent form needs to be technically correct, yet intelligible for non-medical people. Consent forms should be written at approximately the fifth- to eighth-grade levels. This is a challenge in an industry filled with jargon, acronyms, medical terminology and highly educated people.

In general, the shorter the sentences and the fewer syllables per word there are in the text, the easier it will be to understand. Make a conscious effort to use terminology such as “teaspoons” instead of “cubic centimeters” and “milliliters” or “high blood pressure” instead of “hypertension.” There is no substitute for experience; after you have written a few consent forms, it becomes easier. There are formulas that will give you a good estimate of the grade level of your document. For example, Microsoft Word includes the Flesch-Kincaid Grade Level tester, which pops up after spelling and grammar checks have been done on a document.

Elements

The last of the three requirements for a proper consent form is to make it compliant with federal regulations. 21 CFR part 50.25, which contains the elements of informed consent, is one of the more straightforward regulations. It clearly lists the elements that must be present in a consent form (basic elements) and those that are optional (additional elements).

Basic Elements of Consent

The basic and additional elements of consent, taken from the federal regulations, (revised as of April 1, 2017, as per the FDA website) must be present in all consent forms. They are:

(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed and identification of any procedures which are experimental.

(2) A description of any reasonably foreseeable risks or discomforts to the subject.

(3) A description of any benefits to the subject or to others which may reasonably be expected from the research.

(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.

(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and Drug Administration may inspect the records.

(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.

(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.

(8) A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

Additional Elements of Consent

The additional elements of consent, which should be included, as appropriate, are:

(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable.

(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.

(3) Any additional costs to the subject that may result from participation in the research.

(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.

(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.

(6) The approximate number of subjects involved in the study.

Since ICH guidelines mandate the inclusion of these additional elements, they usually appear in most informed consent forms, if appropriate.

One way to ensure that all elements are present in a consent form is to have an explicit heading for sub-sections that address each element. In any case, it must be clear that each of the elements is addressed in the form so subjects are properly informed and that the form will not be found deficient in a regulatory review.

Some states and institutions also have requirements that may have an impact on the content form. California, for example, requires that an Experimental Research Subject's Bill of Rights be attached to all consent forms.

In addition, the final Health Insurance Portability and Accountability Act (HIPAA) rule was published on Aug. 14, 2002, which allows the authorization form for all uses and disclosures of a patient's protected health information to be combined with the informed consent form. This authorization form can also be signed separately. The choice is up to the individual investigative site.

Tips for Effective Informed Consent Form (ICF) Review During Monitoring Visits:

- Review the IRB approval letter to determine that the correct or latest version of the ICF was signed by the subject and or guardian.
- There may be more than one signed ICF per subject depending upon whether the ICF was revised—confirm this.
- Know the IRB-approved current ICF version date, if there is more than one version that requires signature for all Consents/Assents/PK/Tissue Sampling/Pharmacogenetics/Partner Consents.
- Confirm that all sequential pages of the ICF are present and there are none missing.
- Confirm that all pages have been initialed and dated by the subject and/or guardian as required.
- Determine if the HIPAA is a separate document or incorporated into ICF.

- Confirm that the HIPAA has been signed and/or checked "yes" by the subject and or guardian to allow for records review.
- Does this study involve pediatrics? If the answer is yes, assess for pediatric assents in addition to parent/guardian consent.
- Check to ensure that the individual obtaining consent has the authority and has been appropriately delegated this responsibility per the delegation of authority log.
- Cross-check staff signatures on the delegation of authority log with the informed consent form to ensure accuracy and legitimacy.
- Ensure that the subject and/or guardian signed and dated the ICF prior to research procedures.
- Confirm that the subject printed his or her own name and date on the ICF in addition to signing own his or her own name. (Check delegation log and compare signatures of staff.)
- Confirm that the person obtaining consent signed and dated the document on the same day as the subject.
- Confirm that the Witness and/or Legal Guardian signature line was completed appropriately.
- Ensure that the amendments/revisions to the ICF contain appropriate safety or amendment updates per Investigator Brochure changes or protocol amendment release.
- Ensure that the chronological order of the ICF pages is verified.
- Ensure that the subject initialed each page, if applicable.
- Confirm that the PI's address and contact information is in the ICF, including an emergency or after-hours phone number.
- Confirm that the ICF process is documented in the subject's source, and includes such important points as: confirmation that the informed consent was obtained prior to study procedures, that the subject was given appropriate time to review the consent and ask questions, that the investigator was available for questions, the ICF date, time and version, and that the subject was given a signed copy.
- Confirm that the investigator also obtained and/or signed the informed consent as appropriate per institutional or IRB signature requirements.
- If re-consenting of the subjects was required, ensure that the subject's re-consenting was conducted appropriately, and that this was updated in the subject's source.

Obtaining Informed Consent

Informed consent must be obtained from subjects at the proper time and in the proper manner. The first thing to remember is that no person may be involved as a research subject unless the person, or the person's legally acceptable representative (LAR), has given consent. According to ICH E6(R2), an LAR is an individual, juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial. Secondly, a subject's consent must be obtained before the subject is involved in any study-related activity. A CRA should always check a consent and when it was signed during the study enrollment period. The time of consent versus when the subject started the study is almost always checked during FDA inspections of investigative sites.

There are two types of consent forms: short form and long form. Both must be approved by an IRB before use.

The Short Form Consent

The short form consent may be used in circumstances when, in the best judgment of the investigator, it would be the most appropriate way for the subject to comprehend and give informed consent. This form supplements and documents an oral presentation of the information provided to the study subject as part of the consent process. If this method is used:

- The form must state that all elements of consent required by regulation have been presented orally to the subject or subject's legally-appointed representative.
- There must be a witness to the oral presentation.
- The IRB must approve a written summary of what is to be said to the subject or his or her representative.
- Only the short form itself is to be signed by the subject or his or her representative.
- The witness will sign both the short form and a copy of the written summary.
- The person obtaining the consent will sign a written copy of the summary.
- A copy of the short form and the summary will be given to the subject or his or her representative.

The Long Form Consent

This is the standard consent form and process, and is the consent method of choice whenever possible. The main difference between the two forms is that the long form spells out in writing everything that is presented orally when the short form is used. Consequently, no summary is needed. The subject signs and dates two copies, one to keep and one for the investigator.

The importance of consent form signature and completion

After years of reviewing informed consent forms at different investigational sites, you become familiar with different IRB signature requirements for obtaining informed consent. Some IRBs allow a person different from the investigator to perform the consent discussion, obtain consent from subjects and sign the consent form, as long as they are appropriately trained and experienced. This is evidenced by the signature line "signature of individual obtaining consent" or "signature of researcher" on the consent form. Other IRBs require the investigator to sign the consent form, either as the "investigator obtaining consent" or in addition to the individual obtaining consent as "signature of the investigator."

Several years ago, I was monitoring a skin infection study at an investigational site. They were a high-enrolling medical practice and had enrolled 15 patients in the study. It was my first monitoring visit to the site and I was reviewing all the current and new subject informed consent forms for accuracy and completeness.

The IRB managing the study had very specific informed consent signature requirements; the investigator and the individual conducting the informed consent discussion were both required to sign the consent. The study coordinator was new to research and had obtained and signed consent for all of the study patients. I was concerned that her inexperience would affect her ability to effectively obtain consent from a study patient.

In reviewing each consent form, I noticed that the study coordinator had signed each consent form correctly on the "signature of individual obtaining consent" line. However, the investigator had not signed one consent form; the signature line on the last page of each consent form was blank where "investigator signature" was required. Some of these study subjects had been consented three-to-four months ago. I informed the investigator of this oversight, advised the investigator to retrain the study coordinator and advised that the investigator inform the IRB of these deviations immediately so the IRB could advise on their specific corrective action. It served as a crucial reminder of the importance of delegating an appropriately trained and experienced individual the task of obtaining consent for study patients.

— Elizabeth

The Consent Process

As a CRA, you will not be involved in the actual consent process. However, since it is a CRA's responsibility to ensure that investigative sites conduct their studies in accordance with GCPs, the CRA should be able to advise investigators and their staff on consent activities.

It is a best practice for investigational sites to have an informed consent

standard operating procedure, guideline or documented process to ensure consistency and accuracy of staff conducting/signing/documenting the informed consent process.

It is also recommended that investigators directly participate in training staff on appropriate conduct of the informed consent process and/or obtaining informed consent, to demonstrate investigator oversight of staff training and procedures that involve patient safety. Best training practices include:

- Have staff observe the investigator conducting several different informed consent discussions on several different types of patients (adults, children) to have a fully dimensional exposure to the informed consent process.
- Have the investigator observe the conduct of several informed consent discussions with subjects, by the site staff member being trained, to ensure the appropriate process and information provision.
- Have the staff member review several informed consent forms completed by other staff members to ensure proper signatures, dates and content to ensure that all safety information and informed consent elements are present.

Here are some suggestions that can be discussed with investigators and study coordinators regarding the informed consent process; these may be particularly helpful for those at the site who are inexperienced with the consent process:

- Provide the subject with a quiet place to review the consent form; ensure they spend an appropriate amount on this review.
- Ensure the subject is given the opportunity to take the ICF home, if desired, to review with his or her personal physician, family or whomever they desire to assist them in making an informed decision.
- Ensure that an appropriately trained, experienced and delegated member of the investigational staff or an investigator reads the consent form while the subject follows along. This usually improves comprehension and is helpful for subjects who may not read well.
- Have the presenter summarize what was read, emphasizing the important points of the consent and the procedures the subject will need to perform.
- Always ask the subject if there are any questions. Answer them completely and truthfully.
- Ensure that the investigator is on site during the consent process to provide oversight and answer questions.
- Never try to convince a subject to participate.
- Ask the subject some questions about the consent material to deter-

mine how well the subject understood what was presented. This will often generate additional questions from the subject.

- A video presentation of the consent form can be an effective tool. If the investigative site has someone who is a particularly good presenter, this person could describe the study in the video. In addition to ensuring that all subjects hear the same thing, the video documents what was said. Videos, however, should never be used in lieu of the involvement of the investigator, who should always be present to talk with subjects and to answer questions.
- The consent process should not be rushed. Subjects must be given ample time to assess, evaluate and discuss the information they have been given before having to make a decision. Some investigational sites take over an hour to conduct an entire informed consent process.
- A subject may want to take the form home to discuss with family members before making a decision and should be encouraged to do so.
- The investigator or investigational site staff member obtaining consent, should document the informed consent process, in a progress note or similar format, detailing that consent was given, no study-related procedures were done prior to signing the informed consent and a copy of the informed consent document, both signed and dated, was given to the subject.

I was once monitoring ICFs with a colleague at a large academic health center that had a main site and a number of network satellite sites. The main site and network satellite sites had different informed consent forms. The investigator's brochure had just been revised to reflect updated study drug safety information and the informed consent forms for the main and satellite sites were likewise updated with the applicable safety language. My colleague and I were reviewing the ICFs of reconsented subjects, when she noticed a difference in the content of the main site ICF vs. the network site ICFs. She had previously worked as a study coordinator and was trained to automatically review ICF content as well as signature requirements (in her review of the ICFs during monitoring visits). The ICF version for the satellite sites was missing a paragraph from the updated safety information, that was present in the main site consent. It had inadvertently been omitted, and a number of subjects at the satellite sites had been reconsented with the incorrect ICF version. Thanks to my colleague's "eagle eye" we were able to help the site correct a major protocol violation and speaks volumes of the critical need for CRAs to be aware of ICF content, and not just signature requirements, of the sites they monitor.

— Elizabeth

Exceptions to Consent

Exceptions to consent may be made, in two situations, for patients using investigational products. The first situation is for research involving the single emergency use of a test article in a single individual, as provided for in 21 CFR 50.23. The second involves entire studies in which, because of the expected circumstances, it is not generally feasible to obtain consent before patients must be treated (21 CFR 50.24). Both of these situations are discussed below.

Individual Exceptions

Occasionally, a circumstance will arise in which an investigator feels there is a subject who would benefit from the use of an investigational product, but who is not in a study or who would not qualify for the study. For example, there may be a patient who is near death from a severe infection and all suitable marketed antibiotics have been tried, but the infective bacteria are resistant to all of these drugs. The patient does not qualify for any ongoing study. Under this exemption, this patient may be treated with one of the new, powerful antibiotics that might cure his infection. Although a physician may treat a patient with an investigational product in a case like this, he must follow the regulations discussed.

According to the regulations, obtaining informed consent is feasible unless, before the use of the investigational product, both the investigator and a physician who is not otherwise participating in the clinical investigation certify, in writing, all of the following:

- The human subject is confronted by a life-threatening situation necessitating the use of the test article.
- Informed consent cannot be obtained from the subject because of an inability to communicate with, or obtain legally effective consent from, the subject.
- Time is not sufficient to obtain consent from the subject's legal representative.
- There is no alternative method available of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject.

The exception is if immediate use of the test article is, in the investigator's opinion, required to preserve the life of the subject, and time is not sufficient to obtain the independent determination in advance of using the test article. In this case, the determination of the clinical investigator shall be made and, within five working days after use of the article, be reviewed and evaluated in writing by a physician who is not participating in the clinical investigation.

The documentation required must be submitted to the investigator's IRB within five working days after the use of the test article. If the investigator

wants to be able to use the product for this type of patient more than just the one time, the necessary documentation must be submitted to the IRB and approved, as for any study.

Exception to Informed Consent Requirements for Emergency Research Studies

In some types of studies, obtaining informed consent from study subjects prior to their participation may not be possible. Examples of these studies are those in which the subject is in a life-threatening trauma situation, such as a head injury or heart attack. Not only are the subjects in these studies not able to give consent prior to being treated, but there may not be time to identify and locate a subject's legally authorized representative before treatment must begin. Frequently, these studies have a relatively short window of opportunity for treatment; e.g., treatment must commence within two hours of the injury.

Exceptions or waivers from consent must be approved in advance of the study by the IRB. It is not the investigator or the sponsor who makes the determination of whether or not the exception is allowed. It must be approved by an IRB, with the concurrence of a licensed physician (who may or may not be a member of the IRB) who is not associated with the research project. In order for the IRB to make this determination, the following must be documented:

- The subject is in a life-threatening situation, available treatments are unproven or unsatisfactory and the collection of valid scientific evidence is necessary to determine the safety and effectiveness of the particular intervention.
- Obtaining informed consent is not feasible because:
    - The subject will not be able to give consent because of his or her medical condition.
    - The intervention under investigation must be administered before consent can be obtained from the subject's LAR.
    - There is no way to identify the individuals likely to become eligible for participation in the study.
- Participation in the research may have a direct benefit to the subject because:
    - The subject is in a life-threatening situation that necessitates intervention.
    - Previous research, both preclinical and/or clinical, provides supporting evidence of the potential for the intervention to provide a direct benefit to the subject.

    - Risks associated with the intervention are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy and what is known, if anything, about the risks and benefits of the experimental treatment or intervention.
- The clinical investigation could not practically be carried out without the waiver.
- The protocol defines the length of the therapeutic window based on scientific evidence, and the investigator commits to attempt to contact the subject's LAR or family member within that window of opportunity and ask for consent, if feasible, rather than proceeding without consent. The investigator will summarize efforts to contact legal representatives and provide this information to the IRB.
- The IRB has approved the consent form and the process to be used when informing the subject, when possible, or the subject's LAR or a family member.
- Additional protection of the rights and welfare of subjects will be provided to include:
    - Consultation with the community in which the study will be conducted and the subjects selected.
    - Public disclosure (in the community in which the study is to be conducted) prior to initiation of the study of plans for the study and the risks and benefits associated with it.
    - Public disclosure following completion of the study of sufficient information to appraise researchers and the community of the study, including demographics of the study population and its results.
    - Establishment of an independent data monitoring committee to exercise oversight of the investigation.

The IRB also has a responsibility to see that the study subject is informed about the nature of the study and his or her involvement in it in as timely a fashion as possible. If the subject remains incapacitated, then the LAR or, if not available, a family member must be updated. The LAR (or family member) should also be told that he or she may request that the subject be removed from the study at any time without penalty or loss of benefit.

Electronic Informed Consent

The integration of the internet and the technology-driven research process has impacted all aspects of clinical research, including the process of in-

formed consent. Researchers now have additional means to communicate study requirements, informed consent content and obtain informed consent from study subjects, via audio and video delivery systems, remote conduct of informed consent discussions, and utilization of electronic informed consent platforms, computer systems, tablets and devices for this purpose. On December 15, 2016, OHRP and the FDA finalized a guidance on electronic methods of informed consent entitled "Use of Electronic Informed Consent, Questions and Answers, Guidance for Institutional Review Boards, Investigators and Sponsors."

The guidance is a recommendation in a question/answer format, about the use of electronic informed consent and the impact on the regulated informed consent process. This clarifies the FDA-accepted process and measures for electronic informed consent.

As per the guidance document, page 1, section 1, introduction:

This guidance provides recommendations on the use of electronic systems and processes that may employ multiple electronic media to obtain informed consent for both HHS-regulated human sub¬ject research and FDA-regulated clinical investigations of medical products, including human drug and biological products, medical devices and combinations thereof. According to the guidance, "electronic informed consent" refers to:

The use of electronic systems and processes that may employ multiple electronic media, including text, graphics, audio, video, podcasts, passive and interactive websites, biological recognition devices and card readers, to convey information related to the study and to obtain and document informed consent.

The guidance also provides recommendations on procedures that may be followed when using an electronic method to help:

- *Ensure protection of the rights, safety and welfare of human subjects*
- *Facilitate the subject's comprehension of the information presented during the eIC process*
- *Ensure that appropriate documentation of consent is obtained when electronic systems and processes that may employ multiple electronic media are used to obtain informed consent*
- *Ensure the quality and integrity of eIC data included in FDA applications and made available to the FDA during inspections.*

The FDA guidance also covers the important dynamic of addressing the study subject's questions when utilizing electronic or remote informed consent. Whether the electronic informed consent is obtained from the subject on-site or remotely, the process must allow subjects the opportunity to consider whether or not to participate and to ask questions about the study before signing consent as well as at any time during the subject's involvement in

the research. This may be accomplished by in-person discussions with study personnel or through a combination of electronic messaging, telephone calls, video conferencing or a live chat with a remotely located investigator or study personnel. When live chat or video conferencing is used during the process, investigators and study personnel should remind subjects to conduct the discussion in a private location to help ensure privacy and confidentiality.

Whether following the traditional informed consent process (paper informed consent document and face-to-face discussion with the study patient), incorporating elements of, or a completely electronic/digital informed consent process, the rules are constant and relevant; the subject's safety and rights must be protected, the subject's right to privacy must be assured and the informed consent must be worded and communicated so that the subject can comprehend and make an informed decision about study participation.

Conclusion

A primary safeguard for the rights, safety and well-being of human subjects of research is informed consent. The informed consent process is a complex and important part of conducting clinical research. CRAs must have a working knowledge of consent forms and processes so that deficiencies can be recognized and corrected immediately. It is recommended that CRAs read the regulations governing informed consent (21 CFR part 50). A checklist for reviewing informed consent is found in Appendix C.

There is an updated FDA guidance document on informed consent: A Guide to Informed Consent - Information Sheet, July 12, 2018.

Key Takeaways

- Informed consent is a cornerstone of the ethical conduct of clinical research.
- Informed consent documents must be approved by the IRB before use.
- Informed consent must be obtained before a subject enters a study.
- Informed consent must be documented.
- CRAs must thoroughly assess consent forms to ensure they are correct, and that the signatures and dates provided are valid. The proper preparation of forms and conduct of the procedure is vital to truly informed consent.
- Informed consent usually is required for all subjects involved in a research project.
- There are exceptions to the consent process under certain circumstances.

- Electronic informed consent presents an alternative to the traditional face-to-face, paper informed consent process.

CHAPTER TEN

Preparing for a Study: Study Design and Statistical Issues

This chapter covers some of the primary activities that must be conducted before starting a study—determining the study design, writing the protocol and developing case report forms. Working with studies, protocols and case report forms are critical parts of a CRA's job, so the CRA must have a good understanding of each of them, even if he or she is not involved in determining study designs, writing protocols or developing case report forms. The chapter begins by discussing some aspects of design, followed by protocols and then case report forms, since this is the usual pattern of their development in a research program.

This chapter is designed to give you basic information. Much of the material that follows is in the form of an annotated outline that gives you the basic considerations for these documents.

Study Design

CRAs should have a basic understanding of the critical aspects of study design. In this section, we will look at some of the terminology that CRAs should be familiar with, as well as a few of the more common study designs. In general, the statistician, in consultation with the medical monitor for a study, will determine which design is appropriate to use. We will also discuss sample size, the controls used in studies and methods for minimizing bias.

Determining Sample Size

There are a number of factors that must be taken into account when determining how many subjects should be entered into a trial. The first of these is

the sample size. The sample size for a trial is usually computed by the statistician and is based on three variables:

1. The magnitude of the effect expected between the treatments;
2. The variability of the endpoints to be analyzed;
3. The desired probability of observing the effect with a defined significance. (This is known as the power of the test, and is commonly set at least at 80%.)

The magnitude of the effect is the difference between what you expect to see with your drug and the comparator (placebo or another drug). For example, if you expect your drug to work in 70% of the subjects and the drug you are using as a comparator to work in only 50% of the subjects, the magnitude of the effect (the effect size) is 20%. It is always a bit of a guess to determine the effect size, especially in phase II studies with a new compound. This is because you don't have much information about the effect size of your compound until a number of studies have been completed.

In advance of any studies, the effect size is determined by making educated guesses. The problem of approximating the effect size is like the chicken and the egg—you need to know something about the effect size to calculate a sample size, but you can't calculate the sample size without an effect size. Make a guess in the early phase II studies, and information gathered from these studies will help determine the effect size. This information is then used to calculate sample sizes for subsequent studies. As the development program progresses and more is known about the investigational drug, the effect size estimates become more accurate and sample sizes become easier to calculate. By the time phase III studies are done, the effect size estimates are reasonably accurate.

As the effect size increases, the necessary sample size decreases; that is, it takes fewer subjects to show a statistically significant difference between two treatments when the difference in the effect of the treatments is large.

As for effect size, the estimate of the variability is based primarily on educated guesses in phase I and early phase II studies, but becomes quite accurate by the time phase III studies are done. Variability is also a statistical parameter and will be determined by the statistician, based in part on information from past work and from the clinician involved in the trial.

Given the effect size and the variability, the statistician can construct power curves that will show the sample size needed. These help to ensure that enough subjects are entered into the study to show the treatment effect.

The sample size that results from these calculations tells how many subjects are needed at the end of the trial for valid analyses. However, it is rare for participants to see a trial through to completion; subjects drop out along the way for many reasons. Consequently, you must start with more subjects than you need to compensate for those subjects who do not complete the study. If it is expected that 25% of the subjects will drop out along the way, then at least 25% more subjects than your sample size calculation must be

entered. For example, if the sample size was calculated to be 300 subjects per treatment group, it would need to be increased by at least 75 (25%) for a total of 375 subjects per group.

Most of the time a large sample size is better than a small sample size, but both cost control and time become harder to manage as the sample size increases.

Placebo Response versus Placebo Effect

It would be nice to be able to assume that the subjects receiving a placebo treatment during a trial would have no treatment effect at all, but this is far from true. People respond to treatment with placebo, sometimes quite dramatically. For example, in trials for depression or anxiety, it is commonplace to see placebo response rates of 25% to 40%.

Remember that in clinical trials, subjects get a great deal of care, including frequent visits, lots of medical tests and attention from both the investigator and the study coordinator—all this extra attention could be enough to make them feel better, even if they are being treated only with a placebo.

There have also been numerous studies that show an actual disease state can respond measurably to placebo, including, among others, the lowering of blood pressure,[1] alleviation of post-operative pain[2] and relief of psychiatric conditions such as anxiety, depression, agoraphobia and schizophrenia.[3] Pundits have gone so far as to suggest that placebo might be the next wonder drug. There has been much written about placebo response, but it is outside the scope of this book, so we will not discuss it further. However, you must be aware that it is a real phenomenon and has a significant impact on clinical trials.

Subjects do not have to receive a placebo to benefit from the "placebo effect" while in a trial. Remember that all subjects are receiving the same benefits from the trial—more tests, more visits and more attention. Therefore, subjects receiving the active treatment are as apt to experience a placebo effect as are those subjects being treated with the placebo. Ideally the placebo effect will balance out between groups so that the differences seen can be attributed to the actual drug effect.

Statistical Significance

Statistical significance relates to the probability that an event (such as the difference between two treatments) is due to chance alone. When a sponsor is conducting a study to compare a drug to a placebo or to another active drug, it is hoped there will be a statistically significant difference in favor of the sponsor's drug. The significance level is most commonly set at 5%, or p=0.05, where *p* stands for probability.

If the drug appears to be better than placebo in a test at the 0.05 level, it does not prove that the drug is actually better, but it lends a comfort level that there really is a difference in the effect of the two treatments.

Noticing a statistically significant difference does not say anything about the magnitude of the difference or the clinical significance of the difference. Inferences about the actual clinical value of the difference must be made based on the actual value of the variables being studied. For example, let's assume that the final average Hamilton Depression Rating Scale for Depression (HAM-D) total score was 10.6 in the investigational drug group and 13.2 in the placebo group, and that the difference (2.6) was statistically significant at p=0.05. This means, roughly, that the probability of this difference being due to chance alone is only 5%. Whether or not the difference of 2.6 points that separates the two groups is significant clinically would need to be decided by medical personnel.

Control Groups Used in Clinical Trials

What is a control group? Subjects in comparative trials are divided into two (or more) groups: the treatment group and the control group. Subjects in the treatment group receive the investigational drug, while those in the control group receive placebo or an active drug that is already marketed for use. Control groups are used in clinical trials as a baseline against which to compare a new treatment to test that it is both safe and effective. Three main types of control groups—placebo control, active comparator control and historical control—are discussed below.

Placebo Control

Use of a placebo control in a study means that one group is treated with the active drug and another group is treated with a placebo and the results are compared. Use of a placebo helps control for the psychological effect of being in a trial and helps to control for adverse events being attributed to the active drug when in fact they are simply the result of changes in the disease or other outside factors.

In the U.S., placebo-controlled studies are common and are the most desirable to the FDA in all cases, except those for which the use of a placebo would be unethical (such as in an infectious disease known to respond to treatment). In many other countries, the routine use of placebo-controlled studies is less acceptable. However, if a placebo control is not used, it is difficult to tell whether the active medication was really effective, regardless of the size of the effect observed, because the result seen may have been due to the placebo effect rather than to the active treatment.

Active Comparator Control

In cases in which a placebo cannot be ethically used, the investigational drug may be compared to another active compound. The comparator will be an already marketed product; it is frequently an established, standard treatment used for the condition, although it may be the newest and most interesting treatment, or the market leader. It is usually the hope of a sponsor that its investigational drug will be shown to be statistically superior to the comparator

drug. Remember, though, that the effect seen with one or both of the drugs may be due to the placebo effect, and there is no way to distinguish that in an active comparator trial.

Sometimes both a placebo and active comparator are used in a trial, making three treatment groups. This allows both drugs to be compared to the placebo as well as to each other, eliminating the potential placebo effect problem. In general, it allows for more subjects to receive an active drug rather than placebo. If one-third of the total number of subjects are randomized to each of the three study groups (investigational drug, placebo and active comparator), two-thirds of the subjects will receive an active drug treatment and only one-third will receive placebo treatment. Since most subjects would prefer to receive an active drug, this control scheme often makes a study more appealing.

Historical Control

On occasion, a historical control will be used in a clinical trial. There are two types of historical controls. One is the use of data obtained from the same subjects (on no treatment, the same treatment or a different treatment). Sometimes this is done by a crossover study, which will be discussed later in this chapter.

The other type is a comparison to data obtained from other patients, (again on no treatment, the same treatment or another treatment). This type of trial is seen rather often in the testing of new therapies for cancer, when no other treatment exists. The trial results will be compared to the remission rates or death rates seen in the general population of similar cancer patients when there is no treatment. For example, if the death rate in untreated people with a particular cancer is 35% over a particular period of time, and if the death rate in study subjects (receiving the treatment) with this same cancer over the same period of time is 25%, this might show a significant difference with the use of the investigational drug.

Minimizing Bias

Bias, according to Webster's Dictionary, is "a systematic error introduced into sampling or testing by selection or encouraging one outcome or answer over others." In clinical trials, these systematic errors distort the data, which may lead to an incorrect conclusion.

Bias may be introduced in a clinical trial from anyone who might be able to exert some influence over it, including the sponsor, the investigator, a monitor or study subjects. An investigator could introduce bias by placing subjects in study groups based on how the investigator felt each particular subject would react to one treatment over another. Bias may also be introduced in assessing a subject's response to a medication, based on how well the assessor (investigator, coordinator) thinks the given treatment will work. It is difficult to give an impartial judgment if you have a particular point of view, in this case the expected result, of a treatment.

The two main techniques used in clinical trials to eliminate bias are blinding and randomization.

Blinding

Blinding refers to a lack of knowledge of which treatment is being used with a subject in a clinical trial. The primary people who may be blinded in a trial are the subjects, the investigator (and staff), monitors and statisticians. Blinding is achieved by making the treatments look the same for each treatment group. If it is impossible to make the treatments look the same, blinding can be achieved by having someone who is not otherwise associated with the trial administer the treatment, while the investigator remains blinded while doing assessments of the subject. The most common blinding schemes are:

- **Triple blind.** The subject, the investigator, the sponsor's monitors and statisticians all do not know which treatment is being received by a particular subject.
- **Double blind.** Neither the subject nor the investigator knows which treatment is being received by a particular subject.
- **Single blind.** The subject does not know which treatment is being received, but the investigator does know.
- **Open label.** No blind is used. Both the investigator and the subject know which treatment the subject is receiving.

Randomization

Randomization is the method by which study subjects are randomly assigned to treatment groups. It is usually done by means of a randomization code scheme, most often generated by a validated computer program. Randomization helps to reduce bias in a trial by ensuring there is no pattern in the way subjects are assigned to the treatment groups. It also allows the blind to be broken for one subject without breaking it for all other subjects at the same time.

If subjects were assigned to treatment groups A and B one after the other as they came in, the investigator would not be blinded, as he or she would always know which treatment group would be assigned next, even if the drug itself is blinded. (See Table 1)

In a randomized assignment, the investigator will not be able to know the pattern, because it is random. When blinded study drugs are sent to an investigative site, they are labeled by subject number, Subject #101, Subject #102

Table 1: Assignment scheme

Subject	1	2	3	4	5	6	7	8	9	10	11	12
Drug	A	B	A	B	A	B	A	B	A	B	A	B

… etc. The investigator and site personnel will know only the subject number, not the underlying treatment or the underlying randomization scheme. A random treatment pattern for the same two treatments, A and B, might look like:

Table 2: Random treatment pattern

Subject	1	2	3	4	5	6	7	8	9	10	11	12
Drug	B	B	A	A	A	B	B	B	A	B	A	A

Note that there are 12 subjects in each randomization scheme, and that six subjects receive each treatment in each scheme. In the random scheme, however, it is not easy to predict the next treatment, as there is no particular order to the scheme. Sometimes randomization is done in blocks, in which each block of subjects has the same number of people on each treatment. If you look closely at the randomization scheme above, you will notice that each block of six subjects has three people in each treatment group. This is called randomization in blocks. It is important that the subjects, the investigator and the CRA do not know this assignment pattern. If they did, it could effectively unblind them to the treatments, which might introduce bias and negate the benefits gained from randomizing and blinding.

Randomization and blinding are usually used together, and constitute the best defense against bias in clinical trials.

Common Study Designs

There are many different statistical study designs used, but most of the clinical trials that CRAs work on employ only two designs, or variations of them, that are briefly discussed below. If you are interested in reading more about study design, the *Guide to Clinical Trials* by Bert Spilker has a good basic discussion on this topic.[4]

Parallel Design

This is the most common and straightforward statistical design used in clinical trials. In parallel design, each subject is assigned to a treatment group, with all subjects following the same schedule and activities. The groups are followed in parallel. There may be two or more treatment groups. (See Table 3.) The analysis will compare the groups to each other.

Table 3: Parallel study

Group 1	Drug A	
Group 2	Drug B	
	Start	Finish

Crossover Design

A crossover design is somewhat more complicated in that each group will receive both treatments. It starts off like a parallel design study, but halfway through the groups switch to the other treatment. Frequently, there is a washout period between the two treatments. A crossover study in its simplest form is shown in Table 4.

In this design, each group can be compared to itself as well as to the other group. There is less variability in a crossover design as compared to a parallel design. However, many drugs have a carryover or residual effect after they are stopped, which is difficult to measure. This design is frequently seen in bioavailability trials, which allow a period between the treatments of usually 10 or more half-lives of the drug to combat the carryover effect. There are many variations of crossover designs, but the general premise remains the same.

Table 4: Crossover study

Group 1	Drug A		Drug A
Group 2	Drug B		Drug B
	Start	Washout	Finish

Adaptive Design

Adaptive protocol design is being adopted more frequently by sponsors conducting clinical trials. Specific detail regarding adaptive design studies can be found in the FDA guidance document, "Guidance for Industry, Adaptive Design Clinical Trials for Drugs and Biologics, February 2010." The FDA guidance defines adaptive design on page 6.

> *III, Description of and motivation for adaptive designs*
>
> *A. Definition and Concept of an Adaptive Design Clinical Trial*
>
> *For the purposes of this guidance, an* **adaptive design clinical study** *is defined as a study that includes a prospectively planned opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of data (usually interim data) from*

subjects in the study. Analyses of the accumulating study data are performed at prospectively planned timepoints within the study, can be performed in a fully blinded manner or in an unblinded manner, and can occur with or without formal statistical hypothesis testing.

The term **prospective** *here means that the adaptation was planned (and details specified) before data were examined in an unblinded manner by any personnel involved in planning the revision. This can include plans that are introduced or made final after the study has started if the blinded state of the personnel involved is unequivocally maintained when the modification plan is proposed. It may be important to discuss with FDA the documentation that will provide unequivocal assurance of blinding for the pertinent personnel while a study is ongoing. Changes in study design occurring after an interim analysis of unblinded study data and that were not prospectively planned are not within the scope of this guidance.*"

Other Statistical Issues

Intent-to-Treat

In general, there are two groups of subjects analyzed in a clinical trial. The primary analysis is performed with the intent-to-treat (ITT) study population, which includes all subjects who met the inclusion/exclusion criteria, provided written informed consent, and were enrolled and received treatment, even if the treatment was incomplete. Subjects who drop out during the trial (e.g. lost to follow-up) are still included in the ITT analysis. Note that if there are many drop-outs, it can bias the trial, so CRAs should work with their sites to help minimize the number of subjects who do not complete the entire trial.

Additional analyses of study endpoints also will be performed on the per protocol (PP) study population. The PP study population consists of all study subjects who met the ITT requirements and who completed the entire study.

Missing Data

Missing data is a problem when it comes to the analysis of a clinical trial, especially if there is a lot of it. It can be handled in various ways, but none of them make statisticians very happy. One common way is called "last value forward" (LVCF). In this case, the last value preceding the missing value is used as the value of the missing data. Another method is to average all the data points that are present, then use that average data value for each missing data point. An example is shown in Table 5.

As you can see, the imputed values differ with the two methods, and there is no guarantee that either method is close to what the actual values might

Table 5: Missing data example

Original data	1.6	1.3	1.3	—	1.8	1.9	1.8	—	—
LVCF	1.6	1.3	1.3	1.3	1.8	1.9	1.8	1.8	1.8
Average data value	1.6	1.3	1.3	1.6	1.8	1.9	1.8	1.6	1.6

have been. A CRA who works with his or her sites to eliminate missing data will make the statistician very happy and will increase the chance of a successful study.

Primary Outcome Measures

It is best to have primary outcome measures that are simple and easily measured. If your primary outcome measure has multiple components, it muddies up both the analysis and the interpretation of the results. You can look at multiple things and analyze them, but try to keep them separate.

For example a primary outcome measure:

- A 50% reduction in the depression rating scale total score.

This is a "yes" or "no" answer, where "yes" is success and "no is failure." Secondary outcome measures might be:

- Change in the total score on the somatic section of the depression scale.
- Change in the total score on the anxiety scale.
- Change in the total score on the quality of life instrument.

These are easy to measure and easy to interpret. Here are some measures that are not recommended.

Primary outcome measure:

- A 50% reduction in the depression rating score total and a score of no more than one on the suicide cluster and an improvement of at least 30% on the anxiety scale.

Keep it simple, and the results from the study will be much easier to interpret.

Summary

Clinical trials are complex and have their own rules and terminology. CRAs should be familiar with at least the basics of trial design and the terminology used. When the basic design elements have been determined for a trial, it is time to write the protocol. Protocol development is discussed in the next chapter.

Key Takeaways

Study Design

- Determining the sample size for a study is a statistical computation based on the expected effect size, variability and power.
- Both placebo response and placebo effect have an impact on clinical trials and must be considered when a trial is designed.
- Placebo controls and active controls are most often used in clinical trials. Historical controls are also used but much less frequently.
- Randomization and blinding are the two primary methods of reducing bias in clinical trials.
- In blinded trials, it is important that the subject and the investigator (and usually the CRA) do not know which treatment individual subjects are receiving.
- The most commonly used statistical design in clinical trials is the parallel group design. Crossover designs are also used, especially in bioavailability trials.
- CRAs should be familiar with the common designs and terminology used in clinical trials, as well as the reasons for the use of these various methodologies.
- Analysis might be done on both an intent-to-treat (ITT) study population and a per-protocol (PP) population.
- Missing data can be an issue in clinical trials.
- Outcome measures used in a clinical trial need to be carefully determined.

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3. Klerman, G.L., & Cole, J.O. "Clinical pharmacology of imipramine and related antidepressant compounds." *Pharmacology Review*, 1965. 17, 101-104. 87
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CHAPTER ELEVEN

Preparing for a Study: Protocols, Case Report Forms, Electronic Data Capture Systems and Electronic Patient-Reported Outcomes

This chapter discusses some of the primary activities that must be considered before starting a study, including writing the protocol, developing case report forms(CRFs)/electronic case report forms(eCRFs), the use of electronic data capture (EDC) systems and the emergence of more types of electronic patient-reported outcome devices (ePRO)s. Protocols, ePRO devices and CRFs are critical parts of a CRA's job, and the CRA must have a good understanding of each of them, even if he or she is not involved in writing protocols or developing CRFs or ePROs. The chapter begins by discussing protocols, followed by a discussion of CRFs and EDC, because this is the usual pattern of their development in a research program.

This chapter is designed to give you basic information. Much of the material that follows is in the form of an annotated outline that gives you the basic considerations for these documents.

Developing a Protocol

In this section, we will look at how protocols are developed and what is included in them. The protocol is the blueprint for a study and describes how the study will be conducted. If the protocol is well written and the study design is sound, the study will be able to generate valid data that are acceptable to the scientific community, including the FDA.

CRAs will almost never write a complete protocol, but in-house CRAs may be asked to prepare sections of protocols or draft a protocol plan, sections of which will be completed by others on the drug development team, such as the medical monitor and biostatistician. Even if CRAs are not involved in writing protocols, it is important for them to have an understand-

ing of protocol basics. The protocol is the basic tool of clinical trials and will be used in every study that a CRA monitors. Knowing the basics of a protocol makes the CRA more effective and the job easier.

A CRA should be able to read a protocol and determine whether or not it contains all the elements important to a trial, as well as the critical medical information. A CRA should be able to determine if a protocol is realistically feasible to do, at least from a logistics standpoint. There is no other study document so important for a CRA to be knowledgeable about. (It is also a pet peeve of site personnel when the CRA does not thoroughly understand the protocol.)

Designing a study and writing a protocol require knowledge of the scientific method, regulations and the medical condition being addressed. Bert Spilker.[1] has written a complete text on developing protocols for those who want a more in-depth dissertation on the subject.

Contents of a Protocol

No two protocols are the same. Formats will vary from company to company and among different authors within the same company. The content will vary depending on the therapeutic area of investigation. Many sponsors have a pre-defined format for protocols dictated by their standard operating procedures (SOPs).

There are also differences in protocols because of the development phase of the compound. Phase I protocols are more flexible and less detailed than those for phases II and III, because phase I studies are early in the development program and not much is known about how the investigational drug acts in humans. A phase I protocol is primarily an outline of the study and should include:[1]

- A description of the number of subjects to be studied.
- A description of safety exclusions.
- The dosing plan, to include duration, and dose or method being used to determine dose.
- A detailed description of the safety procedures, such as vital signs and laboratory evaluations.

Phase II and III protocols are very detailed and describe all aspects of the investigations. The FDA defines some minimal requirements for these protocols, which must contain at least:

- A description of the objectives and purpose.
- The name, address and qualifications of each investigator.
- The names of all sub-investigators working under the direction of the investigator.

- The institution where the research will be done.
- The name and address of the IRB.
- The inclusion and exclusion criteria for study subjects.
- The number of subjects to be evaluated.
- The design of the study, including the type of control group being used, if applicable.
- The methods employed to minimize bias (usually randomization and blinding).
- The method used to determine the dose(s) used, the maximum dose and the duration of administration.
- A description of the observations and measurements being used.
- A description of the measures (laboratory evaluations, procedures, etc.) being used to monitor the effects of the investigational drug and minimize risks to subjects.

These are minimum requirements; almost all protocols will contain additional elements as well. The common elements of a protocol, and the order in which they usually appear, are:

- Title page
- Protocol summary
- Abstract (optional)
- Table of contents
- Introduction
- Study objectives
- Study design
- Randomization and blinding
- Subject selection
- Subject enrollment
- Informed consent
- Screening procedures
- Replacement of subjects
- Treatment
- Concomitant medication
- Study activities and observations

- Adverse events
- Data recording instructions
- Data quality assurance
- Analysis plan
- Risks and benefits
- References
- Appendices

A brief description each of these elements in a typical protocol follows.

Common Elements of a Protocol

1. **Title Page.** All protocols will have a title page. Essential information for the title page includes:
   - Title: The title should be specific enough to distinguish the protocol from those for similar studies. It should be a concise description of the study providing the reader with the drug, disease, design and study phase.
     Example: A randomized, double-blind, phase III trial of (drug under study) in subjects with generalized anxiety disorder. A placebo-controlled, fixed-dose, parallel-group, multicenter study of 12 weeks.
   - Protocol Number: This should be a unique number that identifies the protocol. Most sponsors have a specific procedure for determining this number that identifies the drug, as well as the study.
     Example: 12AB345/0021, where 12AB345 is the drug identifier and 0021 identifies the protocol within that drug development program.
   - IND Number: The IND number of the drug, for studies conducted under an IND.
   - Date: All protocols should be dated as part of their identifiers. This also allows various versions to be readily identified.
   - Sponsor Medical Monitor: The name and contact information for the sponsor's medical monitor.
   - Principal Investigator: The name and address of the investigator doing the study.
   - Some protocol cover pages include the statistician, CRA, sub-investigators, study coordinator and laboratory contact information, but these are optional.
2. **Protocol Summary.** The protocol summary should give a good overview of the study and is highly recommended. CRAs can use the sum-

mary when they are interviewing potential investigators, even when the entire protocol is not yet complete. The summary will provide enough information for potential investigators to determine if they are interested in and have the capability to do the study. The summary is usually one to two pages long and typically includes:

- Protocol Title: repeated from the title page.
- Study Objective: a statement of the main objectives and purpose of the study.
  Example: The primary objective is to show that (study drug) is more effective than placebo in the short-term (12 weeks) treatment of generalized anxiety disorder. The secondary objective is to gain information on the short-term safety of (study drug).
- Study Population: a brief description of the type of subjects to be included.
  Example: Study subjects will be male or female, 18 years or older, with diagnosed generalized anxiety disorder and no clinically relevant comorbid psychiatric conditions.
- Study Design: a brief description of design, e.g., single-dose, multiple-dose, pilot, safety, efficacy, randomized or not, single- or double-blind, open-label, parallel, crossover, etc.
  Example: The study is a randomized, double-blind, fixed-dose, placebo-controlled, phase III, multicenter trial.
- Study Medication, including the:
  - Generic name and trade name (if known) of the compound. Example: alprazolam (Xanax®)
  - Dosage form. Example: 0.25 mg tablets
  - Route of administration. Example: oral
  - Dose and regimen. Example: 0.25 mg three times a day
- Duration of Treatment: the time period during which the study medication will be administered to the subjects. If the treatment is not continuous, it should be described.
  Example: Subjects will be treated for 10 weeks, followed by a two-week, single-blind taper period.
- Methods and Materials: a general description of the procedures, tests, etc., required.
- Duration of Subject Participation: total duration of subject involvement in the study, including screen and any follow-up.
  Example: Subjects who complete the study will have 12 weeks of study involvement.

- Anticipated Maximum Number of Subjects: total number of subjects in all treatment groups.
  Example: There will be 440 subjects in each treatment group, for a total of 880 subjects.
- Number of Centers: if known.

3. **Abstract**. An abstract is optional. An abstract should be limited to one or two paragraphs describing the objective, design, population, sample size and major study activities.
4. **Table of Contents**. A detailed table of contents should be included in all protocols.
5. **Introduction**. The introduction should identify the reason for doing the study and place it in context with previous investigations and in the overall development plan. If the introduction is lengthy, subheadings should be used. Abbreviations and acronyms should be avoided when possible. Each abbreviation or acronym should be identified in full the first time it is used. Example: Hamilton Rating Scale for Anxiety (HAM-A). The introduction usually contains:
   - A brief discussion of the study medication, including the medical need and rationale for use.
   - A description of the design and major endpoints, including the rationale for use.
   - A description of how this protocol differs from other similar protocols for the same treatment.
   - An identification of the setting in which subjects will be studied (outpatient, hospital, etc.).
   - The rationale for the dose and regimen, citing supporting data.
   - A description of the study control (e.g., placebo) and/or comparator drug, plus the rationale for use.
   - A general description of procedures and length of the study.
6. **Study Objectives.** These should clearly state the primary and secondary objectives and identify the endpoints that will be used to satisfy them. Primary endpoints are usually the key efficacy parameters to be studied. Secondary endpoints usually consist of efficacy variables of lower clinical significance and the safety parameters of the trial. State whether the study is intended to show a difference or similarity between treatments (this also could be included under study design).
7. **Study Design.** This section should include a description of the study design, including:
   - Type of study (methodology, pilot, tolerance, efficacy, pharmacokinetics)

- Controlled or uncontrolled
- Single or multiple dose (fixed or variable)
- Single site or multicenter
- Open-label or blinded
- Randomization scheme
- Design (parallel, crossover, matched pair, block, sequential)

8. **Randomization and Blinding.** This section should describe the randomization and blinding procedure, including any stratification. It should also contain instructions for breaking the blind, if it becomes necessary.
9. **Subject Selection.** This section will include a description of the study population, indicating the number of subjects to be enrolled. If appropriate, it will differentiate between the maximum number of subjects to be enrolled and the minimum number of subjects required to meet protocol objectives. The subject selection criteria (inclusion and exclusion criteria) should include:

    - A description of each requirement for subject eligibility. If there are any exceptions to a criterion, they should be stated.
    - Specific disease-related criteria.
    - Willingness to sign an informed consent form as an inclusion criterion.
    - Allowed and disallowed concomitant medications.
    - Specific contraceptive requirements (as applicable).
    - Criteria that will exclude subjects.
        - Subjects who are taking another investigational medication or who have recently taken an investigational medication within a specified time period (i.e., 30 days) are almost always excluded.

    This section should also include an explanation of when the entry criteria must be met, e.g., before or following a screening period, after a washout period, etc.

    In some trials, subjects who meet some basic study criteria are enrolled in a screening period. During this time, various tests are done (e.g., physical exam, laboratory tests) to determine if the subjects meet the criteria for entry into the entire trial. A washout period is a time when subjects are taken off their current (non-study) medications. When the carryover effect from these medications has had time to dissipate, subjects are entered into the main part of the trial.

10. **Subject Enrollment**. This section should identify the point at which a subject is considered enrolled. For randomized studies, this is usually at the time of randomization. Other possibilities might be after the informed consent form is signed or after successful completion of a screening period.

11. **Informed Consent**. The section about informed consent is sometimes located in the body of the protocol and sometimes in an appendix. It is always a good idea to provide the investigator with a draft consent form, instead of expecting each investigator to write one separately. Consent forms were discussed in detail in the previous chapter. The protocol section on informed consent should include:

    - A complete description of informed consent requirements, emphasizing the requirement for obtaining consent prior to a subject's involvement in any study-related activity.
    - The investigator's responsibility to obtain IRB approval of the consent.
    - Specific instructions if vulnerable populations, such as minors, will be included in the study.

12. **Screening Procedures.** This section should contain the following:
    - A description of all activities and tests related to the screening of subjects for study enrollment.
    - Specific timing relative to tests, meals or the start of treatment.
    - If results of any screening tests will be used as baseline for group comparisons, this should be stated.
    - A description of discontinuation of any concomitant medications, if required.

13. **Replacement of Subjects.** This section should specify whether subjects who drop out will be replaced and any conditions associated with replacement. If replacement is allowed, the protocol should specify how replacement subjects would be assigned to treatment groups.

14. **Treatment.** This section should provide the following information about the investigational medication and any comparator medication, including a placebo.

    - Generic, chemical and trade name (if known).
    - Formulation of the placebo.
    - Dosage forms and formulation, in general terms. If any medication contains excipients to which some subjects may be sensitive, such as lactose, this should be indicated.
    - Packaging (e.g., bottles, blister packs).
    - Special storage procedures and stability considerations. If the medication requires reconstitution, the stability in the reconstituted form should be specified.

- Route of administration. Include any special instructions for reconstituting medication or preparing individual doses. If it is administered intravenously (IV), specify the infusion rate.
- The dosage regimen and time schedule for each dose. Clarify the duration of administration, including any medication-free periods or washout periods. As appropriate, specify the timing of dosing in relation to meals.
- Rationale for the dose and regimen.
- Procedures for dosage adjustments, if applicable.
- Compliance parameters, e.g., so many days allowable, etc.

15. **Concomitant Medication.** This section should include the policy on the use of concomitant medications, including over-the-counter (OTC) medications, herbals and vitamin supplements. Indicate that all concomitant medication must be recorded. If concomitant medications are allowed, there should be information about how they may be used and why the use will not confound the treatment effect. Interaction data should be cited, as appropriate.

    If the analysis will be stratified based on concomitant medication, this should be stated, with reference to the analysis plan.

    If tobacco use, alcohol, caffeine or illicit drugs are prohibited or restricted, this should be mentioned in this section.

16. **Study Activities and Observations.** This section will give all the activities that are to be conducted at each study visit. It should also include an overall activity schedule that shows at a glance each event, procedure, observation and evaluation that will be conducted at each visit. An example of a protocol activity schedule is shown in Table 1. Other considerations to keep in mind for this section are:

    - Each time period should be clearly defined.
    - Avoid the use of "Day 0," as it is confusing to most people.
    - If "Time 0" is used, it must be carefully defined. This is usually the time of the initial dose of medication within a given evaluation period.
    - List and describe all study activities, observations and evaluations to be made during each period.
    - If any non-study medications are to be discontinued during a period (usually a screening period), describe the procedure.
    - Specify the acceptable leeway or "treatment window" for each visit. This is the amount of time that is allowed before or after the scheduled visit date, such as the date plus and minus two days. Specify how the investigator should handle visits that occur outside the acceptable window.

- If there is a tapered discontinuation of the investigational medication, describe the exact procedures, including the specific dose adjustments and time schedule to be followed. Consider a tabular display of the taper schedule.

Table 1: Example of a protocol activity schedule

Study activity	Baseline	Week 1	Week 2	Week 4	Week 6	Final (W8)
Informed consent	✓					
Medical history	✓					
Physical exam	✓			✓		✓
Labs	✓	✓	✓	✓	✓	✓
EKG	✓			✓		✓
Treadmill stress test	✓			✓		✓
Office visit—general assessments	✓	✓	✓	✓	✓	✓
Safety evaluations	✓	✓	✓	✓	✓	✓
Medication dispensing	✓	✓	✓	✓	✓	
Final evaluation						✓

Clinical assessments also need to be described in this section. Things to keep in mind when discussing clinical assessments:

- Describe and provide specific criteria (as appropriate) for the various observations and assessments at each study period. To avoid confusion, be sure to use the same terminology and categories that will be used in the CRFs (See "Case Report Forms" later in this chapter). Relate the various clinical assessments to the primary study observations they support.
- If a detailed description of a particular procedure or assessment tool is needed, consider describing it in general terms in this section, but in more detail in the appendix.
- Provide the rationale for the selection of specific endpoints or assessment tools unless discussed elsewhere.
- Discuss the accuracy, precision and relevance of any nonstandard assessment tool or procedure, citing references when appropriate.
- Specify any special conditions under which assessments are to be made or specific equipment should be used. Quantify descriptions

when feasible and appropriate (e.g., indicate that 15 minutes of rest should precede a "resting" blood pressure reading).

- As appropriate, identify who should make clinical assessments and indicate whether the same evaluator should be used for a given subject throughout the study or for all subjects. List any assessment forms that are to be completed by the subject.
- Specify the rules or criteria for changing the management of the subject if there is either marked improvement or worsening of the subject's condition.

17. **Adverse Events.** There should be a very explicit section covering adverse events and adverse event reporting. (Adverse events are discussed in detail in Chapter 15.)
18. **Data Recording Instructions.** This section should:
    - Indicate how data will be collected. If detailed instructions have been prepared, specify their location (e.g., study manual, appendix, etc.).
    - Discuss the use and management of source documents.
    - Discuss the procedure for correcting errors.
19. **Data Quality Assurance.** This section should:
    - Describe procedures for assessing subject compliance.
    - Describe any special training or other measures for site personnel to ensure valid data.
    - Discuss source document review.
    - Provide Good Clinical Practice (GCP) references.
20. **Analysis Plan.** Generally, the analysis plan will be developed and provided by the biostatistician. Items that may be included are:
    - Discussion of the general study design issues.
    - A statement of the planned sample size, reason for choosing it and power calculations.
    - Classification of study variables (e.g., primary versus secondary).
    - Identification of statistical model(s) to be used.
    - Description of specific analyses, including any subgroup analyses.
    - Information about the timing and purpose of any planned interim analyses.
    - Handling of missing or non-evaluable data.

21. **Risks and Benefits.** This section should briefly summarize the risks and potential benefits associated with the use of the test compound or procedure. If there is any exposure to radiation, it should be discussed here. Note that this section should be consistent with the consent form.
22. **References.** Put all references for the protocol in this section.
23. **Appendices.** Appendices may be used to detail information that might be confusing if placed in the body of the protocol.
    - Include an appendix describing investigator responsibilities, including the requirements for compliance with GCPs and sponsor SOPs. (Investigator responsibilities are discussed in the next chapter.)

Protocol Complexity

Over the past several years, protocols have become more complex and more demanding in their requirements. In looking at more than 10,000 protocols covering all phases and all therapeutic areas, Ken Getz, Director of Sponsored Research and Research Associate Professor, Tufts Center for the Study of Drug Development, found that all measures of complexity have risen considerably between 2000-2003 and 2004-2007.[2] The median number of procedures per protocol has risen by almost half, and the total number of eligibility criteria has risen by more than half. This places an increasing burden on study sites and, of course, will increase the grant cost to the sponsor. Table 2, below, shows these differences over time.

Table 2: Rising protocol complexity, burden and impact

All therapeutic areas, all phases

	00—03	04—07	Difference
Unique procedures per protocol (median)	20.5	28.2	+38%
Total procedures per protocol (median)	105.9	158.1	+49%
Total investigative site work burden (median units)	28.9	44.6	+54%
Total eligibility criteria	31	49	+58%

Source: Getz et al. Assessing the Impact of Protocol Design Change on Clinical Trial Performance. American Journal of Therapeutics. 2008 15(5); 450 - 457

More complex protocols also require larger CRFs, at a greater expense to the sponsor and the study sites.

Not only does it take more time to develop a more complex protocol, but the time from protocol readiness until the first subject is enrolled increases,

as does the time to when the final subject visit takes place. Anything that can be done to simplify a protocol while still making it adequate to meet the study goals will pay dividends to the sponsor, the site and the study subjects.

Protocol Amendments

Protocol amendments, meaning formal changes to a protocol, are very prevalent in the industry and require a huge amount of time and effort. Think about the steps that have to occur if you amend a protocol. The change has to be written, including a section showing both the old and new versions, it must be reviewed by multiple people, sent to sites for review, sent to the IRBs for review and approval, sent back to the sponsor and then implemented. Study procedures may need to be altered, retraining may need to be done and subjects may need to be re-consented. The ability to recruit subjects may be affected, sometimes positively, sometimes negatively. The analysis plan may have to be altered. All in all, it can be a huge amount of work and will involve numerous people in the process.

In 2010, Tufts Center for the Study of Drug Development (CSDD) conducted a study on protocol amendments. It looked at 3,413 protocols and found there had been 3,596 amendments made, encompassing 19,345 changes. This study found that 69% of all protocols have at least one amendment, and almost half of the amendments (46%) occur before any study subjects have even been dosed. Not only that, but they determined that 37% of the amendments could be considered either "somewhat" or "completely" avoidable (see Table 3).[3]

Table 3: Avoiding amendments

	Percent	Cause Categories
Completely avoidable	18	• Protocol design flaw • Inconsistency and/or error in the protocol
Somewhat avoidable	19	• Recruitment difficulty • Investigator/site feedback
Completely avoidable	27	• New data available (other than safety data) • Change in standard of care • Change in strategy/objective
Somewhat avoidable	39	• New safety information available • Regulatory agency request to amend • Manufacturing change

Note: Percentages represent percent of amendments placed in each cause category

Source: TCSDD 2010 analysis of 3,596 amendments and 19,345 changes

This is incredibly wasteful; just think about other activities that could be done with the time used for amendments. In fact, the CSDD study found that it takes an average of 61 days and costs $450,000+ to implement each amendment. So let's see how much this amendment cost was… for just the amendments in this study (3596 of them), that's about 601 years of implementation time and a cost of over $1.618 billion. On top of that, these are only from the protocols included in the study, which came from just 24 companies. Earlier in the book we discussed the huge cost of time and money to develop a new product—eliminating amendments can help lessen these amounts.

Obviously, eliminating or lessening the number of amendments that must be made to a protocol can make a significant difference in the cost of a trial. Let's look at what this study found about the categories of amendments that might be avoidable.[4]

Consider the completely avoidable category: design flaws and inconsistencies/errors. There really isn't any excuse for these. So if they could be eliminated, based on the 3,596 amendments in the study, it would have saved more than $291 million, plus 108 years of implementation time. Note that even some of the "completely unavoidable" amendments, the "regulatory agency request" ones, might be avoidable if more time was spent up-front ensuring that the protocol was well written to begin with.

Constant protocol amendments are also difficult for sites to manage. They are often confusing, especially when it comes to determining what the changes are and when they are to be implemented, which can make compliance to study procedures difficult at the site level. Amendments also cause sites a great deal of extra time, especially with sponsor efforts to disseminate the study amendment to the investigational site, training the Principal Investigator, Sub-Investigator and investigational site staff on the protocol amendment and documentation of training, etc. It can also cause sites a great deal of extra time if subjects need to be re-consented, and they may make the sponsor look inept.

In conclusion, it is important to take the time to carefully review and check protocols before they are formally issued. This is usually a joint task, so if everyone involved takes the time to read the protocol carefully, think about it and make any necessary changes, it should be free from errors and flaws. This is time well spent.

Summary

A good protocol forms the backbone of the research process and is essential for conducting a high-quality study. CRAs must understand what makes a good protocol and the importance of protocols in research. For each study the CRA is monitoring, he or she must have a clear understanding of the protocol and what must be done to ensure adherence to it during the study. Amendments should be avoided whenever possible. Once the protocol is written, CRFs can be developed.

Case Report Forms (CRFs)

Case report forms (CRFs) are used during a clinical trial to record the protocol-required data for each study subject. CRFs standardize the collection of study data and help assure that the medical, statistical, regulatory and data management needs of the study are met. eCRF/EDC systems are utilized in a large number of clinical trials/device trials conducted and represent the same premise for data collection as their paper-based counterparts.

The mere mention of CRFs can evoke images of seemingly endless corrections, piles of paper and query emails from data management with countless excel spreadsheets, detailing the volume of queries to be resolved and outlining outstanding data entry. However, dealing with CRFs is a large part of a CRA's workload and they play a major part in the performance of a clinical trial. (The CRA's involvement in monitoring CRFs is discussed in Chapter 10.)

Many sponsors have designated people or departments responsible for developing the CRFs/eCRFs or this work may be contracted out to a company that specializes in CRF development. Consequently, CRA involvement and input in developing CRFs varies considerably from company to company. However, the impact of CRF design on data quality is so significant that CRAs should have an understanding of the issues involved in CRF design and development. Awareness of the problems with poorly designed CRFs will also help the CRA when reviewing the forms at investigative sites.

CRF Design and Development

Unfortunately, sponsors often cause themselves significant problems because the design and development of CRFs are not given adequate attention. So much time and energy goes into protocol development that CRFs are sometimes an afterthought. However, taking the time to design good forms pays major dividends during the course of the study.

Past experience is extremely valuable, and time should be taken to utilize previous company CRF experiences. Try to use ideas that worked well for other studies. Get input from some of your more knowledgeable sites. Study coordinators know from experience what works well and what doesn't and are usually willing to share their thoughts about good and bad CRFs.

Good case reports come from consistent improvement over time. Since CRAs are in an excellent position to monitor the quality of CRFs during monitoring visits, they should make notes of which forms or parts of forms seem to produce the most errors and those that are relatively error-free; this information should be shared with those involved in designing forms.

Some of the issues involved in producing high-quality CRFs are discussed below.

Standardization of CRFs

Everyone in this business is busy. One way to make better use of time is the judicious use of standardization. An approach to form design that has been used successfully by many companies is "modularization," which employs the benefits of standardization while also capturing and utilizing corporate experience.

The modular process is simple. There are data that are always collected on study subjects regardless of the drug or disease being studied, such as header information, demographics, laboratory work and physical exams. There are also other procedures (ECGs, stress tests, etc.) for which the information gathered is standard across different disease areas. When the group of fields is created for a study to collect the information for one of these items, it should be saved as a form module that can be used for other studies.

Over time, the catalog of form modules will become comprehensive. When new studies are planned, those involved in designing the CRFs can check the catalog to see which form modules will be appropriate for the study in question. Not only does this save design time, but the modules can also be pre-coded by data management, which saves additional time.

Terminology Used in CRFs

Always use standard terminology that is familiar to clinicians. Industry jargon will not be understood in a clinical setting.

Selection of the Media for CRFs

A decision must be made about whether paper or electronic forms will be used. If the answer is "electronic," the software that will be used for EDC will usually define the CRFs. With EDC, data may be entered into a computer placed at the investigative site by a sponsor, or data may be entered into electronic/internet-based forms transferred between the sponsor and the site. There is a sponsor or EDC vendor website or portal, accessible by sponsor or investigative site staff, typically by user account creation. The website or portal houses the electronic data entry. In general, CRAs will have little or no input into the design or layout of eCRFs. Many of the concepts and principals discussed for paper forms are also applicable to electronic forms. This is important, as the majority of studies are using web-enabled systems for CRF capture and collection.

Determination of the Data that Need to be Collected

One of the first things to be done is the determination of what information should be collected on the CRFs and how it will be coded, including acceptable ranges and any exceptions. The best way to do this is to go through the protocol and list all the data that are required, keeping in mind that the forms must collect these data in a way that allows for appropriate analyses. When

this has been determined, the forms design process may start. For example, it is never a good idea to ask for the same data in more than one place in a CRF because, when this happens, the data do not always agree. Sometimes the CRFs ask for both date of birth and age, for example, and they frequently do not match when calculated; it is better to ask only one question.

Determination of CRF Layout

If a module catalog is available, the next step is to determine which modules are appropriate for the study. If not, or if the modules do not cover all of the necessary information, then the necessary fields to collect the remaining data must be laid out. Some things to consider during this process are:

Header and footer information.
There should be standard header information on all forms. The sponsor name or ID, the medical monitor, the protocol number, the page title and a place to enter subject identification information should be pre-printed on all forms. All forms also should be annotated as CONFIDENTIAL. Each form should have a place for a signature and date; this usually appears at the bottom of the page in a footer.

Number of fields per page.
It's tempting to crowd as much information on a page as possible to save costs. However, this approach usually turns out to be "penny wise and pound foolish," as crowding increases the chance for error. There is no easy way to quantify form density; it is a judgment call. The best way is to develop a feel for the optimal amount of information on a page and count the number of fields. Then try to stay within 10% of that number on all forms.

Font size.
Use a font size and style that is easy to read.

Spatial relationships.
The fields on a page, particularly the check boxes, should be lined up as much as possible. It is easier to enter data and to notice missing data when the alignment is straight.

Location of fields on a page.
Something that is almost never considered during form design is where on the page to put specific fields. In one of our development programs, we paid close attention to data collection error rates and what contributed to them. We discovered that most errors on the CRFs occurred in fields that were on the bottom third of the forms. From that point on, we always put primary endpoints and other critical data on the top third of the forms. Although unsure why this phenomenon occurred, it was assumed to be eye fatigue as one worked through the form entering data.

Another consideration related to the position of fields on the form is the use of a logical layout. The material on the form should be organized in a manner that makes sense relative to medical practice. Group fields together for activities that are usually done together or in sequence in a clinic setting. For example, a module for collecting data on eye exams should not be put in the middle of a page that is collecting data from a physical exam and vital signs. In addition, vital signs—pulse, heart rate and respiration rate—should be grouped together rather than in different locations. Remember that the "customers" for your CRFs are the site personnel who must fill them out. Make your forms as user-friendly as possible to help reduce errors.

Narrative fields.
As much of the data as possible should be collected using numeric fields or check boxes. Include a check box for "other" as appropriate, as exceptions do occur.

Comments on CRFs are a problem because it is difficult to computerize and analyze comments. Everything on a CRF must be coded for computer entry and analysis; consequently, comments need to be interpreted and converted to code. The true nature of the comment is often lost or distorted during the translation. On the other hand, there may not be a better way to document an occurrence than by a comment. There should be places for comments on CRFs, but only when really necessary and valuable.

It is incumbent on the CRA to instruct site personnel on the use of comments on CRFs. Many CRF designers intentionally reduce margin space on CRFs to discourage comments. It is a difficult issue, but one that can be dealt with effectively if appropriate attention is given to it.

Shading.
There are many opinions on the value of shading. Based on our experience, adding shading to forms can reduce error rates more than any other single design feature. If a form is shaded except for the places data are to be entered, it makes the fields stand out so clearly that errors of omission are almost eliminated. If an error does occur, finding it is much easier with shading than without it. However, shading adds considerable expense to the cost of forms.

Cross-visit forms.
The most difficult forms to design are those that collect data across visits, such as adverse event and concomitant medication report forms; consequently, a lot of care should be given to the design of these forms. Based on our experience, almost 75% of the errors occurred on about 15% of the CRFs, including the adverse events and concomitant medications cross-visit forms.

Miscellaneous Issues

CRF design and production are complex and time-consuming tasks. Based on your company's capabilities and the specialized equipment required for

the production of them, it is often cost-effective to contract this function to outside vendors.

During a course taken many years ago called "Managing Accelerated Performance," the instructor said something applicable to CRF design. We were discussing things that could be done to significantly improve performance and/or productivity (the "silver bullet"). He told us not to think that way because the silver bullet is seldom there. Instead, usually small improvements done consistently over time will have major impact. So, as a CRA, when you are monitoring your studies, notice what kinds of errors are occurring, and where. Think about what could be done in the design of the form to help prevent them. Take notes. Help your company capitalize on good design features and eliminate bad ones. These are the small steps that lead to continuous improvement.

Electronic Data Capture (EDC)

According to a recent EDC systems market analysis from Grand View Research, the value of the global EDC systems market was $349.8 million in 2016. The report explains that "The increasing complexity in management of clinical information generated before, during and after the trial is expected to propel demand for EDC systems over the forecast period. The statistics published by CSDD states that more than 80% of clinical trials failed as they are unable to meet regulatory requirements, which resulted in delayed drug commercialization. This resulted in loss of revenue for manufacturers. EDC systems help curb this problem by capturing & managing the clinical information in a simple way."[5]

The Pros

Yes, data can be transmitted to the sponsor quickly, without having to wait for CRA review before it is received by data management. Automated validity checks can be run while the data are being entered, so that the coordinator is "not allowed" to make some kinds of errors, such as out-of-range entries or missing data. In fact, it has been shown that there is a dramatic drop in these kinds of errors when EDC is used, as compared to using paper CRFs.[6] Additional automated validity checks can be run by the sponsor immediately upon receipt of the data, and queries can be sent to the site in a timely manner.

The management of queries will also change significantly, since all outstanding queries and edit-check resolutions in an EDC trial can be handled electronically, without the need of paper. Queries can often be resolved in minutes, assuming the site can be online to work with the data manager, instead of needing weeks to send paper copies back and forth to clarify site or sponsor questions. With this data entry and query model, the data manager, remote monitor and the CRA share responsibility for timely data review and correction.

When using EDC, error patterns can be looked at more easily across all sites, which can help define protocol problems, CRF problems or common misunderstandings that pinpoint the need for further training or revisions in study procedures. Catching problems early can greatly enhance study quality.

With EDC, the CRA can review the actual data, including queries, in-house or remotely before making a monitoring visit, so that he or she will be more knowledgeable about any study problems upon arrival at the site. When initial data review is done in-house, the CRA does not have to do it at the site, which allows more time for verifying the data (source document review), training and performing other study management activities. With the emerging role of the remote monitor, remote review of a site's EDC occurs more frequently. It can also increase data quality and data collection/transmission timelines, and can help meet any study data deadlines with additional data review, communication and query resolution with the sites by the remote monitor.

If study data are cleaned as the study progresses, EDC can minimize the time between the last data being transmitted and a clean database. An earlier database lock allows the final report to be written sooner.

The Cons

There are also, of course, some downsides to new technologies.

It takes a large amount of upfront time to design a good EDC system, and a badly designed system can cause significant problems throughout the project. Early systems were often not user-friendly and could not guarantee data integrity. Many of these early systems failed in other ways as well, which is part of the reason it took so many years for EDC to become accepted as a valid part of clinical trials.

All the planning and implementation for an EDC system has to be done before enrollment of the first study subject. This includes the data entry screens, online edit-check specifications and the annotated CRF. Although certainly not recommended, sometimes in a paper-based CRF trial some of these tasks can be delayed until after the trial is underway. Also, as per Mitchel et al., "there must be upfront and full integration in the design of the trial with clinical research, data management and biostatistics to assure that the data entry process is user-friendly for the clinical sites and that the exported database structure is compatible with the planned statistical analysis."[7] Also, with EDC there is not always a paper trail to follow, so computer system failure could be a disaster when it comes to retrieving the data. This is an issue that needs to be addressed when the system is being planned.

If EDC requires a computer at each investigative site, these are usually provided by the sponsor. However, there can be logistical challenges, such as access to a secure space to keep and use them. Another problem, though rare, is the use of internet-based EDC systems; sites have to have access to the internet to utilize these types of EDC systems. This would be more of an issue with clinical trials in developing countries as opposed to the U.S., where

internet access at sites is part of normal operational process.

Determining who is responsible for EDC data entry is another issue. It is usually the clinical research coordinator (CRC) at the site, although sometimes data entry is done by the CRA. It is often difficult for a CRC to find the time for data entry, given all the other tasks for which he or she is responsible. Occasionally a site, especially a larger site, may have a data-entry person for this task, but if this person is not medically trained and is not familiar with the study, this is problematic. Sometimes the sheer number of trials at one site, with different EDC systems for each, makes it difficult to keep everything straight and organized.

Subject confidentiality can also be an issue. Good EDC systems will have strict security measures in place that limit access and use of the system, as well as secure ways of transferring data between the site and the sponsor.

Another issue that can cause problems is that when using EDC, there needs to be significantly more coordination between CRAs and data managers. Working out the roles and responsibilities before the study begins will help things go more smoothly, as will regular communication among all parties throughout the study.

Electronic Patient-Recorded Outcomes, Questionnaires, Diaries and Assessments:

There have been numerous references to "technology-driven data collection" in this guidebook update, and for good reason. The entire clinical trials industry has been impacted by computers and the internet; the landscape will evolve with the introduction of innovative new technologies that drive and improve process for data collection.

PROs and Assessments have been heavily influenced by technology—electronic patient diaries, Interactive Voice Response (IVR)/telephone systems—to report subject symptoms, drug compliance or pain, electronic patient questionnaires, clinician-administered rating scales or cognitive testing. Delivery systems used include tablets, computers or mobile devices for patients to record study drug receipt, accountability and answer questions/report symptoms. Wearable devices may be used by study patients to report/record data—pedometer or electronic technologies integrated into clothing or accessories. Below are examples of digital or electronic means of recording and reporting patient data from the subject and clinician perspective.

Study Subjects:

- Patients call in to an IVR system that uses key pad or voice prompts for patients to answer questions about symptoms or medication compliance.
- Mobile device or tablets for subjects to enter symptom information, medication compliance information or to answer quality-of-life or disease-related questions.

- Mobile devices to track and record study drug shipments or device shipments that go directly to a study patient's residence.
- Wearable devices that record physiologic data (walking, blood pressure, heart rate, sleep patterns).

Study Clinicians:

- Clinicians are able to administer study cognitive or rating scales to study patients via web conferencing, computer systems or computer tablets.

The advantages of electronic recording and reporting of data are numerous:

- Sponsor-provided equipment ensures consistent collection, evaluation and validation of data.
- System-generated queries for incomplete or untimely data entry are available.
- Electronically-generated patient reminders to call in for data reporting or data entry at specific time points.
- Investigator and site staff afforded real-time access to data reports and entry by patients.

There are disadvantages:

- Site staff require training on electronic devices and systems, which requires time and additional cost.
- Site staff, in turn, have to train study subjects on the use of electronic devices and systems, which also requires time and additional cost.
- Sites have to store equipment provided by sponsors for this purpose, and sites that conduct multiple sponsor studies with a variety of electronic equipment need additional space to store it.
- Some study subjects or clinicians are not tech savvy and are resistant to the use of electronic devices in lieu of paper.
- Study subjects lose or do not return tablets or study devices.
- Issues with device entry, uploading or reporting data, or with internet access can impede study data collection.

In Applied Clinical Trials' October 2015 blog, author Chris Watson, discusses some relevant benefits for more efficient data collection and the facilitation of confidentiality and patient engagement via ePROs:

> *Incorporating mobile electronic clinical outcome assessments (eCOA) into clinical studies has a myriad of benefits. Native apps facilitate*

the collection of objective data from medical devices (e.g. spirometers and glucometers) and wearable technology such as activity trackers alongside patient diaries. Data from these devices can be transmitted directly into an app via Bluetooth, removing the requirement for transcribing results manually. Furthermore, date and time stamps for each data point can be captured from a patient source through to an EDC database, and fraud can be eliminated by introducing two-factor authentication. Mobile eCOA has another practical advantage, which is to provide more efficient patient engagement. A patient who has missed diary completions can be reminded of the importance of taking part in the study, and should it not improve future ePRO compliance rates, sites can follow up immediately. Site staff can discuss any difficulties or misunderstandings with patients and provide additional timely education and support to enable continuation in the study before they are lost.[8]

The author noted that, "The rapid evolution of this technology combined with patient-centric data generation provides cost effective options for drug development. On the other hand, reliability and validation of devices and data, privacy concerns and regulatory acceptance are slowing the integration of these valuable tools as novel endpoints into clinical trials. Despite that, wearable devices and smart technology are transforming the drug development process."

Summary

Writing good protocols and developing appropriate CRFs are the backbone of study preparation. Being familiar with all means of electronic data recording and reporting are essential for CRAs in this modern age. Completion of these activities will help to ensure the success of the trial. Since CRAs work with these things at every investigative site they monitor, they should have a good understanding of the issues and processes involved.

Key Takeaways

Protocol

- The protocol is the blueprint for a study. It contains all the information necessary to conduct the study correctly.
- CRAs must have a thorough understanding of the protocol for each study they monitor.
- The writing of a protocol is usually a team effort, involving the medical monitor, the statistician and others.

- Protocols for phase I studies are relatively flexible, while those for phases II and III are more rigid and detailed.
- Certain information is required by regulation to be in protocols.
- As protocol complexity increases, there is a cost to the sponsor (and to the sites) in terms of both time and money.
- Amendments to protocols are very costly in terms of both time and money.
- Care should be taken to avoid amendments whenever possible.

Case Report Forms

- CRFs have a significant impact on data quality.
- Standardize and use modules as much as possible.
- Shading, aligning and limiting the number of fields per page can reduce errors.
- Remember that the investigative site is the customer for your CRFs. Design them with the site in mind. Make them medically and clinically sensible.
- Continually improve your forms by noting good and bad design features.

Electronic Data Capture

- EDC can significantly reduce errors, cut the time for sponsor receipt and management of the data and greatly lessen the time between the last subject's last study visit and the "lock" of the clean database.
- It takes a large amount of upfront time to design a good EDC system.
- It takes a significant amount of experience and knowledge to design a good EDC system.
- CRAs, data managers and study coordinators at the site all share responsibility for data quality when EDC or electronic devices for PROs are used.

Electronic Patient-Reported Outcomes

- The use of ePROs is being integrated more and more into clinical trials, though there still may be some regulatory, data privacy and device reliability challenges to overcome.

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CHAPTER TWELVE

Clinical Investigators

The conduct of studies of investigative sites is the responsibility of the investigator. In the first part of this chapter, investigators and their responsibilities are covered. In the second part, the evaluation and selection of investigators and investigative sites is discussed. How a CRA can help investigators meet their responsibilities during clinical trials will be discussed in subsequent chapters.

Investigators and Their Responsibilities

What is an "Investigator"?

According to the regulations (21 CFR 312.3), investigator means "an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the investigational drug is administered or dispensed to a subject). In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team." Sometimes the investigator is called the principal, or primary, investigator (PI). Other members of the team may be referred to as Sub-Investigators, especially in the case of other physicians who are involved with the study. On occasion, there will be co-investigators for a trial. In this case, both individuals are equally responsible for the trial.

Usually, but not always, the investigator is a physician. Sometimes, a person with a Pharm.D. or a Ph.D. degree may serve as an investigator; in that case, there should be (at least for FDA-controlled studies) a physician as a Sub-Investigator.

With primary care and specialty physician practices (at public and private healthcare organizations) incorporating the services of mid-level prac-

titioners such as Physician's Assistants (PA) or Nurse Practitioners (NP) into the patient treatment dynamic, it has become more common and acceptable for PAs and NPs to also serve as Sub-Investigators on clinical trials. There are several scenarios. A PI may have several Sub-Investigators under his or her oversight; a combination of physicians, NPs and PAs. Alternatively, the physician PI may only have one Sub-Investigator, either a NP or PA, without another physician Sub-Investigator. The setup is dependent upon investigational site model, institutional requirements, clinician scope of practice and sponsor approval.

Some sponsors approve the use of an NP or PA as a Sub-Investigator, provided there is also another physician Sub-Investigator supporting the PI's effort. Other sponsors approve a sole NP or PA as a Sub-Investigator under the PI, without the need for another physician Sub-Investigator. Some PIs will utilize the NP or PA Sub-Investigator for responsibilities such as cognitive assessments or physical exams, provided they have appropriate training and experience. Other PIs will use the NP or PA Sub-Investigator for a broader scope of responsibilities; laboratory or ECG results review, confirmation and documentation of study eligibility criteria, adverse event causality, etc. Again, it depends on institution and sponsor requirements.

No matter the dynamic, the CRA must confirm that the PI is providing adequate oversight of responsibilities delegated to Sub-Investigators.

Regular communication must occur between the PI and Sub-Investigators to ensure the PI remains apprised and aware of subject status and treatment by Sub-Investigators. Some investigational sites will have weekly or bi-weekly meetings between the PI, Sub-Investigators and study coordinators to discuss subjects' status, and other important study topics. This is a formal meeting at regular intervals, often with documented meeting minutes taken. Other sites have informal communication practices between the PI, Sub-Investigators and study coordinators, such as in a smaller clinical trials practice where the PI, Sub-Investigators and study coordinators work the same days or see each other consistently. Both examples of communication practices are acceptable, provided they are consistent. When there is a communication breakdown between the PI, Sub-Investigators and the study coordinator, the impact on study conduct can be detrimental.

The Statement of Investigator Form (FDA Form 1572)

The Statement of Investigator Form (FDA Form 1572) must be completed and signed by the investigator before he or she may begin a study. The investigator then sends it to the sponsor, and the sponsor submits it to the FDA. A copy of this form is in Appendix G.

The 1572 form contains:

- Name and address of the investigator.
- Title (and number, if any) of the protocol, including the IND number.

- Name and address of the facility where the research will be conducted.
- Name and address of any clinical laboratories that will be used.
- Name and address of the IRB used to approve the study.
- Names of any Sub-Investigators who will be associated with the study.
- Investigator commitment section (discussed below).

There is also a section of the 1572 that lists responsibilities of investigators. These include a commitment by the investigator that he or she will:

- Conduct the study according to the protocol.
- Comply with the regulations.
- Personally conduct or supervise the trial.
- Ensure the IRB complies with regulations.
- Obtain informed consent from subjects.
- Report adverse events properly.
- Read and understand the material in the Investigator Brochure before starting the trial.
- Assure that other people assisting in the trial are aware of their obligations.
- Maintain adequate and accurate records.

When the investigator signs the 1572 form, a legally binding commitment has been made to conduct a study according to the regulations and constraints of the 1572. CRAs should be very familiar with the 1572 form and should be prepared to discuss the commitments in depth (section 9, investigator commitments) with potential investigators, as applicable, during monitoring visits. CRAs will also need to assure that these forms are properly completed, and signed and dated by the investigator before a study commences.

For device studies, the 1572 is not used. Instead, a sponsor must obtain a signed agreement from each investigator that includes the following, as per 21 CFR 816.43:

- The investigator's curriculum vitae (CV).
- A statement of the investigator's relevant experience.
- If the investigator was involved in an investigation or other research that was terminated, an explanation of the circumstances that led to termination.
- A statement of the investigator's commitment to:
  - Conduct the investigation in accordance with the agreement, the

investigational plan, the applicable regulations and the conditions of approval imposed by the IRB.

- Supervise all testing of the device in humans.
- Ensure that the requirements for obtaining informed consent were met.

- Financial disclosure information.

Investigator Responsibilities

The investigator has the ultimate responsibility for the safety of participants in a clinical trial. Research participants are under the immediate care of the investigator and subject to the judgment and professional abilities of the investigator. For this reason investigators must be qualified through training and experience before beginning to study a drug or device.

The general responsibilities of an investigator during a trial include ensuring that the trial is conducted according to the signed investigator statement (FDA Form 1572), following the protocol and regulations, and protecting the rights, safety and welfare of subjects in the trial. In the next sections, we will discuss some of the other specific responsibilities of an investigator during a trial.

Control of the Investigational Drug

One of the important responsibilities of an investigator is maintaining control of the investigational drug at all times. The drug may not be used by anyone other than trial subjects, who are under the supervision of the investigator or Sub-Investigators. Remember that the investigator has responsibility for any Sub-Investigators assisting in the trial.

If the investigational drug is a controlled substance, then the drug must be stored in a locked area with limited access. This is a good idea for the storage of all investigational drugs, when possible, as it eliminates potential problems. When not controlled properly, there is a risk of study drugs being used for patients who are not in the trial, or being used by other physicians for non-trial purposes. Losing track of the study drug supply can be a major problem and have a negative effect on the trial.

The CRA will want to ensure that the study drug is properly stored at an investigational site and that provisions have been made to properly administer and account for the drug.

Investigator Recordkeeping and Retention

An investigator must maintain case histories of all subjects and data collected during a trial. These case histories include the case report forms and all supporting documents such as patient charts and progress notes, signed and dated consent forms, laboratory reports, EKGs and any other relevant patient-related documents. The histories must show that the consent form

for each subject was signed and dated prior to participation in the study.

The investigator must also maintain complete records of the dispensing and disposition of the study drug, including dates, quantities, use by study subjects and amounts returned.

All study documents must also be maintained and retained, including copies of the signed 1572, the protocol and consent forms, the IRB approval letters, CVs for the investigator and Sub-Investigators, laboratory normal ranges and correspondence with the IRB and the sponsor. A complete listing of this documentation is found in Appendix C.

All of these records must be maintained for a period of two years after the approval of the drug for marketing, or two years after the investigation is closed and the FDA is notified that the company is not pursuing further investigation of the drug. In reality, most sponsors expect the investigator to maintain the records for a much longer period, if not indefinitely. Most contracts between the sponsor and investigators require the investigator to retain all study documents until the sponsor has informed the investigator in writing that they may be destroyed. Although this is discussed in more detail in another chapter, the CRA should make it very clear to the investigator that the records must be kept until written notification is received from the sponsor that they may be disposed of.

Investigator Reports

There are reports that the investigator must provide to the sponsor throughout the duration of the trial. They include regular progress reports, which usually consist of the completed case report forms, plus periodic updates on enrollment and study status. Safety reports must also be furnished to the sponsor, including reports on any adverse events that may reasonably be regarded as having been caused by the study medication. Serious adverse events, those that are immediately life threatening, or deaths must be reported to sponsors immediately. A final report must be provided to the sponsor shortly after completion of the study. These reports are necessary to allow the sponsor to meet the regulatory requirements for reporting study progress to the FDA.

IRB Review

The investigator is responsible for assuring that the IRB he or she is using for the study meets the requirements for IRBs found in 21 CFR 56. The investigator must submit and wait for approval of a protocol and informed consent form before beginning a study, as well as promptly reporting to the IRB any changes in the protocol or any unanticipated problems involving risk to study subjects or others. The responsibilities of the investigator with respect to the IRB were delineated in detail in Chapter 8.

Disqualification of Investigators

Investigators who do not comply with the regulations governing clinical research, or who falsify data in the investigation or reports to the sponsor and/

or the FDA, may be disqualified from receiving investigational drugs and doing studies in the future. The FDA maintains a list of restricted and disqualified investigators, known in the business as the "black list." This list is available on the FDA website (fda.gov). Once an investigator is put on the list the name stays there forever, even if all conditions for reinstatement are met and the investigator is allowed to do research again. Most sponsor companies will not use an investigator who is on this list, even if the person has been reinstated to do research. More information on this topic is included in Chapter 19. CRAs should always check the "black list" before contacting a potential investigator. There is also a listing of all investigators who have been audited by the FDA with one of three classifications:

- **No Action Indicated (NAI)** – no significant objectionable conditions or practices found;
- **Voluntary Action Indicated (VAI)** – insignificant objectionable conditions or practices found that do not require enforcement but that the FDA expects the investigator to remedy voluntarily;
- **Official Action Indicated (OAI)** – objectionable conditions or practices found are significant enough to warrant FDA enforcement action.

In summary, investigators have enormous responsibility when they agree to participate in clinical research. A good investigator will enable the research to proceed smoothly, while a study conducted by a poor investigator most likely will be fraught with problems. Consequently, the selection of investigators is a crucial element of the research process.

Evaluating and Selecting Investigators

One of the most important tasks that CRAs undertake is the evaluation and selection of investigators. The success of a study depends in large part on the investigator—his or her experience, expertise, commitment, staff, resources and facilities. In this section we will discuss the qualities of a good investigator/investigative site and how a CRA can locate and evaluate sites for successful studies.

A tale of two investigators

Pre-study evaluation visits are important because they allow investigative sites to showcase their capabilities: staff experience, recruitment prowess, facilities/equipment. The CRA and the investigative site theoretically need something from the other; the investigational site wants to be selected for the study and the CRA conducting the evaluation visit wants to select a strong, compliant site for the study. This reciprocal need usually dictates behavior on behalf of vested parties. Most investigational sites are courteous and accommodating during site evaluation visits, and the CRA conducting the visit maintains a profes-

sional and friendly demeanor throughout the process. Relationship development is a large part of this process. The resulting camaraderie between the investigator and CRA, initiated during the site selection process, will benefit the site management relationship during study conduct, just as unprofessional behavior during an evaluation visit will contribute to a negative perception of the site by the CRA or the CRA by the investigator.

One week, I was tasked to conduct two pre-study evaluation visits and there was an incredible disparity between the clinical and personal dynamic at each institution. At the first potential site, the study coordinator was extremely business-like and informed me that the investigator did not care for small talk. We spent the entire pre-study visit without ancillary chitchat; I made the mistake of asking the investigator if he was from the area and was informed in no uncertain terms that the "evaluation visit was not the place for personal chatter." That disappointed me, for though the site had the physical capabilities and staff experience for study conduct, the lack of positive communication would create a challenging dynamic for the CRA taking over the site and trying to build a partnership with the investigator.

The next day, I visited the second investigational site and the differences were startling. They had the facility and experience required for study conduct and provided comprehensive answers to my questions. The level of courtesy and positive communication demonstrated by the investigator and staff, at the start of the process, set the precedent for a visit where dialogue flowed, information was exchanged and feedback was obtained without effort. Their demeanor confirmed their enthusiasm not just to work successfully with me through the evaluation visit, but gave insights into their willingness to work well with the monitor for their study.

A slight shift from a clinical to a personable attitude can have a huge impact on the site evaluation process.

—Elizabeth

Types of Investigative Sites

There are many types of investigative sites conducting studies. It is useful for a CRA to have an understanding of these different organizations when looking for and assessing potential sites for study placement. Some of the more common investigator site organizational types are listed below.

Part-Time Sites

Investigators at part-time sites participate in research studies, but also maintain their regular practices. Sometimes these investigators do only one or two studies at a time, while others may participate in research to a greater degree,

depending on their interest and their resources for conducting studies. Most sponsors like this kind of site because there is greater potential for study subjects and because the physician, if chosen, will become familiar with the drug. By the time it is marketed, he or she will be more likely to prescribe it to patients.

As a CRA, this type of site has both advantages and disadvantages. Because the site may not be as experienced, the CRA can train the site to do things in the way the sponsor would like them to be done, without having to "untrain" or change the way the site is used to doing things. On the other hand, since these sites may have less experience, they may need more training and "hand-holding" throughout the study.

Dedicated Sites

These sites are dedicated specifically to conducting studies; no other medical practice is carried out. They generally are very experienced and need less help from the CRA in learning how to do studies, although they may still need instruction in how to do each particular study, with its unique characteristics. These sites are usually very productive. They also tend to be very aware of which studies they can do successfully and are less apt to accept studies for which they do not think they can enroll sufficient subjects within the given time period. These sites mitigate risk of potential staff turnover by developing guidelines/SOPs that govern research conduct at their facility. This ensures consistency in study conduct and new staff assuming study responsibilities. SOPs cover such tasks as training, consent form creation and administration, study drug storage and administration, source creation and storage and adverse event reporting. Concerns are sometimes expressed about these sites being "study mills" and having "professional study subjects," but, as long as they are not in violation of the protocol, this does not seem to be a problem.

For the CRA, these sites are usually easy to manage. Since they rely on studies for their business, they are usually accommodating as well as compliant.

Academic Sites

Academic sites are those located in universities and teaching hospitals. They tend to do original research on their own and government-sponsored clinical trials, as well as industry-sponsored clinical trials. Often these organizations are headed by "thought leaders," the top specialists in their fields. Clinical trials may or may not be the academic site's primary interest, although in the past few years sponsors have been using academic sites more frequently. Occasionally, industry trials provide added funding to allow these sites to carry on other research. It is desirable for a sponsor to use some academic sites in its development programs. This allows thought leaders to become familiar with the new compounds and, hopefully, to become spokespersons in favor of the compound once it is marketed.

Unfortunately, these sites can present some difficulties for a CRA. It can be difficult for the CRA to meet with the busy investigator; these investigators have been labeled "phantom investigators" because they never seem to be around during the trial. It can also be difficult if industry-sponsored research is not the primary interest of the site, in which case enrollment may wane and study activities may not receive proper attention. Be aware that investigators at academic sites may deviate from the protocol due to their curiosity about where the research will lead them. Also, because publishing is a key issue at academic sites, sponsor policies regarding publication of the trial results should be clearly delineated prior to the initiation of the study. That being said, there are many excellent academic sites with dedicated researchers who add an extra dimension to clinical development programs.

Site Management Organizations (SMOs)

SMOs bring together a group of sites and organize them centrally to conduct studies. They standardize procedures across sites and often provide standardized materials (SOPs, study file procedures, etc.) to each site in the organization. Many SMOs also provide training for their sites and assist the sites in compiling and submitting the required regulatory documents. They usually provide centralized services for marketing the sites (attracting studies) and for subject recruitment. There are several types of SMOs, from those that own the sites in the group to those with other partnership agreements.

The main difference for a CRA when using an SMO is that control over study processes may not reside at the site, but may be handled centrally. If the CRA is working with only one site in the SMO, this can cause a bit of difficulty, as it requires dealing with several different individuals at more than one location, for that one site; regulatory, contract and budget staff are located at the SMO, and the site clinical and research process is handled by the study coordinators at the investigational site. It may be advantageous if working with multiple sites in the SMO because of the consistency of study practices.

A variation of an SMO is the Coordinator Organization. This is usually a group of experienced study coordinators who have formed a business. They recruit investigators to conduct trials and then place an experienced coordinator in the investigator's office to manage and help with the trial. These coordinators usually act as the interface with the sponsor/CRO and manage the operational aspects of the trial; the physician is utilized for his or her medical expertise and patient base. The only difference for the CRA is that the coordinator is the main contact for all business aspects of the trial, including grant payments. (Note that the investigator is usually paid a fee by the coordinator organization.)

Regardless of how the physician's research practice is organized, the CRA must still monitor and manage the trial for the safety of the subjects and the integrity of the data.

More and more physicians are interested in entering clinical research and conducting drug studies. However, there is more to the process than find-

ing the appropriate space and experienced study coordinators. Investigators must first decide what they would like to do: start a research site, integrate a research department into their private practice or affiliate with a dedicated research site as a principal investigator.

There are some critical elements required to establish a physician as a principal investigator, and/or to start a research site or research department, as noted below. These are non-inclusive, generalized guidances:

- Principal Investigator and Sub-Investigator credentials, specialty, training and experience
- Appropriate funding
- Key staff for contract, budget and regulatory activities, business development/recruitment staff for attracting studies and recruiting patients, administrative staff, clinical staff for study coordination and clinical activities/testing (vitals, phlebotomy, specimen processing and shipment, spirometry, etc.), appropriate location for patient examination, lab/imaging/specialized testing and space for staff, etc.
- Documented research process and infrastructure such as ICF SOPs, drug accountability and pharmacy SOPs, training checklists, job descriptions, departmental meetings and plans

There are many more applicable details to this process, but this is just a generalized summary.

Locating Potential Investigators

There are a number of ways to locate potential investigators. One of the best ways is to ask other people in your company for suggestions. In large sponsor companies, people working in one medical group may not be aware of good potential investigators who are, or have been, used by another medical group. Some companies keep a database of their investigators; if your company has such a database, it is the best place to start identifying potential investigators for your trial. An investigator database is especially valuable if it collects such metrics as enrollment rates and numbers, timelines of data submission and error rates on CRFs. If your company does not have an investigator database, ask for suggestions from other therapeutic groups. (See Chapter 18 for examples of site metrics.)

Another excellent way to find good investigators is to ask investigators you know and/or with whom you are currently working. "Dr. Smith, you've been doing a terrific job on this rheumatology study. I have some cardiovascular studies coming along soon. Do you know any physicians who might do as good a job on those studies as you are doing on this one?" If your investigator has some suggestions for you, he or she may be willing to call the other physician as an introduction for you. Some CRAs have had great success using this technique.

There are websites that list investigators and their areas of specialty. These sites will give you names and contact information by region and specialty and make it fairly easy to start a list of people to contact. There are references to some of these websites in Appendix A.

Another successful method is to network with colleagues from other companies. Ask colleagues if they have worked with anyone in the therapeutic area in which you are interested who did competent work for them in the past. This is often a very useful method, but be sure to reciprocate when you can. Other potential methods for locating investigators are:

- Look in medical journals for articles dealing with the therapeutic area in which you are interested and contact authors of relevant articles.
- Look at regulatory submissions from other companies working in the same therapeutic area and contact the investigators they used.
- Contact professional organizations that may have listings of physicians.
- Contact patient advocacy groups that may keep lists of investigators.

Once you have collected a list of potential investigators for your program, you will want to contact them.

Initial Contact

If you or anyone in your company has had no previous experience with a potential investigator, a telephone call is probably the best initial contact. Try to call the physician directly, rather than leaving messages with staff. When you call, if you say only that you are from a pharmaceutical company, the person answering the phone may think you are a salesperson, and you are apt to have a difficult time reaching the physician. You might say you are from the "research division of the XXX company," and that you are interested in talking with Dr. Smith "about becoming involved in research studies." If you still encounter some difficulty, you may want to tell the person that you are not in sales. If you have too much trouble trying to get through, call the next person on your list and forget this one—if he or she is that hard to reach, you'll probably always have trouble with direct contact.

Once you reach the physician, introduce yourself and say why you are calling. If the physician appears to be interested, give a brief overview of the program and the study to be done. Find out if the physician has research experience and, if so, the types of projects he or she has worked on in the past or is working on currently. Ask questions about the patient population, the staff and the facilities.

If interest is high on the part of the potential investigator, and if you feel there is good potential for placing a study at the site, arrange a time to visit the site in person. This will enable you to better evaluate the investigator's capability to complete your project. Depending on your company policies,

you may be able to send the potential investigator some materials about your drug and/or program, such as a protocol or a protocol summary, before you visit. If your company requires a signed confidentiality agreement before sharing these materials, arrange to fax/email it to the site and have it completed and returned before sending any other materials. One clue to the interest of the investigator is the speed with which the signed confidentiality agreement is returned to you.

A number of sponsor companies delegate trial responsibilities to CROs, which include study startup responsibilities such as feasibility and investigator identification/evaluation. Feasibility encompasses initial investigator vetting and contact for the purposes of obtaining investigator/site experience and site capability information. Feasibility has become such an integral part of the study startup process, that there are entire departments dedicated to investigator identification and feasibility services. Initial investigator identification, correspondence and provision of information has become a streamlined, sophisticated process that is completed via the use of online standardized investigator questionnaires with which to capture site capability information. Feasibility departments have investigator information stored in dedicated databases and reports can be accessed to assist with identification and initial evaluation of investigative sites. This dedicated dynamic has shortened the investigator identification and evaluation timelines by streamlining process and harmonizing data collection.

After investigator information has been received and confirmed, the investigator is deemed ready for the official evaluation visit. Best practices dictate that the CRA sends an email or letter to the investigator to confirm the date and time of their visit to the site.

Site Evaluation Visits

When the CRA makes an evaluation visit to a potential investigative site, the CRA will be evaluating the investigator's experience, expertise and interest in the trial, as well as the staff, facility and potential patient population available. The sponsor company may have a specific checklist that will guide the CRA in making an assessment. The advantage of using a checklist is that the CRA won't inadvertently forget to assess some important items. A sample site evaluation checklist is found in Appendix C.

The CRA should have a good understanding of the study requirements, the schedule of assessments, preliminary protocol design, patient eligibility and logistical requirements to be able to have a sound discussion on study requirements and investigator recruitment capabilities with the investigator and staff. At the very least the CRA should discuss following the protocol components: Trial design, inclusion/exclusion criteria, safety reporting, patient population, study endpoints, critical testing/procedures, investigator availability, specialized testing/vendors/schedule of assessments, study drug, investigator access to the study population and investigator commitments. It is optimal if the PI and study coordinator are present for this discussion.

Investigators and their staff are understandably busy with unforeseen schedule changes, and a CRA needs to be flexible and ready to discuss the study with the PI with little notice. This may be in an exam room or the study coordinator's office. However it is imperative to remember confidentiality and never discuss the study design in front of another CRA or staff not covered by a confidentiality agreement. Ask if the meeting can be moved to another location with privacy, such as the investigator's office or an empty area.

Investigator Experience, Expertise and Interest

The investigator's CV will help you make a general assessment of the investigator's experience and expertise. Reviewing the feasibility information (listing details of the investigator and site study experience, access to the population for enrollment and information on site equipment for study conduct) prior to the evaluation visit will give you specific details to review or questions to confirm with the investigator during the site evaluation visit. Conversing with the investigator in person will allow you to determine his or her research activity, especially in the therapeutic area of interest. This is a good time to determine if the investigator has conducted trials similar to the one being proposed or has worked with similar compounds. This is also a good time to determine if the investigator's research experience matches his CV and if the study experience on the CV is as a PI or Sub-Investigator. Sometimes investigational sites will present a potential PI without research experience, which is not clear from the CV. Investigator experience is critical to clarify during the evaluation visit.

A physician new to research should not be immediately disqualified for consideration as a PI. There are many variables to consider with new investigators/sites, such as research/investigator training completed and preparation for the site evaluation visit, study design and therapeutic area.

If the study is a simpler, phase III design for a chronic disease such as type 2 diabetes or hypertension, using a new investigator with expertise in the therapeutic indication and access to a large population, may be appropriate in lieu of research experience. When taken into consideration during site evaluation, confirm any training the investigator has completed to learn his role (GCP training, web-based investigator training modules). Confirm if the investigator has access to another experienced investigator to provide guidance during the first subject's screening and randomization visits. Ensure the new investigator has an experienced study coordinator. There are several variables that may make an inexperienced investigator a viable candidate for study consideration. The CRA should never apply a broad stroke categorization of new investigators. Rather, each site, experienced or not, is considered on a case-by-case basis.

While listening to the prospective investigator answer your questions, be aware of any nonverbal clues being conveyed. Is the investigator actively listening to you? Asking pertinent questions? Being attentive to the conversation and materials? If an investigator professes great interest in conducting

a study but is also replying to his email during the meeting, obviously his interest level isn't very high. One of the most critical factors for the success of a study is the interest of the investigator. If the investigator isn't truly interested, the study won't be foremost in his or her mind and will probably suffer because of it.

The CRA should also try to determine the investigator's commitment to actually participating in the trial, as opposed to delegating all the responsibility to others and being an investigator in name only. These absent investigators are referred to as "phantom" investigators—they assign the study activities to Sub-Investigators and study coordinators and have very little, if any, personal involvement in the trial. This is unacceptable. When an investigator signs a 1572 form, the investigator commits to personally conduct or supervise the trial or, for devices, to supervise all testing of the device in humans. This is a legal responsibility and cannot be taken lightly. Some specific questions to cover with investigator/site staff during the evaluation visit, to better determine investigator involvement and oversight, are listed below:

- How many studies is the PI currently conducting?
- What percentage of study subjects will the PI treat compared to the Sub-Investigators?
- What days of the week/hours is the PI on site and treating study subjects?

Answers to these questions will serve as a strong indicator of investigator commitment and oversight, and will contribute to the decision of investigator selection.

There are situations that mandate that study subject care be divided between the PI and his Sub-Investigators. One common situation where this occurs is when the investigator is part of a large practice with all physicians affiliated with the practice serving as Sub-Investigators. Each PI would be enrolling potential study subjects from his or her respective practice and would be the treating physician to the subjects they enrolled to ensure continuity of care and subject engagement. This is a scenario where the PI would not see the majority of the subjects, but where subject treatment would be divided between the PI and Sub-Investigators. As long as the PI ensures oversight by discussing study subjects with the Sub-Investigators, remains involved and aware of any SAEs and critical safety issues, and assures his or her commitments in accordance with section 9 of the 1572, then this is acceptable.

The CRA will also want to assess the investigator's reactions to the protocol. Is there anything in the protocol that the physician objects to doing? Is the investigator willing to follow the protocol as it is written? Is the physician comfortable with the study design and the use of a placebo, if applicable? Does the protocol match his or her clinical practice, except for study-specific parameters? Making assumptions that everything is acceptable without checking is a risky path to follow—it's better to find out about potential problems and conflicts before the study is offered to him or her.

This is also a good time to review the following differences between clinical practice and clinical research with the investigator. This is particularly important if he or she is new or relatively inexperienced. Failure to understand these differences can lead to protocol violations, which could have a serious impact on the quality of the study or lead to its termination. Some of these differences are:

- During a clinical trial, the definitions used for adverse events are regulatory definitions and are not necessarily based on usual clinical observation (See Chapter 15 on adverse event reporting).
- Concomitant medications that would normally be prescribed for the subject may not be allowed by the protocol or, if allowed, the dose and regimen may differ from standard practice.
- The protocol treatment period for the disease being studied may differ from normal medical practice. It could be longer or shorter and is apt to involve more frequent visits.
- If the study is placebo-controlled, the investigator must be comfortable using placebo in subjects with the condition being studied.

Sub-Investigators

A section on the 1572 form requires the listing of all Sub-Investigators who will be involved in the study, and there have always been questions about who should be listed. In May 2010, the FDA issued a new final guidance document titled, "Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs: Frequently Asked Questions—Statement of Investigator (Form FDA 1572)". This question is discussed in this document.

The guidance states that:

> *The purpose of Section #6 is to capture information about individuals who, as part of an investigative team, will assist the investigator and make a direct and significant contribution to the data. The decision to list an individual in Section #6 depends on his/her level of responsibility (i.e., whether he or she is performing significant clinical investigation-related duties). In general, if an individual is directly involved in the performance of procedures required by the protocol and the collection of data, that person should be listed on the 1572. For example, if the protocol notes that each subject needs to visit a specified internist who will perform a full physical to qualify subjects for the clinical investigation, that internist should be listed in Section #6.*

It goes on to say:

> *Hospital staff, including nurses, residents or fellows, and office staff who provide ancillary or intermittent care but who do not make a direct and significant contribution to the clinical data, do not need to be*

listed individually. It is not necessary to include in this section a person with only an occasional role in the conduct of the research, e.g., an on-call physician who temporarily dealt with a possible adverse effect or a temporary substitute for any research staff.

Different sponsors and sites have had differing opinions on whether the study coordinator should be included as a sub-investigator on the 1572. The guidance document addresses this issue directly. It states:

Generally, a research coordinator has a greater role in performing critical study functions and making direct and significant contributions to the data. For example, a research coordinator often recruits subjects, collects and evaluates study data and maintains study records. Therefore, the research coordinator should usually be listed in Section #6 of the 1572.

Staff and Facility

It is not enough for an investigator to want to do a study; sufficient staff and an appropriate facility are also necessary for success.

It is not a good idea to place a study at an investigative site that does not have a research coordinator (also called a study coordinator). The research coordinator is essential for the administration of the study; he or she coordinates patient enrollment and visits, manages the study documentation, completes the CRFs and is the primary contact for the CRA throughout the study. The CRA will want to meet and spend some time interviewing the research coordinator during the evaluation visit. If the trial calls for other specialized site personnel (a dietician or pharmacist, for example), then the CRA should ask about these people during the evaluation visit. Is the staff experienced in conducting clinical trials? Some questions to ask investigational site staff during the evaluation visit, to determine clinical research experience include:

- How many years of experience in clinical research?
- How many years of experience in the therapeutic indication under study?
- Specific questions regarding staff educational background or medical training.
- How long have investigational site staff worked at the site?

These questions will help confirm that investigational staff proposed for the study have the appropriate experience and training to conduct the study successfully.

And don't forget to ask about turnover among the staff.

Not only must there be appropriate people available for a study, but they must have sufficient time to do the necessary work. On occasion, an investigator may assure the CRA that there are plenty of people to do the work, but when the CRA talks with the research coordinator, it is apparent that

there is already too much work and that adding an additional study would severely compromise the abilities of the coordinator. Are the people in the office pleasant and friendly? If you were a study subject, how would you feel about interacting with them? Determining workload, asking specific questions about the number of studies assigned to a study coordinator, working hours, support staff and roles can help determine if the addition of this study is feasible with the current workload.

CRAs need to obtain information about site recordkeeping practices (electronic or paper medical records/study documents) and the policy of CRA access to study records during monitoring visits. If a site is using an electronic medical records (EMR) system for study patient data and procedures, the institution's IT or medical records department may need extra time to obtain access for the CRA to a study patient's EMR required for the monitoring visit. This may add several days or weeks to the timeframe needed for scheduling monitoring visits. This information should be clarified during evaluation visits to plan for the subsequent monitoring visit cycle.

It is important to confirm if the site has appropriate SOPs or guidelines for study conduct, such as a documented process for informed consent, GCP training, staff training, investigational product, records retention and safety reporting. This will help determine the level of research infrastructure and established process for consistent research methodology at the site.

The CRA needs to confirm who will complete study tasks and responsibilities (PI versus Sub-Investigator versus study coordinator) to ensure that the appropriately trained, delegated individuals are completing tasks commensurate to their scope of licensure and/or responsibility, e.g. if the study coordinator is drawing study blood tests, does he or she have the appropriate phlebotomy training and certification? If the study coordinator is giving injections, does his or her license or credentials encompass this responsibility? If the study coordinator is processing and shipping study blood specimens, does he or she have updated IATA training and certification? It is important to confirm these details as they can impact study conduct with delays, certification/completion of training required to conduct these tasks, or reassignment of duties to appropriate staff.

CRAs need to confirm an investigator's site, facilities and equipment during the evaluation visit, to ensure they are equipped to complete all required study procedures. Examples of things to confirm during a facility tour are:

- Space to store the study drug and other supplies.
- Secure area for the study drug with adequate temperature monitoring systems and limited access to appropriate staff. (Discussions with the pharmacist or study coordinator responsible for the study drug are crucial to ensure appropriate study drug storage, documentation, dispensation and compliance practices at the site).
- Treatment areas (examination rooms, vital signs equipment, EKGs, scale, specialty equipment).

- Laboratory area for ranges, certifications, freezer, centrifuge.
- Imaging and Safety Testing (ophthalmology and pulmonary testing, for example) as required by the protocol
- Records storage area.
- Adequate monitoring area (desk or table space, chair, power outlet, fax and copy machine access, internet access).
- Is there an adequate study coordinator working area?
- Is the facility clean and well maintained?

The CRA should use a checklist, modified to study requirements, to ensure all equipment and required areas are assessed during the tour, including ancillary facilities that may be used for study evaluations such as imaging or safety testing (dermatology, ophthalmology, etc.).

The CRA needs to determine if there are any clinic or hospital policies that would limit the CRA's ability to review source documents, such as patient charts or EMRs.

Patient/Subject Population

One of the primary problems facing the smooth execution of clinical trials is enrolling appropriate patients within the allotted enrollment time. Consequently, when interviewing possible investigators, the CRA should thoroughly assess the enrollment potential of the site. The CRA will want to ascertain if the subjects will come from the investigator's current patient population or if they will be drawn from elsewhere. Will the investigator be able to draw patients from other physicians in the same hospital or clinic? Will the site need to advertise for patients? (Advertising will be discussed in Chapter 16.) Will the investigator be conducting any competing studies, and if so, how will the investigator demonstrate enough access to the study population at the site to adequately enroll all studies?

It is usually easier to assess enrollment potential for chronic disease studies than it is for acute disease studies. For chronic diseases such as arthritis or diabetes, the investigator should already have appropriate patients among his or her current patient base. It does not necessarily follow that these patients will qualify for or want to participate in the research study, but it provides a base from which to start. For acute studies, one must rely on past statistics. For example, if a pneumonia study is being discussed, the CRA will want to know how many patients with pneumonia the investigator saw over the past year. In either case, the more thorough the records are concerning the patient population, the better the enrollment estimates will be.

The CRA needs to assess who will be identifying/recruiting for patients, such as dedicated recruitment staff or study coordinators. The CRA needs to assess how the PI and his recruitment staff communicate and methods used to identify patients (review of the EMRs, medical records, review of the

clinicians practice schedules, utilization of recruitment companies, internet searches, email or paper correspondence to study patients). A successful site will have a diversity of enrollment tactics specific to their site model and target demographic.

Unfortunately, estimates of subject enrollment are almost always too high. Some CRAs use the "halving" technique to arrive at a final estimate: For each major exclusion criteria in the protocol, cut the original number of patients in half. The final number will be much closer to the enrollment you can actually expect to achieve.

The "halving" technique

The investigator says, "I have 500 patients with the disease of interest in my practice." Your protocol has five major exclusion criteria. Cut the 500 in half for each one.

500 → 250 → 125 → 63 → 32 → 15–16

This is probably about the number of subjects you can plan to enroll.

Miscellaneous Factors

There are several other items a CRA will want to discuss during an evaluation visit. One is whether or not the site is conducting, or is planning to conduct within the same time period, any competing studies. A competing study is usually one in which similar subjects are to be enrolled. In order to meet the enrollment targets, it's important that your study does not have to compete for subjects with another sponsor's study. In assessing competing studies, it is not enough to assess only those studies being done at the investigator's site, but those being done in the same community. Those studies will also be in competition for subjects and can have a great impact on the ability to meet enrollment targets.

Another factor is the timing for the study. If the site has too many active studies at the same time, your study may not get the attention it needs to be conducted well.

The CRA also needs to confirm if any regulatory agency or FDA audits of the investigator or site have occurred, and if a 483 was issued for any audit findings. All accompanying FDA audit documents and site audit responses/corrective action needs to be obtained and reviewed by the CRAs, during the site evaluation process, because this can influence the selection decision, especially if the audit findings were significant. The CRA can also check the FDA website and the clinical investigator inspection list, to determine if a PI has been audited by the FDA and if a 483 was issued.

The CRA should be certain that the investigator is familiar with the IRB process and should determine which IRB will be used for the study. How often does the IRB meet and how long does it usually take for the IRB to review and approve a study? The time it takes to review and approve a study or documents related to a study is called "turnaround time."

Some preliminary budget discussions can take place at an evaluation visit. The CRA can discuss with the investigator how the sponsor prefers to work with respect to the budget and payments for trials. The CRA may also want to find out how the investigator normally puts together a budget. If the site looks promising, it might be appropriate to talk about the grant range the company is willing to pay to ensure that both parties are at least in the same ballpark. Details can be left until the CRA is sure that the site is desirable to use for the study.

The CRA should be sure that a thorough evaluation of the site has been made before leaving and that notes have been made for future reference to include the required pre study visit report/recommendation. It is appropriate to send a thank you letter to the site within a few days of the visit. If the investigator is selected to do the study, a telephone call can be made to finalize the site's willingness to participate, followed by a confirmation letter.

Pre-Study Visit

If a study starts soon after an evaluation visit for a selected investigator, the evaluation information is current. Sometimes, however, several months can pass between the evaluation visit and the actual start date for a study. In this case, it can be valuable to do a pre-study visit to reevaluate the site's capability to do the trial. This visit does not vary much in content from the evaluation visit, except that the investigator is already committed to conduct the trial. The purpose of the visit is to assure the sponsor that the site is still appropriate for the work.

At this meeting, the CRA should take time to go over the protocol in detail with the investigator. Does the investigator have a good understanding of what needs to be done, when it needs to be done, subjects that are suitable, etc.? Has the investigator changed his or her mind about any aspects of the medicine or clinical aspects involved? Are there any problems with using a placebo control or with using the comparator medicine? Sometimes if there has been quite a long time between when the protocol was written and when the study is due to start, other new medications might have become standard treatment for a condition and physicians may not want to use an older drug as a comparator in a trial.

Pay close attention to the investigator's attitude, interest and reactions during your discussions. The investigator may be saying one thing but communicating something much different. Interpreting non-verbal clues takes experience and good human relations skills; over time, a CRA can become very adept at "reading" people.

It is much better for an investigator to back out of a program before it starts than to fail at it later. An experienced CRA will let investigators know that saying a project is not right for his or her site is not a negative; saying it can be done and then not following through means a sponsor rarely will come back.

Reassess the staff and their ability to do the study at this visit. Are the

same people at the site? Has there been any major staff turnover? Ask the investigator and the staff if there are plans for anyone to be away for an extended period of time during the study—you might be surprised by what you hear.

Check again for competing studies. Several months may have passed since the last evaluation visit and the site may have started other studies in the interim. It is important to ascertain if these studies will be competing with your study for patients, coordinator time or other resources.

Be sure that the facilities are still acceptable, including storage areas for the study medication and supplies. Ensure that the pharmacy and laboratory are aware of and ready to handle their study responsibilities. If a pharmacy is to be used, find out how much storage area it has for the study drug. It may be necessary to make multiple drug shipments over time instead of sending it all at once if space is limited. (Space in pharmacies is almost always at a premium.) Be sure that the storage requirements for the study drug are clearly understood and that appropriate storage conditions are available. If, for example, your drug requires refrigeration, there should be enough capacity to store an adequate supply of the drug.

The CRA should discuss with the investigator the subject population for the study. This is a good time to review the inclusion and exclusion criteria of the protocol in detail. There may have been changes in the physician's practice since the last evaluation that could adversely affect the site's ability to enroll subjects in the trial.

Hopefully you will have all the documents necessary to start the study in-house by this time, but if not, try to collect the rest of them at this visit. If the IRB has approved the study, the investigator should have a copy of the approval letter. Make a copy for your company while you are at the site if you do not have it already. If the study has not yet been approved by the IRB, find out when the IRB is meeting and when approval can be expected. If there have been any changes in the study team personnel, be sure that the correct people are listed on the 1572 form. If they are not, have the site revise the 1572 and give you a copy while you are there.

Usually the grant for the study has been agreed upon prior to this visit but, if not, now is the time. You don't want any last-minute delays in a study initiation because of stalled grant negotiations. Large organizations (hospitals, university medical centers) may have a separate office that handles grants and contracts. If so, the savvy CRA will get to know this office staff, which may smooth the way for speedier negotiations.

The bottom line is whether you still feel comfortable about using this site for your study. If you are having doubts, pay attention to them. Chances are that if something doesn't feel quite right, it isn't. You will always come out ahead dealing with problems before the study starts rather than later.

If the evaluation and/or pre-study visits have gone well, if you have thoroughly and accurately assessed the site's ability to complete your study and if you feel comfortable about conducting a study at the site, you have done the best you can to ensure a successful study start.

Key Takeaways

- The investigator is the individual who actually conducts, and is responsible for, a clinical investigation.
- The Statement of Investigator Form (FDA form 1572) contains pertinent investigator and site information, as well as a listing of investigator responsibilities. The signed investigator agreement is the equivalent document for device trials.
- Investigators have the ultimate responsibility for the safety of subjects in a clinical trial.
- Investigators must be qualified by training and experience to study a drug or device.
- The investigator must have a suitable facility and qualified staff for study conduct.
- Investigators may be disqualified if they do not comply with the regulations concerning clinical research, or if they falsify data or reports of the trial.
- Some of the best ways to locate potential investigators are by asking:
  - Within your own company.
  - For suggestions from current investigators.
  - Colleagues from other companies.
- Most CROs have feasibility departments dedicated to finding and confirming an investigator's preliminary capabilities for study participation and readiness for a site evaluation visit.
- A site evaluation visit is the best way to assess a site's capability to conduct a clinical trial.
- A pre-study visit should be done to reassess a site if there has been a lengthy period of time between the evaluation visit and the start date for a study.

CHAPTER THIRTEEN

Study Initiation

This chapter discusses a number of activities that must be completed before a study site can begin enrolling subjects. Topics include: study initiation documents, financial disclosure, investigator meetings, study initiation meetings, investigator study files and grants and contracts. CRAs are very involved in these activities and need to have a thorough understanding of them.

Study Initiation Documents

Before a trial can begin, a number of documents must be collected for each site. Most of these are required by FDA regulations, although some sponsors may require their own additional documents. Both the sponsor and the investigator must have copies of each document; usually, the originals are kept at the investigator's site while copies are sent to the sponsor. It is recommended that the CRA also keep copies of most of them, in case one is misplaced or disappears and needs to be replaced during the study. The documents listed below are what a sponsor must have before the trial may start. Note that most sponsors will not ship the study drug before receiving all of the documents.

- Signed, IRB-approved protocol and any amendments.
- IRB-approved informed consent, preferably containing an IRB-approved stamp.
- IRB approval letter, verifying approval of both the protocol and consent document.
- IRB approval of advertising and subject recruitment materials including subject compensation, if applicable.

- Signed, completed FDA Form 1572 (Statement of Investigator). (Note: for device studies, form1572 is not used. The sponsor obtains a signed agreement from the investigator that includes statements similar to those on form1572.)
- Financial disclosure forms for the investigator and any other study personnel listed on form 1572.
- Appropriate CVs of everyone listed on form 1572.
- Current laboratory certification and laboratory normal ranges.
- Signed contract or letter of agreement (not required by regulation, but required by most sponsors).

Some sponsors have specific employees whose primary responsibility is to collect and maintain these documents, while in other companies the CRAs gather the documents for their sites. The CRA is the person who visits the site, so he or she will probably be involved in the collection and maintenance of documents even if another internal group has primary responsibility.

The document that generally takes the longest time to receive is the IRB approval letter. This is the only document not under the direct control of the investigator. The IRB may have approved the study, but until the investigator receives written notification, it is not official. The CRA may need to encourage the investigator to keep contacting the IRB, as some are slow to issue approval letters.

Most sponsors will not ship the study drug until all the documents have been received. Note that some companies do ship the CRFs and other non-drug supplies before receiving all the documents in an effort to speed up the process, while others wait and ship everything only after documentation is complete.

Financial Disclosure

In 1998, the FDA published the final rule for financial disclosure.1 This requirement became effective in 1999 and applies to any study of a drug, biologic or device that is used to support a marketing application. The regulation requires that sponsors certify the absence of certain financial interests of clinical investigators, disclose these financial interests or certify that the information was impossible to obtain. If a sponsor does not do this, the FDA may refuse to file the application. A full description of the requirements is found in 21 CFR 54, which is included in Appendix G.

Disclosable financial arrangements, as taken from the FDA's "Guidance for Industry: Financial Disclosure for Investigators," are:

> *(a) Compensation affected by the outcome of clinical studies means compensation that could be higher for a favorable outcome than for an unfavorable outcome, such as compensation that is explicitly greater*

for a favorable result or compensation to the investigator in the form of an equity interest in the sponsor of a covered study or in the form of compensation tied to sales of the product, such as a royalty interest.

(b) Significant equity interest in the sponsor of a covered study means any ownership interest, stock options or other financial interest whose value cannot be readily determined through reference to public prices (generally, interests in a non-publicly traded corporation), or any equity interest in a publicly-traded corporation that exceeds $50,000 during the time the clinical investigator is carrying out the study and for one year following completion of the study.

(c) Proprietary interest in the tested product means property or other financial interest in the product including, but not limited to, a patent, trademark, copyright or licensing agreement.

(f) Significant payments of other sorts means payments made by the sponsor of a covered study to the investigator or the institution to support activities of the investigator that have a monetary value of more than $25,000, exclusive of the costs of conducting the clinical study or other clinical studies, (e.g., a grant to fund ongoing research, compensation in the form of equipment or retainers for ongoing consultation or honoraria) during the time the clinical investigator is carrying out the study and for one year following the completion of the study.Financial disclosure became an issue with small biotech companies in their start-up phases. Sometimes investigators and companies had closely tied financial interests, which led to a conflict of interest in the testing of potential new products.

A financial interest in a company or product does not mean that an investigator cannot be involved in a trial; it simply means that all parties must be aware of the potential for conflict of interest. The sponsor will want to evaluate the potential for bias based on an investigator's financial interest before deciding whether or not to use that investigator. The FDA will do the same when reviewing an NDA.

Financial disclosure applies to all of the people listed on form 1572 for a study, plus their spouses and dependent children. This is a good reason to not list unnecessary people on the 1572 form.

Financial disclosure information must be collected at the start of the study. Any changes that result in exceeding the threshold(s) must be reported during the course of the study and for one year following its completion. There is no required form for the collection of this information from the investigator. Consequently, sponsors develop their own forms and ways of collecting and maintaining this information.

Financial disclosure information must be reported to the FDA on FDA forms 3454 (certification of absence of financial interest) or 3455 (disclosure of financial interest). These forms are submitted as a part of the NDA.

Although not popular with investigators or sponsors, financial disclosure

information is required to be collected, and usually CRAs are involved in its collection. Because of their involvement, it is recommended that CRAs read the FDA's "Guidance for Industry, Financial Disclosure by Clinical Investigators," which is available on the FDA's website (fda.gov).

The Investigator Meeting

For a clinical trial with six or more sites, most sponsors hold an investigator meeting. Although not required by regulation, this meeting, which includes all investigators, their coordinators and appropriate sponsor representatives, is one of the most important activities pertaining to the conduct of a good trial. This meeting is often the first time the investigators and study coordinators meet the sponsor personnel; it creates an initial impression and sets the tone for the rest of the study.

Investigator meetings may also be web-based, which is more cost effective, and less time consuming than traditional investigator meetings that require attendees to take time off of work, (which is difficult for physician investigators' with private practices and other employees with large workloads), and travel to an agreed-upon meeting site to attend. The Principal Investigator only needs to give typically 3-4 hours to attend their required portion of the meeting, with a larger commitment from the study coordinator or research staff. The downside to web-based investigator meetings is that they may be less interactive and engaging for those who prefer live meetings.

Investigator meetings may be held when there are fewer than six sites, depending on the complexity of the study. Six sites in a clinical trial is merely a rule of thumb. Some investigator meetings include 200 or 300 people, if the trial is very large. Frequently, if the meeting were to be very large (e.g., over 150 attendees), two or three smaller meetings would be held instead. Smaller meetings allow for more opportunity for questions and interaction among the participants. These smaller meetings may be held regionally to lessen travel. Division may also be based on which sites are ready to start the study and which sites still have documents outstanding. It is also common to hold an investigator meeting specific to participating countries or regions; North America, EMEA, Asia Pacific. These are also impacted by when the study conduct is approved for a country.

Investigator meetings are scheduled and conducted by the sponsor (sometimes with the help of a contract company). The purpose of these meetings is to allow participants to get to know one another, which facilitates communication throughout the study, and to review the entire study and its conduct. The major advantages of holding these meetings are that everyone hears the same thing at the same time and people become acquainted. If done properly, the investigator meetings can also be a powerful motivational and training tool.

Due to the meeting's importance to the success of a trial, and frequent involvement of CRAs in these meetings, both in the planning stages and as

attendees, the investigator meeting will be discussed in further detail.

There are a number of items that require serious thought and planning when it comes to investigator meetings. These include when to hold the meeting, the location, who should attend, social activities and the agenda.

Timing and Location of Investigator Meetings

The first decision to be made is when to have the investigator meeting. These meetings are expensive, so CRAs must make every effort to ensure that all their sites are ready to start the study before the meeting. Sites that start the study more than a month or two after the investigator meeting may need to be refreshed on much of the information before work can begin. Ideally, the study drug is shipped while the meeting is taking place and the motivated investigators and their coordinators return home to immediately enroll the first patients. Unfortunately, this rarely, if ever, happens.

A nearly impossible task involves gathering numerous sites for a multicenter trial ready to start at the same time. Given this scenario, the sponsor should try to hold the investigator meeting when as many sites as possible are ready to start, and within a month of when the last site will be ready. The problem of determining when to hold the meeting is compounded by the fact that the meeting has to be planned so far in advance that good estimates of site readiness may not be available.

The meeting location requires a balance between business and pleasure. Everyone wants to go to a nice place for a meeting, preferably warm, with lots of things to do or see. However, from a business standpoint, the ideal place is probably at the sponsor company or at least in the same town.

If the meeting is held at the sponsor's primary location, there will be few budget restrictions on company representatives attending. Consequently, all the clerical personnel needed to make things run smoothly will be available. It will also be possible to have the professional support needed from groups such as Quality Assurance and Regulatory who attend infrequently when travel is involved. CRAs not involved with the study and other clinical or support people can attend as a learning or training experience. In addition, the investigators and coordinators can see the company and meet more employees than they would if the meeting were held elsewhere.

Another popular location for the investigator's meeting is at a large hotel near the airport of a large, centrally located city. A centrally located hub city is very convenient for attendees flying in from various areas across the country, or for those who can only attend part of the meeting. These venues are sometimes less costly and provide less distractions for attendees as opposed to holding the meeting at an elegant downtown hotel or historic site.

Planning and Logistics

Once the date and location have been determined, it's time to start making arrangements. Many sponsors have meeting planners who put these meet-

ings together, so CRAs are not usually involved in this aspect. If you have input, remember that the meeting should be informative, yet pleasant for those attending.

An agenda and general information regarding transportation, hotel information (swimming, tennis, golf, etc.) and reimbursement procedures should be sent to all investigators at least a month prior to the meeting. If the sponsor is providing airline tickets, they should be sent well in advance of the meeting date. Additional information and handout materials should be available for participants when they check into the hotel.

One important consideration to keep in mind is the duration of the meeting. One day is usually sufficient unless it is a large, complicated trial. Physicians may not be able to afford to be away from the office for more than one day. If one day is sufficient, the meeting could be held on the same day or split between the afternoon of one day and the morning of the next. Each has its advantages and disadvantages. Many prefer the split-day format as it allows attendees to arrive the morning of the first day, and because it is split into two shorter sessions. If the agenda is planned properly, investigators may leave after the afternoon session if they need to. The primary disadvantage is that there is little time to relax or rest prior to the start of the meeting and it may make leaving that same night difficult. Airline departures and connections for investigators must also be considered.

It is appropriate to plan a social event, such as a dinner or reception, so the site and sponsor staffs can get to know each other in a less formal environment.

Table 1: Planning the investigator meeting

Study activity	Month 4	Month 3	Month 2	Month 1
Budget	✓			
Select location	✓			
Contact hotels	✓			
Prepare reference/ instruction manuals		✓		
Letters of invitation		✓		
Rooming lists/requirements			✓	
Final agenda				✓
Follow up letter with agenda				✓
Rehearsal				✓
Meal selections/reception				✓
Ship materials to hotel				✓
Final transportation reservations				✓

Another meeting option that has become more popular in the last several years, is to host a welcome dinner the evening prior to the meeting. This presents a less formal "first meeting" for investigators and CRO/sponsor personnel, and the dinner is an entertaining ice breaker to an otherwise formalized, sometimes rigidly structured meeting.

Table 1 summarizes the major activities required in planning. Note that planning starts about four months in advance of the actual meeting date. The bigger the meeting, the more time it will take to plan and execute the preliminary activities.

Preparation for Meeting Presentations

Frequently, presentations held during investigator meetings get the least attention, which can spell disaster. First, the person presenting material from the sponsor must be determined. If key personnel from the sponsor choose not to present, a replacement must be found. It is hoped that said key personnel will attend the meeting regardless.

Remember, Chapter 1 stressed that good CRAs must have good communication skills. Investigator meetings are one activity for which that is very important. CRAs frequently present topics during the meeting. If you are asked to do this, you should be prepared and follow basic presentation procedures, e.g., speak clearly, engage the audience and use visual materials effectively.

Another key part of preparation is rehearsal, a full run-through. Unfortunately, very few companies take the time to do this. At a minimum, everyone who will be attending the meeting should be present for the rehearsal so that everyone gets a chance to hear what the others have to say before the meeting.

One of the most embarrassing things that could happen at an investigator meeting is the possibility of the speaker being interrupted by one of his colleagues who says, "That's not right, we don't want it done that way." Not only could it be embarrassing for the presenter, but the sponsor representatives, as a group, very well may immediately lose credibility. Rehearsals can help prevent embarrassing situations.

Another benefit of a rehearsal is that it allows the presenters to run through their material in front of an audience and check the timing, both for individual presentations and the entirety of the meeting. This allows for editing and overall planning.

The rehearsal should be open to people other than the attendees, because it is a good learning opportunity for less experienced employees and will help prepare them to become involved as a presenter, if they so choose. Everyone, including CRAs, should try to attend a rehearsal or an actual meeting before having to organize and/or participate in one. It is also valuable to have some experienced people from other units or divisions attend to act as advisors. Their experience and ability to look at presentations with a fresh view are very useful.

It is recommended that a moderator be used for an investigator meeting. Companies that use moderators seem to hold better meetings. The moderator should be a good speaker and a "people person." He or she usually opens the meeting, makes introductory remarks about the company, gives an overview of the meeting, makes administrative announcements, introduces company speakers and injects humor when appropriate. The moderator is a huge asset in regard to keeping the meeting running smoothly and on time; this allows the medical monitor and other presenters to concentrate on their presentations and meeting the investigators and coordinators without having to worry about logistical matters.

The Agenda

There is no one agenda that fits all investigator meetings. However, they will almost always contain the items shown in Table 2. An example of an expanded agenda is shown in Table 3. These can be used as starting points for planning a meeting, with other items added and deleted as appropriate.

Table 2: Investigator meeting agenda—Basic

- Introduction of attendees
- Introductory remarks about the company in general
- Background of the project
- Discussion of the protocol
- Administrative responsibilities of investigator and sponsor (and/or CRO) personnel involved in the study
- Sponsor procedures and expectations
  - Monitoring
  - Data collection
  - Adverse event reporting
  - Other sponsor-specific issues
- Financial matters
- Miscellaneous

Attendees

Who should attend investigator meetings? Key people from both the sponsor and the sites should be there; other attendees may be determined by the budget. Table 4 shows the usual cast of mandatory and optional attendees from both the sponsor and investigative sites.

Remember that one important purpose of the meeting is for sponsor personnel and site personnel to become acquainted. Sometimes, the CRAs are the only people who know attendees in both groups before the meeting.

Table 3: Investigator meeting agenda—Expanded

- Welcome
  - Introductions
    - The company (very brief overview)
    - Individuals and their roles
    - Investigators and their staff members
- Overview of the drug development program (include significant timelines, dates)
- Discussion of the protocol (avoid a page-by-page review)
  - Objectives
  - Study overview
  - Main protocol areas
  - Design
    - Primary efficacy endpoints
    - Entry criteria
    - Drug (formulation, dosing and regimen)
    - Risk/benefit
    - Medical events
    - Methods and materials
    - Any special procedures that may be required
- Administration
  - Responsibilities and obligations of the investigator
  - Informed consent
  - The IRB
  - Forms requiring signatures
  - Study documents
    - Protocol, IRB approvals, etc., and filing requirements
  - Financial matters
- Study Materials
  - Clinical supplies
    - Packaging, ordering and receipts (have sample packages if there is anything unique or unusual)
    - Drug accountability
    - Drug-dispensing procedure, forms
    - Reorder procedure
    - Storage
    - Inventory and return
- Laboratory
  - Exhibit forms, supplies, mailers, etc.
  - Demonstrate any unusual procedures

The CRA should take responsibility for the people attending from his or her sites. The CRA should also ensure that the investigators and coordinators

Table 3 continued: Investigator meeting agenda—Expanded

- Special Procedures and Forms
  - Diaries (if used)
  - Demonstrate special medical procedures if appropriate (treadmill, Holter monitor, etc.)
  - Training, rater certification
  - Procedures for randomization and breaking the blind
- Case Report Forms
  - Design
  - How/when to complete
  - Source document management
  - Correction procedures
- Closing remarks and questions

are introduced to the appropriate sponsor representatives they may come in contact with during the study, that they are taken care of and have all meeting materials and that they have an informative meeting. If site personnel have any unanswered questions at the end of the meeting, the CRA should get the information to them within a few days.

As a CRA, you should act as the host for your sites. Let the physicians and the coordinators know they are critical to the success of your study. Ask your site people questions and listen to the answers. Spend time with them. This meeting is an excellent opportunity to establish good relationships with your site personnel, which can make the study go smoothly for you as it gets underway.

The CRA attending the investigator meeting must remember that this is a professional, work related meeting; this is not an opportunity for a mini vacation. The CRA MUST act professionally at all times. Most CRO/sponsor companies have a minimum 1-2 alcoholic beverage per day rule for personnel traveling for business meetings (after work hours or for social dinners with clients) and this is a smart rule to follow during investigator meetings to ensure appropriate behavior. Never forget that you are the sponsor representative, and your behavior will be scrutinized.

Evaluation and Critique

It is important to evaluate how the investigator meeting went and was perceived. To help with this, it is useful to have evaluation forms for attendees to complete. They do not need to be complicated. Sample evaluation forms are shown in Tables 5a and 5b.

After each investigator meeting, the sponsor should create a critique of the meeting, including a discussion of the evaluations. This should help in determining what was done well and should be incorporated at future meet-

Table 4: Investigator meeting attendees

Investigator site attendees	Sponsor attendees
Mandatory attendees: • Investigator • Clinical research coordinator	Mandatory attendees: • Investigator • CRA(s) • Biostatistician • Project manager • Data manager • Laboratory person (usually from a central lab) • Moderator, if one is used • Designated presenters • Meeting facilitator, if needed
Optional attendees: • Co-investigator • Research manager • Pharmacists • Dietician • Others as appropriate	Optional attendees: • Management (Medical director, etc.) • Other monitors, CRAs • Regulatory representative • QA person • Secretary • Consultants, if appropriate

ings, as well as what should be changed or eliminated. Reviewing past meetings is an excellent tool for improving future meetings; each meeting should be better than the last one.

Study Initiation Meetings

The study initiation visit (sometimes known as the start-up visit) is held at the investigative site just before the study begins. The CRA (and sometimes additional sponsor personnel) will meet with the investigator and the supporting staff. The purpose of the meeting is to review the study protocol, processes and procedures to ensure that all site personnel understand what is necessary to perform the study.

The study initiation should be held at the point when all regulatory paperwork is complete for the site and the study drug and other supplies have been shipped, but before any subjects have been enrolled. Many sponsors will not allow the site to begin enrollment until after this meeting is held.

Table 5a: Investigator meeting evaluation form

Protocol _____			Date: _____		
Please complete this form before you leave to help us evaluate and improve our meetings. (Include instructions for where to leave the form.) If you forget, please mail it to us at: (insert address)					
Please rate the level of satisfaction with the facility:	High				Low
Accommodations	5	4	3	2	1
Food	5	4	3	2	1
Meeting room	5	4	3	2	1
Location	5	4	3	2	1
Meeting planning:	High				Low
Pre-meeting communication	5	4	3	2	1
Organization of meeting	5	4	3	2	1
Agenda	5	4	3	2	1
[ ] Too long					
[ ] Too short					
[ ] Too little (much) time on some items (specify)					
Sessions of least value _____					
Sessions of most value _____					
Suggestions for improvement _____					

Deadlines are critical for cost effective site activation and study start-up; even the slightest delay may have far reaching financial implications and cost thousands of dollars in recovery. The integration of computer systems and web-based portals into study start-up activities has made a once convoluted process more efficient, reducing timelines and costs associated with site activation. Examples include:

- Centralized portals or databases that facilitate "real-time" creation and submission of essential regulatory documents between site or CRO staff; documents are shared/edited in real-time in the database, edit changes are documented and are communicated via system-generated emails.
- Electronic submission of protocols, ICFs and accompanying documents to IRBs, via a centralized portal or IRB website, save time and money by circumventing the need for staff to print hundreds of copies of documents for IRB review and make the IRB submission a "rolling" submission as opposed to the historical 2-3 week submission deadline prior to the IRB meeting.

Table 5b: Session evaluations

Session _____ Presented by: _____					
Please rate the presenter of this session in the following areas:	High				Low
Speaking quality	5	4	3	2	1
Adequately established objectives at the beginning of the session	5	4	3	2	1
Presented material in a clear understandable manner	5	4	3	2	1
Material was in a logical sequence	5	4	3	2	1
Provided useful information	5	4	3	2	1
Effective use of audiovisual aids	5	4	3	2	1
Adequately summarized material	5	4	3	2	1
Provided adequate opportunity for participation/questions	5	4	3	2	1
Responded satisfactorily to questions and comments	5	4	3	2	1
Comments: _____					

The CRA must be flexible when it comes to scheduling the site initiation visit; to maximize attendance, it may need to be held early in the morning, in the evening or even in rare cases, on a weekend. A thorough, informative initiation meeting may take half a day, or even longer for a very complicated study.

The CRA is almost always in charge of the initiation meeting, although the sponsor's medical monitor and/or an in-house associate monitor may also be present. It is important that all involved site personnel attend the meeting, to include ancillary personnel such as the sub-investigators, other coordinators, pharmacist, dietician, etc.

If the investigator and coordinator attended an investigator meeting, the initiation visit will serve as a review and amplification of the topics covered during that meeting. If there was no investigator meeting, or if it was held a month or more prior to initiating the study, then the entire protocol, processes and procedure should be discussed in detail. The investigator and study coordinator are usually the only site people who attend the investigator meeting, so other site personnel will not be as familiar with the study. The initiation meeting provides an opportunity for those at the site to become familiar with the study and to understand everyone's study role.

Preparing for the Initiation Visit

The purpose of the site initiation visit is to train study staff on protocol and procedures. It is a teaching visit, and involves extensive preparation by the CRA conducting the visit; how the site staff comprehend and apply

the principles learned will influence study performance and outcome. The CRA should think about how to conduct the meeting and what should be addressed. On occasion, the sponsor's medical monitor will want to attend the meeting, particularly if it is the first time the investigator has done work for the sponsor. In this case, the CRA will need to determine what role the medical monitor would like to play and plan accordingly. However, the CRA should be in charge of the meeting. The CRA must prepare an agenda. Much of the same material will be covered at the initiation meeting that was covered at the investigator meeting, if one was held. The agenda and the amount of detail to be covered at the initiation visit will depend on: if there was an investigator meeting and who attended; how long it has been since the investigator meeting was held; the involvement of other personnel at the site (pharmacist, etc.); the complexity of the program; how much time you are allowed for the meeting.

The items to be covered at an initiation meeting are:

- Detailed discussion of the protocol, including:
  - Overview of study drug or medical device.
  - Inclusion and exclusion criteria.
  - Study rationale and procedures.
  - Study endpoints and objectives.
  - Administration of the study drug.
  - Randomization and blinding.
  - Primary outcome measures.
  - Other pertinent details.
- Drug accountability.
- Adverse event reporting.
- CRFs, eCRF/EDC systems (review of the CRF completion guidelines, logging onto the EDC system to ensure access is granted) going over each unique form in detail)
  - How to avoid errors (See more about this in Chapter 14, Monitoring.)
- Monitoring visits—how often, what should be ready, what will be covered.
- Regulatory requirements.
  - Investigator responsibilities.
  - IRB interactions.

- Any other study-specific or sponsor-specific items of importance.
  - Periodic reports of enrollment.
- Overview of vendors participating/completing assessments/assessment requirements (central imaging, central lab, central EKG, central spirometry, central rating scales, etc.).
- Confirmation of user access and familiarity for any specific sponsor/vendor systems used, such as safety portals, central lab website, central vendor websites (ECG, ECHO, Imaging) to ensure user access and uploading capabilities are confirmed.

It is recommended that the CRA rehearse before the meeting to check timing, for word pronunciation and to be sure the material is clear and understood. It is embarrassing to find out that you don't understand, or can't pronounce something at the time of your presentation. There is nothing harder than explaining a process to someone else when you don't understand it yourself.

If the CRA is not comfortable with any of the study procedures, he or she should ask for help and/or clarification before the meeting. For example, if the CRA is not comfortable with the data management and correction process, it should be reviewed with the data management people supporting the study.

If a study instruction manual has been developed, the CRA should be familiar with what is in it and how the site is expected to use it; if the site does not have one yet, plan to take it with you to the meeting. [Note: The study instruction manual is simply a guide for sites that explains study procedures in detail. It is a quick reference and will usually include practical hints and tips that would not be found in a protocol.]

The remote monitor will also help with the meeting:

- Ensure that regulatory binders, lab kits and required supplies have been ordered for the site.
- Ensure that study drug is en-route prior to the meeting.
- Obtain any last-minute regulatory documents to release study drug.
- Order account and system log-in credentials for sites, etc.

During the Initiation Visit

This meeting involves several people. Since the CRA is in charge, he or she should always be on time or a little early. If you have a morning meeting and it's out of town, plan to arrive the day before. Be sure you know where you are going and how long it will take to get there to allow for problems like morning rush hour traffic; plan accordingly. Depending on the time of day, it is a nice gesture to provide coffee or other refreshments; this should be approved by the sponsor or company management prior to the meeting.

Begin by expressing your pleasure at attending and your enthusiasm to begin working on the study. Leave time for introductions and then start the agenda.

It is important that people know they can ask questions as the meeting progresses. The main purpose of the meeting is for everyone to have a clear understanding of what is involved in conducting the study. It is far better to answer questions now than to have things completed incorrectly later. Take your time. Solicit questions periodically. Look around and see if people look perplexed or comfortable. This is an instance when a CRA's interpersonal skills are critical.

If certain attendees are not able to stay for the entire meeting (investigator, pharmacist), be sure to cover items critical to their participation while they are there. Other items, such as completing CRFs, can be covered with the coordinators (and others who may be involved) in a smaller group.

When the formal presentation part of the meeting is complete, there are some additional activities the CRA should do before leaving. One is to check the study drug and other study supplies to be certain they arrived in good condition and are appropriate and in the proper quantities. If computer equipment was provided, be sure it is in order, set up properly and working. Check with the pharmacy to be sure that it understands the drug dispensing, if appropriate. Check the investigator's study file to be sure that all the necessary documents are present and correct. If the file has not yet been set up, the CRA can help with this. (See next section, "Investigator Study Files.")

Once everything has been covered, the CRA should be sure to thank everyone involved before leaving. One of the important intangibles at this meeting is the opportunity it gives the CRA to establish good working relationships with all of the site personnel. Do everything possible to make the people at the site feel good about you, the study and the sponsor. This will pay huge dividends as the study progresses.

After the meeting, the CRA must complete a visit report detailing what was discussed and completed during the visit. Many companies have a special visit report for this meeting. ICH guidelines call for a trial initiation monitoring report that documents that trial procedures were covered with the investigator and his or her staff; this report is to be kept in both the sponsor and investigator study files. The same can be accomplished by sending the investigator a letter listing what was covered during the meeting.

If questions arose during the meeting that need further follow-up, the CRA must be sure to get the needed answers and relay them to the site. A written thank you letter is a nice gesture on the part of the CRA.

Conducting this meeting well will go a long way toward helping the site complete a successful study. It deserves the full attention of the CRA.

Investigator Study Files

Either before or during the initiation meeting, the CRA should discuss with the investigator and coordinator how to establish and maintain an investiga-

tor study file. This file will have a significant impact on the quality assurance for a study and, subsequently, the validity and usability of the data.

If the site is experienced, this will be a routine activity. If the site is new or relatively new, the CRA should be prepared to recommend how the files should be organized and instruct the site regarding the documents that must be maintained in the file.

By regulation (21 CFR 312.62), the investigator must keep records relating to disposition of the study drug, including dates, quantity and use by study subjects and case histories, including CRFs and all supporting documentation. Supporting documentation includes the signed and dated consent form, medical records, progress notes, hospital charts, nursing notes and any other source documents. It should also be documented that informed consent was obtained prior to the subject's participation.

This is the minimum by regulation. In reality, study files contain much more information. One recommendation is to have three major categories for study files: Regulatory, Administrative and Clinical.

In the regulatory files, the following will be kept:

- Completed FDA form 1572 (Statement of Investigator).
- Copies of the CV for the investigator and sub-investigators.
- Financial Disclosure forms for the investigator and sub-investigators listed on the 1572
- IRB-approved consent form.
- Written IRB approval of the protocol (study) and consent form and advertising and subject compensation, if applicable.
- Signed copy of the protocol and any amendments.
- Copies of the laboratory certification and normal ranges.
- Investigator brochure.

In the administrative section of the file, the following will be kept:

- Correspondence, email and telephone logs, including contacts with the sponsor, CRO (if involved), IRB and the institution (if applicable).
- Instructional material:
  - CRF completion/correction.
  - Guidelines for handling adverse events.
  - Procedures for handling and storing laboratory specimens.
  - Study drug information, including instructions for storing, dispensing and accounting.
- Drug shipment, dispensing and return records.

- Sponsor/CRO contact information.
- Log of study subjects (Master Study Subject Roster).
- Records of meetings and contact with the sponsor and/or CRO.
- Monitoring log (a record of CRA monitoring visits).
- Miscellaneous.

The investigator will also have a clinical file for each study subject, which will include:

- CRFs and supporting documents for each subject.
- Signed consent forms.

Files will vary depending on the site, the sponsor and the nature of the studies.

There are two items not mentioned in the list above: the grant and any reports from sponsor QA audits. This information is not routinely made available to FDA auditors and should not be kept in study files.

File retention is discussed in Chapter 17, Study Closeout. Investigators must be aware from the start of the study that all study documents must be retained long after the study is over. The CRA can be a valuable help to the site by assisting it with setting up and maintaining its files throughout the study. The CRA must also check the files regularly throughout the study and again at study closure. Keeping the files in order during the study will ensure that they are ready in the event of a site audit by the sponsor, the IRB or the FDA. Some companies provide clearly marked containers for study files to help minimize loss after the study is completed.

More investigational sites are opting to store their regulatory files electronically or in a separate database. Some sites provide CRAs temporary username/password access to review their electronic regulatory files during monitoring visits, while some sites will provide the CRA with a flash drive of the regulatory files and a site computer with which to view the regulatory documents on the flash drive.

Grants and Contracts

Involvement of the CRA in grant negotiation and investigator contracts varies considerably among sponsors. In general, the larger the company, the less the CRA is involved; this is because large companies tend to have a separate department that handles the financial aspects of trials. However, CRAs need to have an understanding of the grant and contract process in order to work well with study sites.

Grants

A good CRA will have an understanding of how grants are determined, both by the sponsor and by the investigator. Frequently the CRA can help move negotiations along to everyone's benefit.

Most sponsors operate on a fee-for-service basis. This means they will pay for actual work performed, i.e., subjects enrolled and subject visits. Most grants are formulated on a per-subject amount and prorated for the number of visits a subject actually completes. The amount per visit will often vary, as some visits are more labor- and time-intensive than others. Sponsors feel that they are buying a service from the investigator and do not expect to pay if the work (subjects and data) is not delivered.

There are different ways in which sponsor grant figures are determined. Some companies use commercially available grant management systems that estimate costs for protocol activities. This gives the sponsor a realistic grant range to work from when determining how much it wishes to pay for per-patient grants. Other companies determine grants based on their own actual data, or data gathered from other sources. Others rely on information from the investigators they are considering for the study.

Some sponsors will determine a range or a single per-subject grant figure they will pay and will not budge from this figure. Investigators either accept it or will not be able to do the study. Other sponsors will allow more flexibility, depending on experience with an investigator or geographic location. Costs differ in different parts of the country, so it makes sense to allow some flexibility.

Some companies expect their CRAs to negotiate grants with their investigators. Ideally, there will be a range or a starting figure given for the negotiations. A CRA must understand enough about calculating reasonable grants to help a site, especially if the site is inexperienced and has not done this before.

A good way to calculate a grant figure is to look at each study activity, have the investigator attach a cost to it, add an additional amount for overhead and other required activities and total it up. An example of a grant worksheet for a hypothetical study is shown in Table 6.

For this hypothetical study, there are eight visits. One common way to determine a prorating schedule is to look at the number of visits and the amount of work to be done at each visit. If some visits demand considerably more work than others, count them as two visits; generally speaking, the baseline visit and the final visit are the most demanding.

In the example shown in Table 7, there are three visits that are more labor intensive (Visits 1, 5 and 8) which involve physical exams and stress testing. To determine the prorated dollar amount, each of these visits should count as two and the other five visits should each count as one, for a total of 11. If the cumulative amount of $5,152 is divided by 11, the cost per visit is $468.36. Based on this, the three more intensive visits should be pro-rated at $937, and the other five at $468 (with the extra dollar added to the cost of the last visit). Note in Table 7 that if a subject drops out after visit 3, the investigator

Table 6: Budget worksheet—Protocol XXX

Study activity	Number of visits	Cost	Expanded cost
Phone pre-screen	1	50	50
Medical history	1	50	50
Physical exam	3	150	450
Labs	8	150	1,200
EKG	3	200	600
Treadmill stress test	3	250	750
Office visit—general assessments	8	75	600
Phone assessments	2	50	100
Sub-total for procedures			**$3,800**
Coordinator time	8	50	400
Pharmacy charge	8	35	280
Subtotal			**$680**
Total			**$4,480**
Overhead—15%			672
Grand total per completed subject			**$5,152**

would be paid $1,837. For a subject dropping out at Week 7, the payment would be $4,214, and so forth.

This is a simple way to calculate grants and prorate visit costs, but it is quite effective if the initial amounts for each procedure and activity are realistic. It is easy to explain and should help the CRA when negotiating a grant amount that is fair to both the sponsor and the investigator.

When a grant has been agreed upon and the study is underway, the CRA's responsibilities for grant activities are again variable. Some companies utilize the CRA in determining when grant monies should be paid, while others handle all grant payments in-house without the CRA's involvement. These companies usually pay either on a timed schedule, such as quarterly, or on the basis of CRFs received in-house. Whatever the scheme, the CRA should understand it and be able to discuss it with the investigator.

Note that many companies will pay a small amount of the grant up front (maybe two subjects' worth), but will then apply this amount to the work being done. This allows the investigator to set up study procedures, pay for initial labs and other tests, etc., without having to use site funds.

If grant payments are based on input from the CRA, the CRA will need to keep track of the work done and payments made. It is advisable not to pay in advance, with the exception of a possible up-front payment, just in case the site does not enroll any subjects at all. If an investigator is paid in advance and doesn't earn that amount, there is always the sticky business of trying to

Table 7: Grant amounts for one subject

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
Amount per visit	$937	$468	$468	$468	$937	$468	$468	$938
Cumulative amount	$937	$1,405	$1,837	$2,341	$3,278	$3,746	$4,214	$5,152

get the funds back. This is unpleasant for both the sponsor and the investigator, and even more so for the CRA, who is often caught in the middle.

Although some CRAs find it difficult to be involved in negotiating and paying grants, it does add stature in the eye of the investigator and gives the CRA more clout at the site. No matter how involved the CRA is, he or she should have a good understanding of both the process and the specifics for a site, to be able to discuss the grant with the investigator and answer any site questions.

Contracts

A contract between the sponsor and the investigator will be signed before the trial begins at a site. This document usually contains the responsibilities of the investigator, including the number of subjects the site is expecting to enroll, timelines for enrollment, grant amounts and the regulatory requirements for the investigator. It also contains the responsibilities of the sponsor, including when and how grants will be paid, monitoring of the study and sponsor regulatory requirements. It will be signed by the appropriate company representative, and by the investigator. [Note that in large institutions contracts may be signed by someone in the contract office rather than by the investigator.]

Contracts are rarely written, negotiated or signed by the CRA. The CRA may, however, be asked to take the contract to the investigator and/or collect the signed contract. The CRA will want to have a copy of the contract, if possible, to know what was agreed to for enrollment, timelines and payment schedules.

Key Takeaways

Study Documents

- There are a number of documents required before a study can begin at a site.
- Most sponsors will not ship the study drug until all required documents are collected.

- Copies of all documents must be kept in both the site's and the sponsor's study files.
- The CRA should keep track of the IRB approval process and letter, so the study is not unduly delayed.
- Shared databases and regulatory portals used for startup activities can reduce timelines and cost.

Financial Disclosure

- The purpose of financial disclosure is to identify any potential conflict of interest that could bias a clinical trial.
- Financial disclosure information must be gathered for all people listed on form 1572 and their immediate family members.
- These data are collected for the time period of the study and one year following.
- Financial disclosure information is reported to the FDA when the NDA is filed.

Investigator Meetings

- All investigators and coordinators, as well as relevant sponsor personnel, should attend the meeting.
- The meeting should be held at the time when most sites are ready to enroll.
- The purpose of an investigator meeting is to ensure that all sites have the same understanding of all protocol and administrative procedures.
- Sponsors should always have a full rehearsal before the meeting.
- CRAs should act as the host for their respective sites and ensure that site personnel meet the sponsor representatives.

Study Initiation Visit

- The purpose of an initiation meeting is to ensure that everyone at the site has a clear and accurate understanding of how the study is to be conducted.
- This meeting should be held after a site has all the study supplies, including the study drug, but before study personnel enroll any subjects.
- All relevant site personnel should be present for the meeting.
- The CRA is in charge of the meeting.
- The meeting should be documented in both the investigator's and

sponsor's study files.

Investigator's Study Files

- Investigators are required to keep study records and documents during the trial and after the trial is closed.
- CRAs can help the investigator set up and organize these files and must check them regularly throughout the study.
- Maintaining files appropriately will ensure that they are in order for an audit.
- It is often simple to catch and correct problems with the files on an ongoing basis throughout the study. It may be impossible to correct the files once the study is over.

Grants and Contracts

- A CRA should be knowledgeable about grants and how they are calculated.
- If involved in payments, the CRA must track the study progress to keep abreast of money owed.
- Most grants are prorated by visit for each subject.
- Contracts between the sponsor and the investigator are signed before the study begins at the site.

CHAPTER FOURTEEN

Study Monitoring

This chapter will discuss the CRA's main activity: study monitoring. Previous chapters discussed the importance of a good protocol, case report forms, investigator selection, investigator meetings and startup and initiation meetings in producing high-quality clinical trials. Without good study monitoring, however, the best preparation will not produce a high-quality study. Poor study monitoring is probably the largest single contributor to inferior study quality.

A good CRA can produce good studies under a variety of circumstances, with investigators and protocols of varying quality. On the other hand, a poor CRA will almost always generate a substandard study, regardless of the quality of the protocol and experience of the investigator. Good CRA site monitoring and management are essential for good studies.

The Monitoring Plan

The game plan used in athletics is a strategy that the coach and players develop before each game and includes what needs to be done to maximize the chance of winning. It changes for each game because the conditions, circumstances and opposition are different each time. So it is with monitoring. No two study sites are the same, even if they are following the same protocol. A CRA should spend some time putting together a monitoring plan (or familiarize themselves with the monitoring plan created by the study project manager), including both general and specific information for each site. The primary components addressed in this plan are: how the study will be monitored, how often monitoring visits/remote monitoring visits should occur and specific activities to be performed.

How to Monitor

How to monitor a study in the field (meaning you must travel from your company/home office to the study site) requires considerable thought. Almost all field monitoring requires regular visits to the site by the CRA throughout the period of the study. On very rare occasions, an extremely simple, low-risk study might be monitored almost exclusively by telephone except for the startup and closeout visits.

Over the last several years, more sponsors/CROs have adopted a risk-based monitoring model for clinical trials conduct. The risk-based element targets critical study endpoint or influential visit data for review, based on risk analysis of the protocol and data. The risk-based model includes alternative monitoring practices as opposed to traditional, 100% on-site routine monitoring visits conducted at specific time intervals. These alternatives include centralized or remote monitoring of critical endpoints and data (via EDC or source documents/CRFs uploaded by site staff to a shared drive or transmitted electronically), and on-site review of targeted, critical visit data and source documents in lieu of 100% CRF/source document review (such as targeted review of drug administration and accountability data, inclusion/exclusion criteria, study endpoints and adverse event or safety reporting). This can occur in between or in lieu of some on-site monitoring visits.

Alternative site management practices such as email correspondence, teleconference and video conference provide opportunities for consistent training, site management and dissemination of information to ensure better oversight of the investigational site study performance and data collection practices.

Risk-based monitoring specific to central/remote monitoring of eCRFs and source documents will be reviewed later in this chapter.

A CRA must determine how to integrate telephone, email, fax and regular mail communications into a monitoring strategy. This will differ depending on the program and site. It will depend on the technologies available, both sponsor and site SOPs and personal preferences at both the site and the sponsor company. In monitoring, like any business, many problems can be traced back to a lack of communication, inappropriate communication and/or unclear communication. Consistent and effective communication strategies should have a high priority in your monitoring plan.

The intensity of monitoring will vary across studies and among sites. Must or should the CRA be present while the site is seeing study subjects? Will the CRA have any interaction with study subjects? In early phase I studies, the CRA may be required to be present during all or part of a subject's treatment. Therefore, the CRA must determine how long he or she will need to be there and make appropriate arrangements.

Sometimes a CRA is the sole monitor for a site, while at other times the CRA will co-monitor with other company CRAs. Establishing who will monitor requires consideration of the sponsor's SOPs for field monitoring, the complexity of the protocol, the condition being studied, the experience of the

investigator and his or her staff and the training and experience of the CRA.

The CRA's overall monitoring plan should remain fairly consistent, but the strategy for individual sites may change considerably during the course of the study, depending on many factors such as study conditions, protocol changes, site status and performance.

Frequency of Monitoring Visits

A key determination in a monitoring plan is the frequency with which the CRA will visit each site. There are a number of factors that must be considered in making this decision:

- Complexity of the protocol.
- Disease being evaluated.
- Experience of the investigator/staff.
- Number of study subjects enrolled at the site.
- Rate of enrollment.
- Site performance.
- Site performance (clean data vs. data discrepancies, protocol deviations, noted findings during monitoring visits).
- CRA experience and effectiveness.
- Whether or not the study is using risk-based monitoring or 100% CRF/SDV review during routine on site monitoring visits

The protocol dictates the conduct of the study by establishing the procedures that subjects must undergo and their frequency. The more activities required during a study visit, the more monitoring will be required. The disease being studied also dictates the frequency of visits. For example, if the CRA is monitoring an infectious disease study, the course of therapy will probably be complete for each subject in about 10 days. This requires a different frequency of visits than a cholesterol-lowering study with a treatment period of one or two years. Some studies require unblinded pharmacy staff to prepare study drug and blind the administration (injection or infusion). In this case there will be an unblinded monitoring plan for the unblinded CRA responsible for unblinded pharmacy monitoring at the site.

All sites should be visited soon after the first subject or two are enrolled just to be sure the site understands and is correctly following protocol procedures (industry standard is that the first monitoring visit occurs within one to two weeks of the first study patient enrolled at a site). Catching and solving problems early will save a lot of extra work as the study progresses. (See more about this in Chapter 18, Quality Management.) A critical benefit to central or remote monitoring of source documents or EDC is the ability for CRAs to review preliminary study visit data entry by sites, early on in a trial, (before

the first monitoring visit) to proactively determine site trends in protocol deviations, GCP non-compliance or eligibility/enrollment discrepancies. This expedites preventive action and can potentially lower incidence of corrective action. The rate of enrollment will also affect monitoring frequency. Generally speaking, the more subjects a site has, the more frequently the CRA will have to visit. The faster a site enrolls and the more data generated, the more frequently the site will need monitoring.

The CRA should visit a site regularly even though enrollment may be slow or non-existent. Slow subject enrollment may indicate a lack of enthusiasm on the part of site personnel regarding the study. In that case, a bit of CRA encouragement may help, which will probably involve visits. Site personnel often view frequent visits by the CRA as an indication of the importance of their study to the sponsor. Not only that, but seeing the CRA walk through the door reminds the site staff of their commitment to enroll subjects and complete the study on time. Call it encouragement or call it guilt—it generally works. Sometimes a few extra visits are all that is necessary to get a study back on track or to re-establish priorities at the site.

The frequency and duration of monitoring visits will also vary from site to site depending on the experience of the investigator and the staff. A less experienced site may require more or longer monitoring visits, especially at the beginning of the study. Once the site has demonstrated the ability to do the study well, the CRA may be able to space the monitoring visits further apart.

In some instances, sponsor SOPs dictate the frequency of monitoring visits. If so, the SOP normally establishes a minimum schedule, e.g., "all sites must be visited every six weeks or less." In this case, the CRA must adjust the visit schedule to ensure compliance with the SOP.

The frequency of monitoring visits may change as the study progresses. Some sites will do a better job complying with GCPs than others and may need less frequent monitoring. Subject enrollment may complete or level off after a period of time, allowing for more time between monitoring visits. Subject visits may be spread out over the course of long-term studies and require less review; for example, weekly visits may be required initially, followed by monthly, and perhaps even quarterly, visits as the study progresses. In short, a CRA must visit each site often enough to stay on top of the activities that are required for good monitoring. The more experienced the CRA, the easier it will be to make this determination.

Another factor that affects CRA visit frequency is the number and location of sites for which he or she has monitoring responsibility. There is always the chance that the CRA simply cannot physically visit the sites as often as he or she would like to or need to because of travel time and the actual number and location of sites. Here again, the CRA will have to spend some time integrating travel requirements with site experience and study complexity.

Another factor not often considered, that can impact monitoring frequency at a site, is the CRAs relationship with the investigator and site staff. If a CRA is professional and positive during monitoring visits, respectful of

the study coordinator's time (keeping the established visit schedule, arriving on time to monitoring visits, sending timely confirmation letters and site reminders) and is proactive about scheduling visits in advance, that is the CRA who gets the desired monitoring visit days (Tues, Wed, Thurs), and locations on site (conference room versus examination room). That is not the CRA who is consistently late to monitoring visits, frequently cancels visits and fails to schedule visits in a timely manner.

The CRA should schedule four hours, at the very least, for a site visit. With the complexity of protocols, regulatory requirements and good monitoring practice, the CRA will need to spend a day or more at most sites. Creative scheduling of your travel itinerary is a must. It helps to use the "loop method" for travel, in which the sites closest together are linked in your itinerary for a single trip. (See Appendix B for additional tips on traveling.)

As a general rule, a good CRA should be able to effectively monitor 12 to 18 sites. The number will change depending on the complexity of the study, site and CRA experience and locations. If the CRA is in a situation in which it is simply impossible to visit sites with the degree of frequency necessary for good monitoring, this should be discussed with his or her supervisor.

Planning the Amount of Time for a Monitoring Visit

Planning the amount of time you need to allow for a monitoring visit at a site is not always easy. Time management can be a difficult challenge, especially when you also may have to figure in schedules and other travel factors. When you are planning a visit, think of the activities you need to complete while you are there, which will include at least some, if not all, of the following:

- Meeting with the investigator.
- Meeting with the study coordinator.
- Review of study documents.
- Drug/device accountability.
- Case report form review and source document verification.
- Query resolution.
- SAE listing Review.
- Protocol deviation reporting/review.
- Training.
- Facilities reconfirmation.
- Addressing unresolved findings/issues from the previous visit.
- Review of the investigator site file.
- Review of staff GCP and training certificates.

The most difficult amount of time for a CRA to estimate is often the case report form review, including source document verification. When you start a new study, keep track of approximately how long it takes for you to review a subject visit (average). A subject's status in the study (screening versus randomization versus follow-up) will greatly determine the time for visit review. A good rule of thumb is to remember is that a screening visit can take two to three times longer to review than a regular study visit. Once you have this information as a guide, you can estimate your total time for subject review by multiplying the number of visits you have to review by this amount of time. If you add the time you expect to need for the other activities you have planned, you will have a reasonable estimate of how much time you will need for your visit.

A good tool for planning CRF review is a monitoring log that shows the number of subjects enrolled and where each subject is in the study. Even if the study is using EDC, and there is a means to electronically "check-off" a study visit or study patient record after review, or even if the system reconciles your review automatically after completion, it is recommended you make and keep a monitoring log for all of your studies, as this will show you the progress of the study. Some CRAs maintain monitoring logs on excel spreadsheets, word documents or a handwritten monitoring log.

Figure 1: Monitoring log—Protocol 1234-XYZ—Dr. J. Smith

Subject	Consent date	Baseline	Week 1	Week 2	Week 4	Final status	Comments
001 FGB	3-1-21	3-1-21	3-9-21			Drop-out	Dropped at Week 1—adverse events
002 KKO	4-12-21	4-12-21	4-20-21				
003 MKJ							

Above is an example of a monitoring log (Figure 1). Note that the column headings are study-dependent. You can, of course, add other headings that might be useful. In this example, the dates are the actual dates the subject completed each visit. You might want to put a check or highlight the visits when you have collected the CRFs or add the date you collected the CRFs for each visit (collected can mean electronic review and transmission with an EDC system or physical collection of paper CRFs).

Let's say on your first monitoring trip, these are the subject visits that were completed. You added these dates to your log as you reviewed each subject.

Before you make your next monitoring visit, you add any new subjects enrolled to your log (you get this information from the weekly enrollment update by the site or from the eCRF database updates). Then you can pencil in any visits the subjects should have had since you were last there, count up

these visits and have a pretty good idea about the time you will need to spend reviewing them.

Assume you will visit on 5/25/2021. How many visits might you expect to see? Pencil an "X" in these boxes and add them up. It looks like you may have nine new visits to review. If each one takes you approximately half an hour, you are looking at about four and a half hours for this activity. See this example of the updated monitoring log in Figure 2.

Figure 2: Monitoring log—Protocol 1234-XYZ—Dr. J. Smith

Subject	Consent date	Baseline	Week 1	Week 2	Week 4	Final status	Comments
001 FGB	3-1-21	3-1-21	3-9-21	X	X	Drop-out	Dropped at Week 1—adverse events
002 KKO	4-12-21	4-12-21	4-20-21	X	X		
003 MKJ		4-30-21	X	X			
004 DDS		5-3-21	X	X			
005 RFD		5-15-21	X				

Add in the other tasks you have to complete at the visit and you will have a reasonable estimate of your time requirements.

Monitoring Activity

The CRA should have a general plan for what will be monitored at each site visit. Most sponsors have a site visit report or monitoring report that the CRA completes during and after a site visit. This report is a standard document that a CRA will use for all field monitoring visits. It serves as both a checklist for the CRA and as documentation of the visit. However, the CRA must not view this as the only list of activities that must be completed.

To be successful as a CRA, it is important to develop a sense for what you should monitor at each site and how much attention should be given to each activity. Some CRAs develop source document subject sheets that they maintain on study subjects. These sheets note such items as date of consent, re-consenting, SAEs, protocol deviations, study status (visits completed), CRFs reviewed and other items of note to help keep themselves up to date.

It helps to be aware of where problems are most likely to arise during the conduct of a study. A good indication of potential problems is the list of activities that receive the most deficiencies during FDA audits. The top five deficiency categories for site inspections done by the FDA's Bioresearch Monitoring Program in 2017 were:

- An investigation was not conducted in accordance with the [signed statement of investigator] [investigational plan].
- Failure to prepare or maintain [adequate] [accurate] case histories with respect to [observations and data pertinent to the investigation] [informed consent].
- Investigational drug disposition records are not adequate with respect to [dates] [quantity] [use by subjects].
- Informed consent was not properly documented in that the written informed consent used in the study [was not approved by the IRB] [was not signed by the subject or the subject's legally authorized representative at the time of consent] [was not dated by the subject or the subject's legally authorized representative at the time of consent].
- Not all changes in research activity were approved by an Institutional Review Board prior to implementation.

These areas, in addition to the items the sponsor wants to emphasize, should receive specific attention during monitoring visits. Sponsor expectations for studies are important. Independent CRAs and those employed by CROs need to review sponsor monitoring visit SOPs, familiarize themselves with the sponsor's data review requirements and pay attention during sponsor co-monitoring visits to ensure a clear understanding of those expectations.

A good practice in prioritization is to review the most critical data first, such as: informed consent forms, screening and randomization visits for newly enrolled patients, newly reported SAEs and accompanying information and impending subject efficacy or endpoint data for study patients. Interim or safety analysis during a study will drive priority in data review at sites. The interval of time between remote or on-site monitoring visits at a site will dictate priority of data review (how long unreviewed data has been sitting, how long has it been since the earliest enrolled patient data was reviewed).

Many successful CRAs rely heavily on checklists that they have developed and refined over time. Basic checklists cover those things that should always be reviewed, regardless of the program, sponsor or site. This list can be modified as needed to fit each monitoring assignment. Sample checklists are in Appendix C. If a CRA thinks experience is a substitute for checklists, remember that all airline pilots use checklists every time they fly, regardless of how many hours of flying time they have. Which plane would you prefer to fly on: one whose pilot uses a checklist or one whose pilot thinks personal experience is enough to ensure the safety of the flight?

Checklists
"I have trained new CRAs and CRA managers and I always impress upon these folks the importance of using a checklist, no matter how brief it is. Toward the end of my career as a CRA, I was training a new CRA in Pittsburgh. We were going to do site/investigator evaluations that day and I had told him to have a checklist for the various meetings. The first interview went fairly well, but he left out a few things. After the visit, we discussed the fact that he had not used a checklist. The second interview went the same as the first and the ensuing discussion was the same. It was the third interview that really gave me pause to wonder if he would make it as a CRA. Once again, no checklist was utilized. The new CRA seemed to have asked all the right questions, except for one: "How many patients do you have, doctor, who might qualify for this study?" I had to ask it for him. On our way back to the car, the young man looked at me and said, "I guess I should have used a checklist."

—A CRA friend

Preparing for a Monitoring Visit

Once the CRA has a good idea how to monitor, what to monitor and how frequently to monitor, it is time to prepare for the visit. There is a military saying: "Proper Preparation Prevents Poor Performance." Remembering the "5 Ps" will serve you well. A CRA should spend a considerable amount of time preparing for each site visit. In addition to a working knowledge of good clinical practice (GCP) and any state and/or local requirements, the CRA must know everything possible about the activity at the site, the protocol and the sponsor's monitoring SOPs before arriving at the site. A CRA's preparation will be evident to the investigator and his or her staff; a lack of preparation can cause a loss of credibility.

Once a CRA has lost credibility, control of the site and the ability to generate a good study diminishes significantly. It takes an enormous amount of extra work to re-establish lost credibility, if it can be done at all. Remember that you only get one chance to create a good first impression. Establishing and maintaining a high level of credibility should be among a CRA's primary goals. The easiest way to achieve credibility is to be prepared.

The CRA must work closely with the remote monitor to prepare for monitoring visits. The remote monitor will inform the CRA of any outstanding regulatory documents to be retrieved, and will prepare listings of outstanding queries to be resolved, new study subject data to be reviewed and new protocol deviations or SAEs to be reviewed. Duties of the CRA and the remote monitor will overlap, so it is critical that there is communication so they do not do duplicate work and contact the sites separately regarding the same issues. This can negatively impact site management and the site/CRA dynamic.

One thing a CRA should do is set up site travel files for each site he or she monitors. These files should contain the items shown in Table 1. It is also useful to have a small travel kit containing mailing envelopes and labels, UPS or FedEx mailers and labels, paper clips, pens, pencils, sticky notes and a wireless card for internet access. If you are going to a site without internet access for CRAs, be sure to have a notepad and your calendar/planner/smartphone PDA. Your files should also contain any other items you think would be of value when you are at the site. These files should be kept current. When preparing to leave for a monitoring trip, the CRA can simply pull the files for the sites to be visited. It also helps to have a generic travel file that includes checklists and a copy of the regulations (there are copies of some of the pertinent regulations in Appendix G). When leaving for a monitoring visit, the CRA can easily pack the generic file, the site-specific files and any other necessary supplies, and he or she is ready to go.

Table 1: Travel file content

- Personal notes
- Copies of the last site visit report
- Study progress or enrollment logs
- Key site documents
  - Protocol
  - 1572
  - Latest drug shipment form(s)
- Pertinent correspondence
- Copies of any queries received
- Subject monitoring notes
- CRF guidelines
- SAE listings
- Essential document listings

Prior to a site visit, the CRA should check with colleagues involved in the development program for the investigational drug, particularly the sponsor's medical monitor. This is especially important for CRAs who are based regionally and may not be aware of correspondence or other communications that have occurred between the site and the sponsor since the last visit. The CRA should also check for any authorized protocol deviations or other changes in the conduct of the study at the site, as well as changes in enrollment or other study-related activity (for sponsor or CRO companies who utilize a clinical trials management system database, enrollment, protocol deviation and SAE listing reports can be system generated by the CRA prior to the monitoring visit or during the monitoring visit for reference).

Some sponsors have in-house CRAs who oversee study activity, particularly error correction and data management, by monitoring incoming CRFs. Some of these in-house monitors have frequent contact with study site personnel. If a CRA is field-based, he or she should check with the in-house CRA to see what has transpired at a site since the last monitoring visit. The in-house CRA may also maintain some site performance, site communication or status logs; the CRA should review current copies of these documents prior to a site visit.

Before leaving for a monitoring visit, the CRA should contact the site by phone or email to confirm the visit. This serves a number of purposes. First, it reminds the site of the visit. Second, it confirms that the necessary site personnel will be there and available; if key people will not be available during the visit, it should probably be rescheduled. This call, or email, also allows the CRA to remind site personnel of expectations for the visit, any prior preparation that is needed and approximately how long the visit will last. Finally, it can help to avoid a wasted trip if the site is not prepared, or if there has been a scheduling change or misunderstanding about the date.

Lastly, know where you are going. This may sound funny, but there are stories of CRAs who have become hopelessly lost on their first visit because they did not take the time to get directions or study a map. (There is more on travel in Appendix B.) As a hint, place the directions for finding each site in its travel file—including how to find the office within the hospital, etc. It's easy to forget when monitoring several sites and visiting only every six weeks or so.

With the advent of shared ride services like Lyft and Uber, transportation has become reasonable and convenient, especially in large cities where traffic is heavy and car rental is expensive and inconvenient. Using a shared ride service is especially beneficial when your investigative site is a large academic health center where parking is nonexistent and not centrally located to the investigative site.

If you are driving to the site, at the very least, ask the hotel staff how long it will take to get there as they have realistic predictions of traffic patterns and rush hour timeframes. You should not rely on GPS or map apps alone to predict how long it will take to get to the site.

If the CRA has prepared properly for a visit, the site will be expecting his or her arrival and will also have prepared for the visit.

Site Monitoring Visits

Professionalism

Before getting into the details of monitoring a site, it is important to focus briefly on conduct and appearance. Even in today's casual environment, it's important to look and act professional. CRAs can get off to a bad start because of the way they work and dress. The CRA should wear appropriate business attire and should always arrive at the site on time or a little early; remember to always call if you're not going to be on time, even when you are going to be just a few minutes late. The CRA must remember that he or she is an official representative of the sponsor and should always behave in an appropriate businesslike manner.

It is always important to regard a monitoring visit to an investigational site like a visit to an individual's home. You are their "guest" and must respect their policies for monitoring hours and conduct. Do not touch, move

or "reorganize" anything (like regulatory binders) without permission. Do not leave your monitoring area a mess. Throw away trash, put things away or back in their respective places after use.

The respect you show to investigational site staff is reciprocal; often how a CRA is treated is a reflection of how he or she manages their sites. CRAs who manage by intimidation and criticism may have squeaky clean data, but resentful site staff who may complain to the sponsor and be uncooperative with interim analysis deadlines or last minute monitoring visit needs. CRAs who take to heart the "site/CRA" team dynamic, who work with their sites, impress with a positive influence, professionalism, education and mentoring, will not only have credible data, but cooperative and happy site staff. A happy site is willing to help the CRA with almost anything, and will strive for excellence in study conduct. They will also want to work with the sponsor/CRO again and again.

Monitoring requires a lot of unsupervised time "on the road;" consequently, CRAs must have excellent self-discipline. There are many temptations when traveling that can distract a CRA from work—shopping, museums, television or the latest bestseller. Although there may be some down time when in the field, the CRA can use this time to catch up on writing reports, reading protocols and other tasks. An employer deserves an honest day's work, whether the CRA is in the office or on the road.

Meeting with the Investigator

If possible, the CRA should spend a few minutes with the investigator at the start of the visit, so he or she knows you are there and what your activities will be while at the site. This is a good time to update the investigator on the overall progress of the study, including enrollment, timelines and any changes or other news from the sponsor.

Exit visits with the investigator should be routine. Since the investigator has ultimate responsibility for the study, the CRA should keep the investigator apprised of findings during the visit and how the study is going in general. The exit meeting is a good time to discuss how the study is progressing at the site, any corrective actions that need to be taken, grant or budget matters and any other items that need to be discussed with the investigator.

Investigators tend to be very busy and occasionally, after the study gets underway, they become less accessible. A CRA must make certain from the beginning that the investigator knows a short meeting is expected each time the site is visited. Good communication with the investigator is essential for a good study. If a CRA is having problems trying to meet with an investigator during an on-site monitoring visit, offer to have a telephone discussion. Though not as optimal as a face-to-face meeting, the willingness to work with busy investigators by having a discussion via teleconference will make them more amenable to future discussions.

If a CRA continues to encounter challenges with speaking to the investigator during monitoring visits, discuss this with the sponsor medical moni-

tor. Often the monitor can help, perhaps by calling the investigator personally—doctor-to-doctor contact sometimes works wonders.

Another aid for dealing with difficult investigators is to occasionally review the responsibilities that appear on the 1572 (Statement of Investigator) forms that they signed with them; specifically, section 9 of the 1572, investigator commitments. That can be a reminder that they agreed, in writing, to good study conduct, which includes good communication with the CRA. Sometimes nothing will work and an investigator will simply not meet with a CRA. In this case, the CRA must to do the best he or she can to keep the study on track. CRAs should always discuss these situations with their supervisors so that everyone is aware. Problems like these should also be documented in a visit report so that informed decisions can be made regarding future use or possible termination of the site.

Working With the Study Coordinator

For actual study conduct, the study coordinator or clinical research coordinator (CRC) is the most important person at the site. A CRA must establish a good working relationship with the coordinator. The coordinator can either make monitoring relatively easy and enjoyable or a nightmare, and the choice is usually dependent on the CRA.

A CRA needs to spend time developing a rapport with the coordinator and developing a monitoring routine that works well for both of them. Each should understand how the other works. The CRA should determine the best times and methods for routine communication with each coordinator and let the coordinator know his or her expectations as the field monitor.

Some CRAs have such a good relationship with their coordinators that all the materials to be reviewed at a visit are laid out and ready when the CRA arrives at the site. With others, the relationships are not as good, so study materials are not ready for review and monitoring becomes a challenge. A good relationship is worth nurturing; a bad one is costly.

Some CRAs simply have better interpersonal relationship skills than others. It's amazing what a smile and good manners will do and it's easy to develop a friendship over the course of a long study. Remember to always maintain a professional relationship, no matter how much you like the study coordinator. The CRA still must be able to enforce compliance if the study gets out of line. It is not easy to maintain your position of authority if the relationship becomes too friendly.

Site Management

There are a number of general issues the CRA will want to be aware of when monitoring a site, including interpersonal relationships at the site, the stability of the staff, organization, how site personnel manage their time and an overall impression and feeling about the site. The atmosphere at a site affects the study. The better it is and the smoother things run, the better the study

will progress.

Be observant when monitoring a site. Do people get along well with one another? Do they work together? Are there obvious antagonisms, one-upmanship, etc.? If one person is very busy, do others help out? If there are problems, the CRA may need to work around them in order to achieve monitoring objectives. At the same time, the CRA will need to be careful not to add to any bad situations; the CRA should always treat everyone well, be pleasant and smile. Stay out of site politics.

Look at the organization of the office. Are things running smoothly or are they always scattered? If they are scattered, the study will often run the same way, unless the CRA puts in additional time to help organize things for smoother operation. Do site people have enough time to do their usual jobs plus the study? Are things always late or done quickly but incorrectly? Were they prepared for the monitoring visit? Sometimes the CRA may need to put extra effort into helping site personnel organize and manage the study efficiently.

Another CRA responsibility is problem solving. Things rarely go exactly as planned and clinical trials are no exception. The CRA must be prepared for a variety of potential problems such as enrollment difficulties, personnel turnover, waning interest in the study by site personnel, poor conduct of the study and protocol violations. Experience, knowledge and good common sense are your best tools for problem solving.

A CRA needs to think about how to approach a site that does sloppy work. Some CRAs try to crack the whip right from the very start, while others adopt a more moderate approach. In general, a moderate approach is the best, using the minimum amount of pressure required to get the necessary results. It is important for a CRA to learn how to take care of site problems without alienating the investigator and site personnel. If the site staff are unhappy with the CRA, the study will languish and everyone loses.

If a problem arises that a CRA feels uncomfortable dealing with, or does not know how to solve, the CRA should speak with his or her supervisor or the sponsor's medical monitor. Don't ignore problems; they seldom go away by themselves. If there are problems with site management, the CRA may have to monitor more often to ensure that the study is run properly and that things are done in a timely manner.

Monitoring Strategy

A CRA will need to develop an overall "hands on" monitoring strategy for site visits. In general, it is best to start with the most important activities, or at least the ones that must be done at each visit. This will ensure that if time runs short and everything cannot be completed, at least the most important things will have been reviewed.

One monitoring plan consists of the following activities, done in the order listed:

- Serious Adverse Event review
- Informed consent review
- New subject/subject screening visit review
- Protocol adherence check
- Case report form review and source document review
- Queries and error correction
- Investigational product review and accountability
- Review of previous findings from the last monitoring visit for resolution
- Review of laboratory samples
- Study document file review

Of course, you will also want to spend some time with the investigator, the coordinator and, perhaps, other site personnel.

Some CRAs schedule additional time with study coordinators at the end of the monitoring visit to review and address findings generated during monitoring visits. Study coordinators do not appreciate a CRA generating a long list of findings and leaving it for the study coordinator to review without assistance. The extra time spent with the study coordinator will help ensure a greater level of study understanding and compliance. It will perpetuate a positive site dynamic.

Serious Adverse Event (SAE) Review

One of the first things a CRA should do at each monitoring visit is ask the investigator and coordinator if there have been any serious adverse events since the last visit and, if there have been, if they were reported to the sponsor. Whether or not the serious events were reported to the sponsor, the CRA should examine the SAE transmittal form, information available about the events, including a review of the patient chart/CRF and any supporting documentation.

If additional information about an SAE is available, but has not yet been sent to the sponsor, the CRA can collect it and ensure that it is submitted to the appropriate person at the sponsor in a timely manner. The CRA can also discuss with site personnel the need for any additional information necessary for complete reporting. (Serious adverse event reporting is discussed in detail in Chapter 15.)

Informed Consent Review

At each visit, the CRA should check the informed consents for each new subject enrolled since the last visit. Informed consent forms should be signed

and dated by the subject or the subject's legally authorized representative. Check the dates (and times, if available) against the date/time the subject started the study; both should precede study entry. Others, such as a study subject, investigator or witness, should initial or sign the consent form, if required. The person signing the consent should also date it; site personnel must never date the subject's signature on a consent form.

The CRA should check how a site documents the informed consent process. Information pertaining to the appropriate documentation of the informed consent process was discussed in detail in Chapter 9.

The CRA should check to be sure the correct consent is being used, especially if the site is doing more than one study.

If the consent form for a study has changed (e.g., protocol amendment), the CRA must be sure all newly enrolled subjects sign the appropriate consent. Except for a file copy, any copies of the old, inappropriate consent should be destroyed so they are not used inadvertently. If subjects who signed the old consent are still part of the study, they should sign the new consent before continuing. The CRA should also check to be sure this was done.

It is a good idea to periodically go back and check all signed consents at the same time. One reason is to ensure they are all still there and available. It is also a good idea to flip through and look at all the signatures at once; they should vary, and it should be obvious that they were signed by different people.

If a site is using electronic informed consent, the CRA may be able to review the ICFs remotely, under the correct circumstances, ahead of the visit, which will help cut down the time and amount of activities to be completed during the monitoring visit.

Checking Protocol Adherence

CRAs should check protocol adherence when monitoring each subject's data. It is easy to become so involved in checking the CRFs and source documents that the overall protocol adherence can be missed—it's the "not seeing the forest for the trees" syndrome. To ensure adherence, the CRA will want to check the following items:

- **Subject Eligibility**. Did the subject meet all the inclusion and exclusion criteria?
- **Randomization**. Was the subject randomized to the correct subject number and did he or she receive the appropriate packages of the investigational drug?
- **Medical History/Adverse Events/Concomitant Medications.** Do concomitant medications match corresponding medical history or reported adverse events. Were concomitant medications given to treat adverse events captured in the source/CRFs? Does current medical history require treatment with a medication not listed in the source or

CRF (diabetes, hypertension, thyroid disease, etc.)? A cross analysis of all three elements will help with accuracy in reconciliation.

- **Protocol Activities**. Were the correct activities done for or by the subject at each visit?
- **Visit Schedule and Windows**. The visit window is the number of days around the actual projected visit date when the subject can be seen. The window is usually the date plus and minus a number of days. For example, if the subject is due to be seen on May 6th and the window is plus and minus two days, the subject can be seen between May 4th and May 8th. Did the patient come in for each visit during the appropriate time period?
- **Drug Dispensing**. Was the subject given the appropriate drug and the appropriate amount at each visit? Did the subject return any unused study drug? Was enough study drug taken so that the subject met the rules for drug compliance?

Case Report Form (CRF) Review and Source Document Review (SDR)

Case report form review and source document review take most of the CRA's monitoring time. A suggested approach to this activity is the following:

- Start with new subjects, those enrolled since the last monitoring visit.
- Next, review the other currently enrolled subjects.
- Check all the CRFs for a subject before doing source document review.
- Then do SDR before checking the next subject's CRF.
- Finish one subject at a time.

The reason for starting with new subjects is that the CRA will want to be sure they qualify for the study. If the subject does not qualify, or if other mistakes are being made, it is best to catch them soon after the subject is enrolled, rather than later.

CRF review and SDR require a different focus. It is easier to review the CRFs before looking at the source document. We will look at each of these activities in more detail. Finishing one subject at a time is simply a good organizational tool. When the CRA has finished with the activities for a subject, put those items away. It is too easy to get mixed up when trying to review multiple subjects at the same time.

Case Report Form Review

When reviewing the CRFs for a subject, first check each single page. The CRA should check for completeness to ensure that each item has been completed and each blank is filled in. Are the answers within range? Is the header

complete and correct? (The header is the top part of each form that lists the subject and study identifiers.) Is the form signed, if appropriate, and by the correct person? Are the format/forms legible? If the CRA has trouble interpreting what has been recorded, the data entry person may also have trouble reading what has been recorded.

Next, check all of the pages for a single visit. Check for completeness and correct dates. Is the visit within the window allowed? Check to be sure the timing of procedures was appropriate. If, for example, there was to be a blood draw followed by another activity, the blood draw should have been done first, and the times should reflect this. Any time there is a specific order to be followed for activities, that order must be followed. Check for consistency across forms. If the subject is getting better according to various ratings, then the overall rating should reflect an improvement. If a form says there was a concomitant medication administered for an adverse event, then the medication should be listed on the concomitant medication form and the adverse event entered on the adverse event CRF. In addition, the CRA should think about what appears on the forms and whether it makes sense, given the subject condition and the study activities. If something does not make sense, the CRA should discuss it with the study coordinator and/or investigator.

The CRA should also check across visits. Are the data consistent from visit to visit? Is the timing of procedures appropriate? Do the data match where necessary? Are the visit windows correct over time? Usually each visit window is calculated by going back to the starting or baseline date, not from the previous visit. The reason is if a subject is always two days late, and if the window is always calculated from the last visit, you are adding two days and two more days and two more days and so forth. After a while, there is not enough study drug for the subject to finish all the visits specified by the protocol.

The CRA should look for data trends and inconsistencies to ensure the data is authentic across subjects at a site.

Lastly, be sure it is the same subject at each visit, with the same initials, number and other identifier. It is always better to straighten out any problems while reviewing CRFs at the site, as opposed to having the forms sent in and making corrections later. After completing the case report form review, it is time to do the source document review. Error correction will be discussed following the source document review section.

If electronic data capture (EDC) is being used for the study, the CRA will not need to do this kind of case report form review. Most basic edits will be done automatically by the computer program, or in-house by the sponsor's data management group. The CRA will still need to work with the site on data queries. More discussion of this can be found in the EDC section of Chapter 11.

Source Document Review

Source document review, sometimes called source document verification, involves checking the data recorded in the CRFs against data found in avail-

able source documents, including the patient's medical chart, electronic medical record (EMR) data, laboratory reports, radiology reports, hospitalizations and other supporting documents. A source document is any document on which the data are first recorded, and can range from a patient's blood pressure recorded on a sticky note, to a physician's note, to a dictated X-ray report.

The purpose of source documentation is twofold: first, to verify that the subjects exist, and second, to verify that data in the CRF are consistent with the information found in the source documents, which verifies the integrity of the data.

One would expect to see basic demographic information in an office medical chart for a patient, including name, address, phone number, insurance information and social security number. The CRA is not interested in the particulars of this information, but only that it exists. The usual office medical chart will also contain lab reports, or reports of other diagnostic or confirmatory medical tests. The name and identifying information should match the other information in the chart. This information is indicative that the person entered in the trial actually exists.

Many hospitals, health organizations and physician/medical practices are transitioning or have transitioned to an electronic medical record (EMR) system for patient medical record data. Historically paper-based, EMRs have been implemented to comply with the mandate that healthcare providers and other eligible professionals (EP) must demonstrate "meaningful use" of EMRs in order to maintain current Medicaid and Medicare reimbursement levels.

The transition to a patient EMR system (at investigational sites) has forced the classification of EMR data as "source." A patient's original medical record has always been considered a part of source documents, of course, to varying degrees dependent on site data collection practices. Some sites only class the medical record as study source for the accompanying demographic, diagnostic, medical history, medication information that is recorded in the study patient's CRF and confirmed by CRAs during monitoring visits; they use paper source documents for capture of specific study visit or procedures data. Some investigational sites record study-specific data in the patient's medical record, or typically use standard of care information or patient visits as part of study data. Regardless of site process, with the transition to an EMR system, the patient's EMR is also a source document.

There are numerous EMR programs being utilized. Some sites use systems that require direct entry of notes made by physicians or nurses, or patient medical information into the system. Other sites complete progress notes or charting on paper forms and scan/upload them in the EMR system.

Monitoring practices have adapted to include electronic record review.

There are several means by which investigational sites will provide CRAs with access to a study patient's EMR for review:

- A printed EMR.
  - Site staff will print a study patient's EMR and place it in a subject study folder for CRA review during monitoring visits. The site staff will be requested to confirm that the EMR printout is consistent with the actual patient EMR and that everything applicable has been printed as far as patient visits and medical data. They should also "certify" the printout. The person tasked with printing out the EMR should initial and date the document. Sites provide EMR printouts because they do not have the capability to provide the CRA access to the EMR for review of study patient data or they are not permitted to provide the CRA access to the EMR due to institutional HIPAA or data privacy rules.
- Review of a study patient's EMR with the study coordinator or site staff.
  - The study coordinator or site staff member is logged in to view the EMR and the CRA sits with them to review the required portions of the study patient's EMR. This usually happens when a site does not have the technological means to provide the CRA direct EMR access to review study patient data.
- Direct, read-only review of a study patient's EMR.
  - Sites will provide CRAs with "read-only" access to study patient's EMR data. The CRA's review is limited to designated study patients; they cannot access other data in the system.
- CRAs are provided with their own unique username and password to log into the system.

How a CRA is provided a study patient's EMR for review varies per investigational site model and technology practices. Most small single-investigator practices will only have the means to provide the CRA with printed copies of the study patient's EMR for review. Either their EMR system does not have the capability to provide read-only access to only a study patient's EMR, or they don't have a staff member who can sit with a CRA for several hours during a monitoring visit, to allow the CRA to review study patients' EMR data (with the staff member logged in to the EMR and observing the CRA).

Larger health organizations or academic institutions may have the IT infrastructure and technology to provide CRAs with read-only access to the study patient's data they need to review at specific monitoring visits. They may also have extra staff sit with the CRA for a few hours during monitoring visits, for the purpose of study patient EMR review, as noted above. The CRA may have to sign a confidentiality agreement to obtain username/password access to the institutional EMR, but it is critical that the CRA have his or her manager review the confidentiality agreement for appropriateness before signing anything. Remember that investigational sites may need sev-

eral weeks' notice to obtain the CRA's login credentials for the EMR system. Providing site staff advance notice of this is important. In this age of technologically driven data review, the only investigational site model almost completely exempt from EMR system integration of data is dedicated research sites. As they are not a fee-for-service medical practice and, historically, treat only research subjects during study conduct, research sites do not maintain traditional medical records. Most dedicated research sites maintain paper source documents to note a patient's medical history, demographics, medication and study-related data. Research staff may have requested and successfully obtained a copy of a study patient's medical record from their primary physician, but it was a paper-based printout or copy of the patient's electronic medical record. Research sites may be the only remaining investigational site model that exclusively maintain 100% paper study records.

During site selection, sponsors need to ensure the integrity of a site EMR system by ensuring it meets all or the integral elements of 21CFR11: unique username/password access, audit trail with data changes, system validation and system backup. This can be confirmed with the site IT representative, or EMR users (study coordinators, data managers, etc.).

When the data in the case report forms are in agreement with data contained in source documents, it is an indicator of the quality and veracity of the information being gathered for the study. It is not necessary for every entry in a CRF to have a matching entry in a source document, but where the data do appear in both, they should agree. Neither ICH GCPs nor FDA regulations require that source documents be kept for all entries on case report forms. Under 21 CFR 312.62(b), "An investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation. …Case histories include the case report forms and supporting data including, for example, signed and dated consent forms, progress notes of the physician…hospital chart(s) and nurse's notes."

ICH GCPs say only that the study monitor shall verify that "the data required by the protocol are reported accurately on the CRFs and are consistent with the source data/documents." Despite the lack of any regulatory requirement, many companies require a matching source document for nearly every CRF entry. Whether or not this is the case, the CRA should verify that, where matching data do exist in source records, they are consistent with the CRFs.

On occasion, the original collection of data may be done directly on the case report form; in effect, the case report form becomes a source document. This is frequently seen in rating scales, such as the Hamilton Depression Rating Scale, because it is easier to collect the information directly on the CRF as opposed to transcribing it later. It is not wrong to do this, but a note should be made to the investigator's study file that this is being done. The sponsor may request/require this to be done.

What happens if there is a discrepancy between the case report form and the source document? Usually the source document takes precedence, but the CRA should always ask the investigator or coordinator to determine

which one is correct and to make the appropriate corrections. If the source document is corrected, the site staffer making the change should sign and date the document, including an explanation, as appropriate. CRAs should not make changes on either the source documents or the case report forms; this is the responsibility of site personnel. The CRA must remember that even one change on a CRF can have an impact on other data. Be sure to check this, both within the visit and across visits.

There are significant differences among sponsors with respect to the amount of source document review a CRA must do, and there are no guidelines in the regulations. Some companies require "100% source document review," but the definitions of 100% source document review also vary, from the expectation of a source document for every data point for every subject, to 100% verification of the data insofar as it exists in source documents. Other sponsors have a sampling scheme, and these also vary considerably. Whatever the scheme, however, a majority of the subjects' case report forms are normally reviewed for critical information, such as inclusion and exclusion criteria, a signed consent, adverse events and critical study-specific parameters.

Some source document review sampling scheme examples are:

- 10% of the subjects are done.
- The first subject and then every other subject thereafter are done.
- The first two subjects are done. If there are no problems, every fourth subject thereafter is done. If problems are found, do two more subjects. Iterate as needed.
- All subjects, but only certain variables, are done.

No matter how much source document review/verification is done, it will never replace common sense. A CRA must think about what is being seen on the CRFs (paper or electronic) and in the source documents, and determine if it makes sense in terms of both the study and good medical practice.

The acronym, ALCOA is an industry standard for appropriate source document content and standards, and must be considered during review of study/patient source documents.

A-attributable
L-legible
C-contemporaneous
O-original
A-accurate

The wrong consent form
I was monitoring with a CRA and decided to check all the consents while he was doing the case report form and source document review. The site was a busy one, doing a number of studies. As I looked through the consents, I noticed one that was different—in fact, it was not for our study at all. It was for a very similar study, but one being done for a different sponsor. It was interesting reading, but not the right consent.

The study coordinator was chagrined, as was the CRA. The subject was, in fact, in our study, the correct CRF was being used and the correct activities were being done. The coordinator had just inadvertently grabbed the wrong consent for him to sign.

To remedy this situation, the investigator contacted the subject, explained the problem and asked him to sign a new, correct consent form. The situation was documented in the site's study file, including the changes they made to their procedures to ensure that it would not happen again. From then on, consents for each study were placed in a separate folder, clearly marked and stored in separate locations, rather than together in one file.

—Karen

Electronic Source

The FDA has a guidance document for electronic sources that came out in September 2013, entitled, "Guidance for Industry: Electronic Source Data in Clinical Investigations." As noted in the introduction section of the guidance, page 1:

> *This guidance provides recommendations to sponsors, Contract Research Organizations (CROs), clinical investigators, and others involved in the capture, review and retention of electronic source data in FDA-regulated clinical investigations. In an effort to streamline and modernize clinical investigations, this guidance promotes capturing source data in electronic form. It is intended to assist in ensuring the reliability, quality, integrity and traceability of data from electronic source to electronic regulatory submission.*
>
> *This guidance addresses source data in clinical investigations used to fill the predefined fields in an electronic case report form (eCRF), according to the protocol. The guidance discusses the following topics related to electronic source data:*
>
> – *Identification and specification of authorized source data originators.*
>
> – *Creation of data element identifiers to facilitate examination of the audit trail by sponsors, the FDA and other authorized parties.*

- *Ways to capture source data into the eCRF using either manual or electronic methods.*
- *Clinical investigator(s) responsibilities with respect to reviewing and retaining electronic data.*
- *Use and description of computerized systems in clinical investigations.*

This guidance is intended to be used together with the FDA guidance for industry on Computerized Systems Used in Clinical Investigations (the computerized systems guidance) and FDA regulation on Electronic Records and Electronic Signatures. Electronic structures and standards related to electronic submissions are out of scope for this guidance.

The background section, page 2, describes what the FDA considers electronic records and source data.

With the use of computerized systems for capturing clinical investigation data, it is common to find at least some source data recorded electronically. Common examples include, but are not limited to, clinical data initially recorded in electronic health records maintained by healthcare providers and institutions, electronic laboratory reports, digital medical images from devices and electronic diaries completed by study subjects.

FDA regulations define an **electronic record** *as any combination of text, graphics, data, audio, pictorial or other information represented in digital form that is created, modified, maintained, archived, retrieved or distributed by a computer system. An eCRF is an example of an electronic record.*

The eCRF is an auditable electronic record of information that generally is reported to the sponsor on each trial subject, according to a clinical investigation protocol.

The eCRF enables clinical investigation data to be systematically captured, reviewed, managed, stored, analyzed and reported.

Source data *includes all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical investigation used for reconstructing and evaluating the investigation. Access to source data is critical to the review and inspections of clinical investigations. The review of source data by both the FDA and sponsor is important to ensure adequate protection of the rights, welfare and safety of human subjects and the quality and integrity of the clinical investigation data. Source data should be attributable, legible, contemporaneous, original and accurate (ALCOA) and must meet the regulatory requirements for recordkeeping.*

Capturing source data electronically and transmitting it to the eCRF should:

- *Eliminate unnecessary duplication of data*
- *Reduce the possibility for transcription errors*
- *Encourage entering source data during a subject's visit, where appropriate*
- *Eliminate transcription of source data prior to entry into an eCRF*
- *Facilitate remote monitoring of data*
- *Promote real-time access for data review*
- *Facilitate the collection of accurate and complete data*

Electronic source data origination is further clarified on page 3.

Electronic source data are data initially recorded in electronic format. They can include information in original records and certified copies of original records of clinical findings, observations or other activities captured prior to or during a clinical investigation used for reconstructing and evaluating the investigation.

It gives further examples in "data capture, electronic source data origination" on page 3:

A data element in an eCRF represents the smallest unit of observation captured for a subject in a clinical investigation. Examples of data elements include race, white blood cell count, pain severity measurement or other clinical observations made and documented during a study. Each data element is associated with an authorized data originator. Examples of data originators include:

- *Clinical investigator(s) and delegated clinical study staff*
- *Clinical investigation subjects or their legally authorized representatives*
- *Consulting services (e.g., a radiologist reporting on a computed tomography (CT) scan)*
- *Medical devices (e.g., electrocardiograph (ECG) machine and other medical instruments such as a blood pressure machine)*
- *Electronic health records (EHRs)*
- *Automated laboratory reporting systems (e.g., from central laboratories)*
- *Other technology*

A list of all authorized data originators (i.e., persons, systems, devices and instruments) should be developed and maintained by the sponsor and made available at each clinical site. In the case of electronic, patient-reported outcome measures, the subject (e.g., unique subject identifier) should be listed as the originator.

When identification of data originators relies on identification (logon) codes and unique passwords, controls must be employed to ensure the security and integrity of the authorized user names and passwords. When electronic thumbprints or other biometric identifiers are used in place of an electronic login/password, controls should be designed to ensure that they cannot be used by anyone other than their original owner.

When a system, device or instrument automatically populates a data element field in the eCRF, a data element identifier … should be created that automatically identifies the particular system, device or instrument (e.g., name and type) as the originator of the data element. For example, if an ECG machine automatically transmits to the eCRF, a data element identifier should be generated that identifies the ECG machine as the originator.

Risk-Based Monitoring: Remote and Central Monitoring Practices

The FDA has a guidance document for risk-based monitoring that came out in August 2013 entitled "Guidance for Industry: Oversight of Clinical Investigations-A Risk-Based Approach to Monitoring." The guidance aims to assist sponsors of clinical investigations in:

… developing risk-based monitoring strategies and plans for investigational studies of medical products, including human drug and biological products, medical devices and combinations thereof. The overarching goal of this guidance is to enhance human subject protection and the quality of clinical trial data by focusing sponsor oversight on the most important aspects of study conduct and reporting.

This guidance makes clear that sponsors can use a variety of approaches to fulfill their responsibilities for monitoring clinical investigator (CI) conduct and performance in investigational new drug (IND) studies conducted under 21 CFR part 312 or investigational device exemption (IDE) studies conducted under 21 CFR part 812. The guidance describes strategies for monitoring activities that reflect a modern, risk-based approach that focuses on critical study parameters and relies on a combination of monitoring activities to oversee a study effectively. For example, the guidance specifically encourages greater use of centralized monitoring methods where appropriate.

The dynamic of traditional on-site monitoring and data review practices has shifted in the advent of internet-based programs that adequately support real-time, remote data review. Central or remote monitoring practices allow sponsors faster and more efficient access to critical study data points via electronic data capture systems or shared research drives for CRF/source document uploading. This provides an additional level of oversight and serves as one indicator of site compliance to study conduct and patient safety.

Over the past several years, some CROs/pharma/biotech companies have adopted a risk-based/remote monitoring program, replacing the frequency and intensity of on-site monitoring visits that focused on 100% source/CRF review with a hybrid of remote data review and on-site targeted monitoring of source documents/CRFs. The complexity of a study, treatment and procedures dictate the ability to perform a portion of remote or on-site monitoring. A thorough risk assessment of the protocol and investigational sites is required. Targeted review of critical endpoint data to assess trends in non-compliance, protocol deviations and data errors on site will also determine the need and frequency of on-site versus remote monitoring visits. Those sites with higher instances of data errors or protocol non-compliance will require more frequent on-site monitoring visits, not just for the purpose of additional source document/CRF review, but for the purposes of site auditing, training and CAPA.

There are several means of remote/central monitoring practices, including:

- Data management, remote monitor or CRA staff review EDC data from a central or remote location to pinpoint critical study visit discrepancies and trends.
- CRAs review EDC and source documents during "remote" monitoring visits; targeted data review of such things as informed consent forms, eligibility criteria, drug accountability logs, regulatory documents, medication logs, SAEs, endpoint of efficacy data—anything identified during a risk assessment as critical. Investigational site staff transmit study source documents to accompany the EDC or source documents and CRFs are uploaded to a shared drive for this review purpose.
- Email/telephone/videoconferencing occurs to discuss discrepancies, retraining or corrective action. The investigator may need to be present for some of these telephone calls.
- On-site monitoring of data also occurs.

It is a challenging transition for investigational sites to accept the dynamic of remote and on-site monitoring plans. Traditionalists fear the that reduction of on-site monitoring visits, and 100% source document review, in the face of increased remote, targeted data review may result in additional discrepancies and protocol deviations.

The guidance explains, however:

During the past two decades, the number and complexity of clinical trials have grown dramatically. These changes create new challenges to clinical trial oversight, particularly increased variability in clinical investigator experience, site infrastructure, treatment choices and standards of healthcare, as well as challenges related to geographic dispersion.

At the same time, increasing use of electronic systems and records and improvements in statistical assessments, present opportunities for alternative monitoring approaches (e.g., centralized monitoring) that can improve the quality and efficiency of sponsor oversight of clinical investigations.

The FDA encourages sponsors to develop monitoring plans that manage important risks to human subjects and data quality and address the challenges of oversight in part by taking advantage of the innovations in modern clinical trials. A risk-based approach to monitoring does not suggest any less vigilance in oversight of clinical investigations. Rather, it focuses on sponsor oversight activities on preventing or mitigating important and likely risks to data quality and to processes critical to human subject protection and trial integrity.

Moreover, a risk-based approach is dynamic, more readily facilitating continual improvement in trial conduct and oversight. For example, monitoring findings should be evaluated to determine whether additional actions (e.g., training of clinical investigator and site staff, clarification of protocol requirements) are necessary to ensure human subject protection and data quality across sites.

CRAs who are not already comfortable with the use of internet or web-based programs for the purposes of remote monitoring will need to quickly orient to computerized review of study data to stay current with technology-driven data collection practices.

Errors, Queries and Corrections

Perhaps the most important errors a CRA might find are those that result in protocol violations. These include such things as a subject not meeting the inclusion/exclusion criteria, a wrong diagnosis, a subject taking disallowed medications, problems with visit windows, unreported or late reported SAEs and others. Often these are found during source document review. Other errors are also found during source document review and run the gamut from incorrectly transcribed data to things that are just plain wrong. Then there are the CRF errors discussed earlier, such as missing data or out-of-range values.

Correcting errors is easier if the CRA has an effective procedure for dealing with them. It is helpful to have an Error Query/Correction form that is

simple and easy to work with. A sample of this form is in Appendix C. Some CRAs rely heavily on sticky notes. Although they are good reminders, and mark CRFs nicely, they can fall off and get lost; plus, they do not generate an audit trail. A written correction form/log is more effective overall.

When potential errors are found, the CRA should note them in the corrections/questions log and discuss them with the study coordinator. When they are resolved, the coordinator should make the necessary corrections to the CRFs, and sign/date the correction form/log; CRAs do not make the corrections. Corrections are made by drawing a line through the incorrect entry, making the correct entry and dating and initialing it. If the reason for the change is not clear, a reason should also be added to the form. It is never acceptable to use whiteout or to erase a wrong entry before correcting it; anyone reviewing the forms must be able to see what was changed, when and why. Write-overs are also unacceptable. See the example below for a change made correctly.

Date 01/16/~~08~~ 09 JAK 2/5/09

It is in the CRA's best interest to find and have the coordinator correct errors at the site before sending the case report forms to the sponsor. Despite everyone's best efforts, additional errors are usually found when the CRFs go to data entry. Computer-generated errors will be sent back to the site and/or to the CRA. These are usually called queries. Different sponsors have different methods of conducting queries, but usually there is a query form sent to the site; it lists the errors and where they are located on the CRF and asks for a correction or explanation to be made and sent in. Sometimes the CRA is involved in the correction process; sometimes it is solely between the site and data management.

Electronic Data Capture Systems or eCRF systems require electronic review and generation of queries for questions/discrepancies on eCRF data. They can be user- or system-generated. They are worded in the same manner as handwritten queries on correction forms/logs. The user generating the query (CRA or data management staff) and the individual resolving the query, and related activity (study coordinator or data manager) are recorded electronically, including further clarification and resolution. There is an electronic audit trail for query creation and resolution. This is detailed in Chapter 11, Preparing for a study: Protocols, Case Report Forms and Electronic Data Capture.

Whether errors are found by the CRA or come in the form of queries, they should be used as training tools by a CRA. The CRA should explain to the site personnel why each one is an error and how it can be avoided in the future. It is important to review and enter the forms for the first few subjects as early as possible, in order to give timely feedback to the site, with the goal of eliminating similar errors in the future. This is especially important in the case of consistent errors, which are usually due to misunderstanding. Most study coordinators want to do the job correctly and will be pleased to have feedback if it is friendly and constructive.

Error rates should decrease as the study progresses, due to feedback and training by the CRA and data management, as well as to experience on the part of site personnel. If a site continues to have a high error rate due to carelessness, the CRA will need to discuss this with both the investigator and coordinator.

Errors are very costly, both in terms of money and people hours to correct. Although most of the cost is borne by the sponsor, about one-third of the cost is borne by the site. From some informal work done looking at errors, each field that needs to be changed costs approximately $50 to correct (based on salary and benefits costs) and takes about 45 minutes. If a CRA is having difficulty with error rates at a site, these figures extrapolated over the number of errors seen might make an impression on the investigator and coordinator. (See Chapter 20 for additional discussion of errors.)

Good, High-Quality Data

We talk a lot in this business about "good, high-quality data," but this term isn't usually defined. By asking a number of people how they would define good, high-quality data, the following list of characteristics was generated. The general characteristics for good data are:

- They can be evaluated and analyzed.
- They allow valid conclusions to be drawn.
- They are complete and accurate.
- They do not need to be queried.
- They are consistent across subjects and sites.

More specific characteristics are:

- Subjects meet the entry criteria.
- All fields are complete.
- Entries are legible and understandable.
- Values are within range.
- Entries make logical sense.
- The units (for measurements) are correct.
- There are no extraneous comments.

If these characteristics are met, the data should lead to valid conclusions and results that are reproducible. This is the goal for clinical studies.

There are a number of steps sponsors can take to help eliminate errors and generate good, usable data. First, the sponsor should develop good CRFs that are readable, easy for sites to use and have clear directions. Second, don't

ask for the same information more than once in the CRFs; when this happens, the data frequently do not match. (See the section on case report form development in Chapter 11.)

Clear, detailed instructions and good training are also instrumental in minimizing errors. Most errors are due to misunderstandings and these misunderstandings can be eliminated with training. CRA monitoring soon after the first few subjects are enrolled is a big help in clearing up misunderstandings. Fast turn-around on edits and queries will eliminate repeat errors, as well as cross-form edits of which the site was not aware. All of these items will help the site achieve lower error rates, with big cost savings in terms of both time and money for both the site and the sponsor.

Investigational Product (Drug, Biologic, Device)

Both the sponsor and the investigator have a number of responsibilities when it comes to the investigative drug/device. Sponsor responsibilities include:

- Keeping records showing the receipt and shipment, including the:
  - Name of the investigator to whom the drug was shipped.
  - Date, quantity and lot number shipped.
- Retaining accountability records as per regulations.
- Retaining drug samples and reference standards.
- Discontinuing shipments to investigators who fail to maintain proper records or make them available.
- Assuring the return, or destruction, of all unused drug.
- Investigator responsibilities for drug accountability include:
- Maintaining control of drugs under investigation.
- Assuring that the administration of the drug (or device) is under his/her (or a sub-investigator's) supervision.
- Administering the drug/device only to those authorized to receive it.
- Maintaining records of the drug distribution, including dates, quantities and use by subjects.
- Returning unused drug to sponsor or destroying it upon sponsor authorization.

These responsibilities are found in regulations 21 CFR 312.57, 312.58, 321.59, 312.61 and 312.62.

In addition, if the drug is a controlled substance, the sponsor must assure that adequate precautions are being taken for storage of the drug at investigational sites. Storage should be in a locked, sturdy cabinet or similar space,

with limited access. Records for controlled substances must be made available to the DEA if requested.

The CRA is the sponsor representative most likely to be involved with ensuring that the drug/device is being handled correctly at a clinical site, including both storage and accountability. Consequently, the CRA will want to check on the investigational drug or other product at each monitoring visit.

During the site visit, the CRA will want to check that the drug is being used properly and distributed correctly to study subjects, according to the protocol and the randomization scheme.

The CRA should check, at a minimum:

- Master- and subject-specific drug accountability logs for drug shipment receipt and drug inventory notations, as well as subject-specific drug dispensation and return entries.
- Source documents for subject-specific drug compliance counts by the study coordinator and that they reconcile with the drug accountability log.

The CRA should cross-check study drug randomization documentation/kit assignment against drug accountability logs to ensure accuracy. The CRA should review patient drug diary entries to ensure the data reconciles with site source/drug accountability counts.

Some sites are using electronic drug accountability systems to document all IP shipments, dispensation, return, high-level inventory, subject compliance counts and all drug accountability in lieu of the traditional paper drug accountability logs. The CRAs are either given direct access to these systems to review drug accountability during monitoring visits or the drug accountability logs are printed out from the electronic system during monitoring visits for CRAs to review. Regardless, CRAs need to be flexible with the drug accountability logs/systems used by a site as long as the systems are study compliant and the sponsor approves their use.

The CRA should also be sure that the drug is being stored properly, in a secure manner and that any special conditions, such as refrigeration, are being met. The CRA should check study drug temperature monitoring and documentation, to ensure study drug is being stored in the required temperature parameters. Sites will use min/max thermometers, or web-based 24-hour temperature monitoring systems with the ability to print temperature ranges for a specific time period, for CRA review.

If sufficient supply of the study drug has not been sent to complete the entire study, and additional shipments are required, find out where the shipments are received, who receives them and when the receiving area is staffed. Avoid having drug shipments delivered when they might end up sitting on a receiving dock over a weekend or holiday. Not only is loss a concern, but it is also not a good idea for a product to be exposed to heat or freezing temperatures for very long. Know how long it takes a drug shipment to arrive at the site after an order is placed, and be sure that whoever is responsible

for requesting shipments is aware of when new shipments to a site will be necessary. Whatever method of shipment is being used for investigational supplies, it should require a signature upon receipt. This significantly reduces lost or improperly handled study drugs and provides an audit trail for the receipt of the product.

It is important to verify that the study coordinator is accounting for the study drug (product) on a regular basis as the study progresses. It does not work to wait until the end of the study and then try to reconcile how much study drug is left with how much study drug is supposed to be left; it is much more successful to do this on a continuing basis. The concept of drug accountability is pretty simple: the amount of study drug shipped to the site minus the amount of study drug used by the subjects should equal what is left at the end of the study. The problem is, it never seems to work out like this. It depends on how well the site manages the study drug. It is often better if the drug is stored and dispensed by a pharmacy; it tends to do a better job of accounting for it and maintaining records, since that is its primary responsibility. A sample drug accountability form is in Appendix C.

Some sponsors require that the unused study drug be returned. In general, this is a CRA responsibility. On a periodic basis, the CRA will inventory and return to the sponsor the amount of study drug that was unused and returned by subjects, or not used at all because of early discontinuations. After it has been inventoried and packed by the CRA, the site can contact a shipper to pick it up for return. Again, it is usually better to do this periodically throughout the study rather than once at the end. It is easier to keep records straight, and it gets the unnecessary containers out of the way at the site or pharmacy.

Some sponsors will approve of sites destroying unused or used drug, provided the site has an appropriate and documented destruction process, or utilizes a third party with appropriate and documented destruction methods. CRAs will need to review the site's drug destruction process, and/or have the sponsor review the site's drug destruction process, before allowing a site to destroy used or unused drug during the course of a study.

More and more sponsors are utilizing Interactive Voice Response Systems (IVRS) or Interactive Web Response Systems (IWRS) to manage study patient randomization, drug assignments, drug shipment supply and resupply and tracking/acknowledgement of drug shipments to investigational sites. They are centralized systems with the means to centrally manage these responsibilities: IVRS require use of telephone key pad entry of subject data for randomization and study drug assignment. IWRS utilize web-based entry systems to achieve this.

The use of an external pharmacy:

Some investigators may need to outsource the responsibility of study drug storage and preparation if they do not have appropriate equipment or capabilities at their own site. This can happen with complicated therapeutic indi-

cations and/or study designs that require specific study drug preparation and calculation for dosing, frequency of dosing and extensive dosing timeframes (e.g., a two-hour infusion every six hours).

The author has seen firsthand the 483 findings issued by the FDA to an investigator (who used an outside pharmacy) regarding inappropriate study drug dosing, timeframes, storage and transport because they did not ensure adequate training and oversight of third-party pharmacists/staff used in study conduct.

Investigators should ensure that all pharmacy staff involved with study drug storage, preparation and dosing attend the site initiation visit and receive specific training on study drug and pharmacy manuals. The investigator may want to visit the pharmacy in person or send a trusted staff member, at consistent intervals during the study, to confirm that drug preparation, dosing, and dispensation/return documentation is being completed accurately. Investigator responsibility extends to all third-party or external vendors they involve in study conduct.

Unblinded Pharmacy Monitoring

A number of trial designs include a placebo arm, which may warrant the need for key unblinded personnel to help preserve the integrity of the Investigational Medicinal Product (IMP) blind. This is required when placebo differ in size, appearance, preparation or storage requirements as compared to the IMP.

The investigator/site personnel would be exposed to the identity of IMP assignment, should they be involved in the preparation or accountability of said IMP/placebo. They must therefore remain "blinded" to all components of IMP identification and designate an appropriate individual to serve as an unblinded pharmacist, e.g. the individual to receive, document, prepare and sometimes administer the IMP in lieu of blinded site personnel.

This can also occur when a comparator drug has a different appearance than the actual study drug after preparation, and unblinded staff are required to prepare the study drug and comparator and blind the vehicle for administration (e.g., injection or infusion and masking the syringe or infusion bags/lines).

Though the circumstances vary according to trial requirements, the "unblinded pharmacist" typically is the only member of the site staff privy to the IMP process, and is responsible for maintaining appropriate IMP storage, accountability logs and drug assignments from the IVRS or IWRS vendor, not accessible by blinded site personnel. He or she also is tasked with conducting unblinded pharmacy monitoring visits with the unblinded pharmacy monitor.

The individual serving as the unblinded pharmacist is not required to be a licensed pharmacist, nor is he or she necessarily required to have research experience. He or she should be appropriately trained/experienced/licensed (as required) with the storage and preparation of most forms of medication and accompanying administration (oral, parenteral, patches, buccal, etc.).

Investigative sites typically utilize licensed personnel, or personnel involved in medication administration, for this task, such as nurses, respiratory therapists, pharmacy technicians, etc. It varies by state law and the delegation parameters of the investigator and sites must ensure they comply with state law, sponsor and regulatory requirements. The most important thing is that the identity of a patient's IMP assignment is preserved and that the assignment is prepared and dispensed correctly.

The CRO or pharmaceutical company responsible for managing all aspects of trial monitoring must also assign an appropriate unblinded pharmacy monitor to review subject IMP dosing and administration information and perform IMP accountability. Unblinded pharmacy monitoring is conducted exclusively with the unblinded site pharmacist and never with blinded site personnel.

The responsibilities of an unblinded pharmacy monitor include counting pills or measuring unused/used IMP vials to ensure appropriate subject dosing. The unblinded pharmacy monitor will review and cross reference IVRS or IWRS randomization and IMP assignments with source documents, diaries and drug accountability logs to ensure accuracy of IMP assignment, dispensation, dosing, compliance and documentation. The unblinded pharmacy monitor schedules unblinded drug accountability visits, and works with site unblinded pharmacy staff. They may train unblinded pharmacy staff on IMP preparation, dispensation and provision to blinded staff. They provide secure and appropriate correspondence regarding drug assignment and dosing and giving the investigator timely IMP accountability status. They review unblinded pharmacy documents and correspondence and ensure a clear separation of blinded and unblinded monitoring activities.

Clear instruction regarding unblinded pharmacy activities, monitoring, communication and documentation practices will ensure the integrity of the IMP blind and that IMP preparation and administration is conducted in compliance with the protocol and the best safety practices for clinical trial participants.

The unblinded pharmacist will help create an unblinded pharmacy monitoring plan that includes a communication plan between key unblinded personnel, specific timelines for monitoring frequency and appropriate confirmation, report and follow-up letter templates. It should also include the means by which unblinded pharmacy monitoring is conducted—a decided number of on-site visits, or one on-site visit per site with subsequent review of subject drug accountability data performed remotely.

The blinded and unblinded CRAs for a study should not schedule monitoring visits on the same days to ensure all means are employed to prevent unblinding study/site personnel.

Sample Collection

If blood or other samples are to be collected during the study, the CRA should ensure that this is being done and is being done properly. The timing

should be checked to verify that the collection is being done in accordance with protocol requirements. If the samples are stored and batched for shipping, the CRA should verify that storage conditions are appropriate and that sample collection, storage and shipment is documented.

The shipping must be done properly and according to all applicable laws and regulations. There are significant fines for not following appropriate packing and shipping procedures. Proper shipment of dangerous material protects the shipper from exposure to these risks. To verify potential exposure, refer to 49 CFR 107.301-107.339 (hazardous material transportation regulations).

Reports generated on the samples should be communicated and kept according to instructions.

Study Document Review

Another monitoring task is checking the investigator's study document file. It is recommended that the CRA check this file at the first monitoring visit after the study starts to ensure that copies of all pertinent documents are available and filed. If something is missing, it should be relatively easy to get a copy of it early in the study. The CRA may have a copy in his or her file, or the sponsor will have it. Having everything present and accounted for is a good way to start the study.

The CRA should be able to cross-check the investigator study document file with the site trial master file at the sponsor/CRO company, or the Electronic Trial Master File, (eTMF). The eTMF is an electronic filing/storage system, e.g. a structured means of storing essential and other study documents, and other digital content for clinical trials that are required to comply with regulatory agency requirements and institutional requirements. The eTMF will house each study investigator's study/essential documents in one section, as well as maintain other eTMF sections for country specific documents, sponsor internal documents, master ICF and other templates, etc. The investigator section of the eTMF at the sponsor/CRO should be a mirror image of the site regulatory file and the CRA should cross review both files at each monitoring visit to ensure the appropriate documents are file/stored. This is accomplished when investigational sites have internet access or the CRA has a wireless card or can tether via a smartphone for internet access.

The CRA will not need to check the investigator's document file at every visit, unless the sponsor requires it. However, it should be checked periodically, especially if the CRA is aware of changes or when new documents have been added. It is also critical to check it at the end of the study, before it is filed for long-term storage.

Here are some hints for a CRA when checking study documents. Use a checklist for this activity, as it is easy to miss something without a list; a sample checklist can be found in Appendix C. Be sure that the current versions of documents, primarily the protocol and consent, are being used. Earlier versions should be retained in the file for reference only.

Copies of form 1572, IRB approvals and drug shipment invoices (the most common missing documents) should be in your travel file. This way, missing documents can be replaced with your copies. If you don't have a particular document, you can email the in-house CRA or remote monitor and request the document, which will probably be sent to you during the course of your monitoring visit. Any time you replace a document, make another copy for your own file. These tips can save you time and hassles over the course of the study.

Investigator and sponsor document files are now maintained electronically, and reconciliation and provision of missing investigator study documents has become more efficient; reconciliation and identification of missing study documents can be completed remotely, which saves time during on-site monitoring visits.

Great study, wrong protocol

Once, while doing an antihypertension study in a physician's office in North Carolina, we discovered an unusual amount of errors in the case report forms (CRFs). We reviewed the study requirements and then corrected the errors properly; yet, something did not seem quite right. Our in-house folks checked their records and I, as the field CRA, checked the investigator. We discovered that the physician had inadvertently been sent a different protocol than he had signed up for. But… he had done the wrong protocol correctly! He had used the CRFs from the study he had signed up for, but performed an entirely different protocol! We never truly discovered how it happened, and we submitted appropriate documents to fix the problem. A CRA truth learned the hard way: Never assume the investigator has the correct protocol. Check the files and make sure the proper and current protocol is the one being done. Make sure the CRFs are for the correct protocol.

—Senior CRA

Confidentiality

During all monitoring activities, the CRA must be attentive to confidentiality. No study record, other than the consent form, should identify the subject. The CRA has an obligation to help protect the confidentiality of all study subjects. The study documents are also confidential. During site visits, sometimes CRAs have seen competitor's protocols lying around unprotected. All one needs to see is the protocol cover page to know the name of the drug and phase of development. The CRA should periodically remind the investigator and coordinator of the confidentiality of these documents, and ensure that they are kept in a secure location.

Monitoring Locations and Preservation of Confidentiality

Appropriate monitoring space is an ongoing challenge with investigational sites. There is sometimes barely enough room to accommodate investigational site staff, let alone several CRAs during a monitoring visit. The most important thing to ensure during monitoring visits is that the CRA is in a location that ensures a level of privacy and prevention of outside review of confidential study files. CRAs from different sponsor or CRO organizations should never be placed at the same desk/table area to monitor. A large, dedicated monitoring area with individual cubicles and space between cubicles, or a room with separately placed desks, or individual monitoring rooms/exam rooms are most appropriate. Conversations between monitoring colleagues from the same company, working in a shared area, should occur outside of the shared room or in a manner so that other CRAs do not hear or understand the content. Telephone calls to or from the headquarters or the home office should occur in a private area. Confidentiality should be preserved and maintained at all times.

The Health Insurance Portability and Accountability Act (HIPAA)

The purpose of the Health Insurance Portability and Accountability Act is to improve the efficiency and effectiveness of the healthcare system by encouraging the development of healthcare information systems using electronic data interchange for health-related administrative and financial transactions. In addition, HIPAA seeks to establish the required use of national transaction standards while maintaining patient privacy when business and patient information is transmitted electronically between organizations.

All vendors of electronic medical record (EMR) systems must conform to the standards in the Administrative Simplification component of HIPAA. This component encompasses four standards:

1. Electronic transactions and code sets.
2. Privacy of individually identifiable health information.
3. Security to preserve patient confidentiality.
4. Creation of unique health identifiers for patients, health plans, providers and employers.

The fourth standard is one part of HIPAA that will directly affect clinical research. It addresses standards by which unique patient-identifying information can be transmitted electronically, possibly over the internet.

The final HIPAA rule came into effect in 2003. Specific areas of the final regulation affecting researchers are: de-identification of patient health information, as mentioned above; single authorization from the patient required for all uses and disclosures of patient health information; the combining of patient authorization forms with the informed consent document; and the elimination of an expiration date or event for research authorization. The

final regulation also has one set of transition provisions for all forms of research regardless of whether they involve treatment or not. The full text of the final HIPAA rule and an explanation of modifications can be found at hhs.gov/ocr/hipaa.

The End of the Visit

Before concluding a monitoring visit, there are some miscellaneous items to attend to. It is important to check the last site visit report for any noted problems or unresolved issues. These items should be followed up on until they are resolved, and the site visit reports must show how they were followed up. This is something an auditor will look for if the site is inspected later, plus it is good monitoring practice.

The CRA will also want to see if more study supplies need to be ordered, including drug/product, case report forms, lab kits and anything else that may be necessary for the study. If so, ordering should be done before the CRA leaves the site.

If the CRA is involved in grant requests, this should be discussed with the investigator and, if appropriate, a grant request should be submitted.

Before leaving, plan ahead for the next monitoring visit. Explain what materials should be ready for review. If there are scheduled enrollment updates planned, remind the coordinator. The CRA should always schedule the next visit before leaving the site, while both the CRA and the coordinator have their calendars available.

If possible, it is good to write the CRA visit report before leaving the site. If not, write it as soon as possible after leaving, while the details are still fresh in your mind. Before leaving, be sure you have everything you need to take with you and that it is organized. If you have collected CRFs, they should be inventoried, in order, and ready to mail. The investigator and the CRC should have been debriefed about monitoring findings and the status of the study. Before leaving, the CRA should thank everyone for his or her time and efforts during the visit.

If the CRA has told site personnel that he or she will find out any particular information for them, be sure this is done and reported back. It is also nice to follow the visit with a letter recapping any pertinent information, thanking the site personnel for the work they have done and verifying the date of the next monitoring visit.

Monitoring Visit Reports

Most sponsors have a standard monitoring visit report form used to document visits to investigative sites. If a sponsor does not have one, the CRA will want to devise a form to use for this purpose; there is an example of a monitoring report in Appendix C.

The purpose of the monitoring visit report is to document the findings from the monitoring visit. The CRA should use this form to summarize what was done at the investigative site, including CRFs gathered for shipment to the sponsor. This is also where problems must be documented, including what was done to solve them, or to make recommendations of action items for the next visit.

It is important to remember that the visit report is a business document and can be accessed by the FDA in case of a sponsor inspection. The language used should be businesslike and factual; this is not the place to vent frustrations with a site. If the monitoring visit was not as successful as the CRA had hoped, these frustrations can find their way into the report; this is not appropriate. Here are some examples of unacceptable and acceptable language for a visit report:

- **Unacceptable**: "Coordinator doing sloppy work!!! She is the worst coordinator I have ever seen."
- **Acceptable**: "CRFs incomplete and needed many corrections. Coordinator was instructed in the proper way to fill in the forms."
- **Unacceptable**: "Investigator shows no interest in the study. He is never available to meet with me and probably doesn't even know what is going on in the study."
- **Acceptable**: "Investigator not available during this visit. Time with him was scheduled for my next visit, and a letter will be sent verifying the appointment time."
- **Unacceptable**: "This study is so screwed up nobody can tell what's going on. We should close it and never let them do studies again. This is a really terrible site. The coordinator is a dunce, and the investigator thinks he walks on water."
- **Acceptable**: "There are many aspects of this study that need clarification and correction. It is recommended that someone from our compliance department visit the site with me within the next two weeks so that we can determine what needs to be done to ensure that the study is brought into compliance with good clinical practices. After this visit, we will recommend any further actions that appear necessary."

Remember that monitoring visit reports are the official record of CRA visits and will stay in the sponsor trial file for many years. They should reflect what took place at the visit, what was transmitted to the sponsor and problems that were found, plus potential solutions. The ICH E6 Guidelines for Good Clinical Practice summarize monitoring reports very well:

- The monitor should submit a written report after each monitoring visit.
- Reports should include the date, investigative site, name of the monitor, name of the investigator and any other individual(s) contacted.

- Reports should contain a summary of what was reviewed and statements concerning significant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken and/or actions recommended to secure compliance.

Follow-up Letter to the Investigator

It is a good practice for the CRA to send a follow-up letter to the investigative site after a monitoring visit. In this letter, the CRA should thank the site for its time and recap the findings from the monitoring visit. If there are things the site must do, or correct, before the next visit, they should be listed. If there were any questions the CRA could not answer while there, they should be addressed in the letter. A good way to end the letter is to give the date of the next monitoring visit and say you are looking forward to seeing them. For example:

> *I'm looking forward to seeing you again at my next monitoring visit, August 17, 2019. I will be in touch with (Study Coordinator) a few days before the visit.*

Keep your letter friendly, but very professional. These letters are usually kept by the site and become part of its study document file.

> *When I was a brand new study coordinator, I noticed that the monitors would send these nice letters after each monitoring visit, summarizing what they accomplished and what was still outstanding for resolution. What I did not realize was that the list of pending items in the follow-up letter was meant as a "to do" list for me to start working on in between monitoring visits. I thought it was a list of activities for me to accomplish at the next monitoring visit, with the monitor. No wonder my first monitors kept asking me why I waited until they arrived to work on things. They must have thought me lazy. The truth was, I was so overwhelmed and busy learning how to be a study coordinator—reviewing protocols, regulatory binders and case report forms left by my predecessor—that I did not have time to address the items until the monitor came back to remind/help me. The lesson learned by all; never presume an inexperienced study coordinator knows what to do with a monitoring visit follow-up letter.*
>
> *—Elizabeth*

Performance Evaluation Monitoring Visits/CRA Sign-off Visits

It is important for CRAs of all experience levels to be aware of the performance evaluation monitoring visit/CRA sign-off visit process. The appropri-

ate preparation for and proficiency demonstrated during this process will positively impact a CRAs job performance, whether as a new CRA being signed off for the first time to independently conduct the monitoring visit types, or an experienced CRA having continuing proficiency confirmed.

Even if deficits are noted in the performance of the CRA being evaluated, the manner in which the deficiencies are communicated can transform perceived criticism into a positive learning opportunity that will exponentially improve performance.

The performance evaluation monitoring visit is the process of assessing appropriate monitoring visit conduct and confirmation of monitoring task completion by field CRAs. This process includes confirming the performance of new CRAs to independently conduct monitoring visits, also known as the "sign-off visit," assessing the conduct of experienced CRAs in job performance, and ad hoc evaluation of CRAs with suspected performance or quality issues.

The very nature of the field CRA's position working autonomously at investigational sites (away from the CRO/sponsor company office) creates an important need to physically evaluate the CRA's conduct of interim monitoring visits at these very same institutions.

Research organizations historically require annual performance evaluation visits for established CRAs, to confirm continuing proficiency or areas of improvement, and "sign-off visits" as required, for CRAs new to an organization or new to the CRA role.

The individuals qualified to evaluate and sign off CRAs are experienced or Senior CRAs and/or clinical team managers, CRA managers, or others in a management role experienced with monitoring. There is a specific training process and qualification process for sign-off visit leaders that requires periodic refresher training.

The sign-off visit process for new CRAs involves observation of the intended monitoring visit type, prior to the new CRA being evaluated on the conduct of said monitoring visit type. CRAs participating in having their monitoring visit observed (by the new CRA trainee) do not necessarily need to be sign-off visit leaders, but at the very least, competent CRAs in good standing. CRAs conducting performance evaluations should be mindful of the fact that their behavior during the observation of the monitoring visit is almost as important as their performance during the sign-off visit. They must communicate with the CRAs they are observing to obtain the investigational site location, and the tools used in the conduct of the monitoring visit, such as protocols, checklists and study manuals. They should be punctual, professional and never interfere in any aspect of the monitoring visit as they are only there to observe.

The new CRA being signed off (after the observation monitoring visit, during their own official monitoring visit) must show competence in the activities and tasks required to conduct a successful monitoring visit (meeting with the investigator and staff, drug accountability, source/CRF review and regulatory binder review). The individual evaluating the CRA is making a subjective assessment of their performance based on their own experience

with the role and responsibilities of a field CRA. However, it is important for the evaluator to remember that the new CRA needs to show competence, not expertise. A new CRA during a sign-off visit may show uncertainty in an element of monitoring visit completion, but that should not dissuade the evaluator from approving them for independent visit conduct as the entire picture of performance must be assessed.

Evaluating experienced CRAs can be challenging as those being evaluated may presume their experience alone will validate performance, and they may be unresponsive to recommended areas of improvement.

The CRA being evaluated must remember three vital points during the evaluation process:

- Prepare for the performance evaluation visit by reviewing the protocol, checklist, study tools and anything that will keep skills sharp.
- Communicate with the evaluators throughout the process, informing them of a plan to prioritize and complete tasks on site, scheduling times to speak with the investigator and study coordinator, pointing out important study changes or areas of focus, and helping the evaluator identify appropriate data to review to complete the evaluation.
- Follow through with required actions and correspondence with investigational site staff and the evaluator, e.g. whomever appropriate to ensure transparency.

The evaluator must request and review all required study tools to be knowledgeable enough to adequately evaluate the CRA. The evaluator should review source/CRF data already reviewed by the CRA to ensure the data was reviewed/retrieved adequately. The evaluator must be punctual, professional and not overly interfere with monitoring visit conduct. They are there to assess, and not conduct, the monitoring visit.

The tools utilized for CRA evaluation differ by organization, but include a checklist for the evaluator during the monitoring visit and a report that is completed (after the visit) and provided to the CRA's line manager regarding specific performance and areas of strength or deficiency.

Deficits identified will guide the level of retraining, or additional evaluation, as required. This process is communicated in a professional, effective manner at the visit's conclusion. The delivery of the message is most critical to the recipient's understanding and acceptance of corrective action. Comments regarding the evaluation should never be made in front of or in ear shot of investigational staff. It would undermine the CRA and could weaken the site's confidence in the CRAs performance.

Someone who does not initially "pass" the evaluation visit would naturally be disappointed, or even devastated, as it negatively reflects professional diligence and performance (to them). However it is important to understand that failure to pass the evaluation can also be a result of poor training or management. Each situation must be considered separately.

What is of paramount importance is that, once a deficiency is identified,

it is corrected with retraining to educate and prevent future error. The site, the study and, most importantly, the CRA benefit from the process.

An example of a performance evaluation monitoring visit report is included in in Appendix C.

Conclusion

Successful monitoring is the result of experience; knowledge of the protocol, CRFs, the study drug, therapeutic area, regulations and SOPs; people skills and management ability. It is not easy, but can be fun and rewarding when done well.

To close this chapter, here is a story from a CRA friend that's a great example of the strange things a CRA experiences.

The most fruitless trip for no real reason

Our company was doing a very large phase IV study to support changing a prescription drug to an over-the-counter drug. Subjects were recruited through pharmacies and they received a telephone call quarterly to check on their status. If subjects reported that they had been hospitalized, we physically went to their location to investigate the case.

I received notification to investigate a case of a person who had been hospitalized with "AH Blood Poisoning." This was a very unusual report, because no one had ever heard of such a thing. Besides being an unusual case, the person and his physician lived in Star Lake, N.Y.

It was January, and Star Lake is located in Upstate New York between Watertown and Lake Placid. The snow was about two feet deep, and I arrived late. The hotel was old, with one telephone and a bar, whose elderly keeper was also the hotel room clerk. If one asked politely, he would make you a burger for dinner. The next morning breakfast was at the local grocery store because there were no restaurants.

The hospital was very small, and the physician's office was just next door in a small building. The physician was pleasant and most helpful, but he, too, had no clue what "AH Blood Poisoning" was. He told me the man had an infection in his arm because his pet cockatoo had bitten him and this resulted in cellulitis. The man recovered after a course of antibiotics. I reported the cellulitis to our in-house study coordinator and apologized for not being able to ascertain exactly what "AH Blood Poisoning" was. A few days later, he called me back and said, "I think I know what happened." He said, "The telephone operators who interview subjects take down whatever they say verbatim. I checked with the interview service and confirmed that the man had answered the question about whether anything untoward had happened with, 'I had, ah, (AH) blood poisoning.'" And that was the end of the great "AH Blood Poisoning" mystery.

—A CRA friend

Key Takeaways

- A CRA should develop a plan for monitoring each investigative site.
- The frequency and timing of monitoring visits depend on the complexity of the study, the rate of enrollment and site experience and performance.
- Investigative sites should be visited soon after the first subject or two are enrolled.
- CRAs should use checklists for various monitoring activities.
- CRAs should maintain a file for each investigative site.
- CRAs should confirm each scheduled site visit before leaving on a trip.
- CRAs should spend some time with the investigator and the coordinator at each monitoring visit.
- Serious adverse events should be checked at each visit.
- Informed consents must be checked for all study subjects.
- The bulk of CRA monitoring time is spent on case report form review and source document review.
- The purpose of source document review is to verify that the subjects exist and the integrity of the data.
- Risk-based monitoring programs/plans are being implemented more regularly.
- Quick feedback and explanation of errors and queries will help reduce the number of corrections needed in the future.
- CRAs must never correct or modify source documents or case report forms themselves. Corrections can be done only by site personnel.
- Drug accountability should be done throughout the study.
- Study documents need to be checked at the beginning and at the end of the study, and periodically throughout the study.
- The monitoring visit report should summarize the activities that took place during the visit, including what was reviewed, what was sent to the sponsor and any problems that were found, along with solutions.
- A follow-up letter should be sent to the site after each monitoring visit.
- The performance evaluation monitoring visit is a critical component of organizational quality and confirmation of a CRAs performance.

CHAPTER FIFTEEN

Adverse Events and Safety Monitoring

This chapter discusses adverse events and safety monitoring. It is critical that adverse events are monitored during clinical trials, for the protection of the subjects enrolled in the trial as well as future patients and proper use of the drug once it is marketed.

Monitoring safety during a clinical trial is one of the most important tasks a CRA performs. At the same time, safety reporting is one of the most difficult tasks for a study site. There are often misunderstandings about what is deemed necessary for reporting on safety issues in trials, stemming at least in part because of the differences in clinical studies as compared to clinical practice. Also, although the regulations charge the investigator with protecting the rights, safety and well-being of subjects in trials, they don't give much information about actual safety reporting. We will look at the regulations in detail.

Regulations

21 CFR 312.64 (Investigator reports) requires investigators to report adverse events during clinical trials. It states:

> *Safety reports. An investigator shall promptly report to the sponsor any adverse effect that may be reasonably regarded as caused by, or probably caused by, the drug. If the adverse effect is alarming, the investigator shall report the adverse effect immediately.*

By signing form 1572, the investigator also commits to reporting to the sponsor adverse events that occur during the course of a trial, in accordance with 21 CFR 312.64.

ICH E6(R2) has somewhat more information. In the glossary both adverse events and adverse drug reactions are defined as follows:

> **Adverse Event (AE)**
> *An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product. It does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product.*

> **Adverse Drug Reaction (ADR)**
> *In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established, all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out. Regarding marketed medicinal products: A response to a drug that is noxious and unintended and that occurs at doses normally used in man for prophylaxis, diagnosis or therapy of diseases or for modification of physiological function.*

ICH E6(R2) also contain a section (4.11) on safety reporting. In this section, it states that:

> *All serious adverse events (SAEs) should be reported immediately to the sponsor except for those that are designated in the protocol or investigator brochure as not needing to be reported immediately. The initial report should be followed by a detailed written report.*

In clinical studies, sponsors are required to report serious, unexpected, related events that are fatal or life-threatening, to the FDA by telephone, electronic or facsimile transmission within seven calendar days of the date the sponsor first becomes aware of the event. The reporting clock starts when the first person in the sponsor company hears of the event. If the sponsor is using a CRO, the CRO becomes, in effect, the sponsor company; in this case, the reporting clock starts even if a person in the CRO is the first to become aware of the event. Note that the first person may be a secretary or anyone else who happens to answer the telephone or receives the email or fax—it doesn't have to be someone involved with managing the study.

A written report detailing all the information the sponsor has about the event is sent to the FDA within a 15-day time period. This is a total of 15 calendar days from the initial report of the AE, not 15 days after the seven-day telephone, electronic or facsimile report. The sponsor must also send out IND Safety Reports, which will be covered later in this chapter.

Adverse events that are serious, unexpected and related to the investigational drug but not fatal or life-threatening must be reported to the FDA by

the sponsor in writing within 15 calendar days of the date that anyone in the employ of the sponsor first becomes aware of the event. Anyone in the employ of the sponsor is defined exactly as described above for seven-day reporting.

Definitions

There are a number of definitions related to adverse event reporting that are important to know and understand. These are regulatory definitions, not clinical definitions, which is an important distinction to understand when working with investigative sites. These definitions are:

- **Adverse Event.** An adverse event is any untoward medical occurrence in a subject administered a drug (biologic, device). It does not necessarily have a causal relationship with the treatment/usage.
- **Serious Adverse Event.** Serious adverse events are those that result in death, are life-threatening, require hospitalization (or a prolongation of hospitalization in already hospitalized patients), result in a persistent or significant disability or incapacity, are congenital anomalies or birth defects. For clinical studies, these serious adverse events also include any other event that the investigator or the sponsor company judges to be serious, or is defined as serious by the regulatory agency in the country where the event occurred.

It is important to distinguish between the terms "serious" and "severe." The term "serious" is used with the definition above and categorizes events (i.e., they either meet the definition for serious or they don't). The term "severe" refers to the intensity of the event and can be used with any event, without regard to whether or not it meets the criteria for being classified as "serious." For example, a subject can have a severe headache, but it is not a serious event.

- **Related to or Associated with the Drug.** This means that there is a reasonable possibility that the event could have been caused by the investigational product (drug, biologic, device).
- **Expected/Unexpected.** An expected event is one in which the specificity and severity of the event are consistent with the information in the investigator brochure or labeling for the product. Unexpected events are all others.
- **Life-Threatening.** A life-threatening event is one in which the patient is in immediate danger of death unless there is intervention. It does not mean that the patient may die at some time in the future from the event or may have died if the event had been more serious or specific.
- **Significant Disability.** A significant disability is one that causes substantial disruption to the person's normal life and activity.

Later in this chapter, we will discuss ways a CRA can work with sites to help investigators and their staff understand these definitions and how to apply them.

Adverse Events (AEs) on Marketed Products

Companies must collect safety information on each of their products throughout the entire life cycle of a product—from the first time it is used during clinical trials to the time the last dose of marketed drug is sold and used.

Events collected after a product is marketed are called spontaneous adverse events. They are so called because they are reported spontaneously/voluntarily to the sponsor by medical professionals, patients or others, as opposed to being collected systematically during clinical trials. CRAs are not usually involved in the gathering or reporting of AEs on marketed products. Since these events are reported voluntarily, they are all classified as "related" to the drug for reporting purposes. The reasoning behind this classification is that if someone feels there is enough of a relationship to report the event, it makes sense to assume it is related in some way. Remember, however, that an AE must meet all three criteria to require expedited reporting to the FDA; it must be serious, related and unexpected.

The bulk of spontaneous AE reports come to a pharmaceutical company from health professionals. Health professionals often call a pharmaceutical company to report unusual things they have seen in patients who are taking the drug; frequently these are calls asking for further information about the compound. Reports may also come from patients, other consumers or the FDA or other regulatory agencies.

The requirement for reporting AEs on marketed products stems from the fact that clinical trials are never sufficient to provide a full AE profile for a drug. Some of the differences between clinical trials and the marketed use of a drug are shown in Table 1.

All these differences can have an impact on the AE profile of the drug. As an example, assume there is an adverse reaction to a drug that occurs

Table 1: Differences between clinical trials and the marketed use of a product

Clinical trials	Marketed use
• Relatively small number of patients	• Millions of patients
• Tight control	• No control
• Extra care	• Standard care
• Highly-trained physicians	• Any physicians
• Narrow patient population	• Anyone prescribed the drug

about once in every 50,000 people who take it. Chances are this adverse reaction will never be seen during the clinical trial program, which usually consists only of several thousand patients. Even if the clinical program enrolled 20,000 subjects, an event occurring only once in 50,000 probably would not show up more than once, if at all. When the drug is marketed, however, and is available for use by millions of people, these events will become apparent. The purpose of the FDA's safety surveillance program is to ensure that there is a mechanism to report, and learn about, these events.

Adverse Events (AEs) in Clinical Trials

CRAs will be most involved with AEs that occur during clinical trials of a drug still in the development process, before it's reached the market.

Most of the AEs seen during clinical trials will not be serious, as defined in the regulations. In general, these non-serious AEs will be recorded regularly on CRFs and will be reviewed and collected by the CRA during regular monitoring visits. Remember that non-serious events can be severe in intensity but still not meet the definition of serious.

Most sponsors would like all SAEs that occur during a trial to be reported to them by the investigator as soon as he or she becomes aware of them. This is for two reasons: first, to ensure the continued safety of subjects in the trial; and second, to meet the reporting requirements of the FDA. The FDA reporting rules for SAEs occurring during clinical trials are similar to those for spontaneous AEs, although there are some differences.

Sponsors must still report (in writing) all AEs that are serious, related and unexpected to the FDA within 15 calendar days, and those that are also serious and alarming (death, immediately life-threatening) must be reported by telephone, electronic or facsimile transmission within seven days, with a written report within 15 days.

Safety Reporting Sections in Protocols

Every protocol for a clinical trial should contain a detailed plan for the collection and reporting of all AEs, both serious and non-serious. Several key items should be included.

Definitions. The protocol should include the regulatory definitions for an AE and a SAE, as well as the definitions for related/associated and for expected/unexpected events.

Sources of AEs. In general, the standard sources of all AEs will be the investigator reporting about:

- All directly observed events. [I see you have a rash on your arm…]
- Events elicited from the subject by means of a general non-directive question. [Have you had any problems with your health since you were here the last time?] The use of a specific question allows the

sponsor to standardize procedures across all sites. A non-directive question does not prompt a subject to answer in a specific way. Asking subjects about specific events [Have you had any headaches?], although appropriate in some studies, will lead to a higher reporting rate for the specific event than a non-directive question.

- Events spontaneously volunteered by the study subject. [You know, Doc, ever since I started taking these pills, I have had an upset stomach.]
- Laboratory, EKG or other test results that meet protocol requirements for classification as AEs. [Such as laboratory values that are more than 10% outside the normal range.]

Event Collection Periods. The study periods during which AEs will be collected should be specified. Some protocols require them to be collected during a pre-treatment period as baseline data, while others require collection only during active treatment. It is also quite common to collect AEs during a post-treatment follow-up period. AEs are always collected during the entire period that a subject is on, or could be on (in the case of blinded trials), the investigational product or study drug.

Diaries and Other Data Collection Instruments. Whenever data collection instruments are used that may elicit information about AEs (e.g., quality of life questionnaires, patient diaries), the methods for handling these events should be specified in the protocol. Although they certainly have a place in data collection, instruments such as diaries can complicate the orderly collection of AEs. The problem is that subjects may write comments in diaries that refer to potential AEs, and there is often no orderly way to officially collect the pertinent information. There is an example of a patient diary with a written comment about a potential event in Table 2.

Notice that this patient was filling in the times she took her investigational medication, but she also added some additional information—the migraine headache. Certainly, the study site personnel would want to know about the migraine, but this is not the place for it to be recorded. The study coordinator will need to ensure that this event is recorded on the appropriate AE CRFs, and not missed.

Unresolved Adverse Events. Sometimes AEs that occur during a study are unresolved at the time the subject's study participation ends. The protocol should state what is to be done in this case. Usually serious AEs are followed to resolution, that is, until they resolve, disappear or become stable. There is often a time period during which any events that are ongoing at the end of the study are followed. Thirty days is a frequently used time period, but it varies depending on the compound, its half-life, the amount of time the subject was in the trial and the complexity of the diagnosis and protocol.

Exposure in Utero. If women of childbearing potential are allowed into the trial, then the protocol should include instructions for reporting exposure in utero and the subsequent outcome of the pregnancy. In general, the

Table 2: Example: Patient diary

ACMEPHARMA STUDY 1234 Patient diary—Week 4

Name: _____ Betsy Smith_____

Each day, please enter the time you took your study medication. Remember, you should always take one pill just before breakfast (about 8:00 am) and two pills before dinner (about 6:00 pm).

Sunday Date: _____ 2/2/18_____

Morning dose time _____ am

Evening dose time _____ pm

Monday Date:_____

Morning dose time _____ am

Evening dose time _____ pm

Tuesday Date:_____

Morning dose time _____ 8_____ am

Evening dose time _____ 6_____ pm migraine—felt dizzy

investigator will be required to follow up on any cases of pregnancy that occur during the study until the child is born or the pregnancy is terminated. There is usually no requirement for interim visits throughout the pregnancy, just an assurance that the subject will be contacted periodically to determine the outcome.

Timely Notification. The sponsor will want to be notified of serious events by the investigator in a timely manner, usually within 24 hours of the investigator's first knowledge of the event. It is extremely important that the investigator notify the sponsor of each SAE as soon as possible, even if all the details are not yet available. Additional details can be reported as they become available; the initial report should never be delayed while awaiting more information. An investigator may not know about an event for some time after it has occurred, especially if he or she is not the subject's primary physician. The study site may not know about the event until the subject comes in for his or her next appointment or fails to show up for the appointment because of the event. However, the investigator should inform the sponsor of the event as soon as he or she becomes aware of it.

Non-serious AEs are also reported to the sponsor. This reporting is done by way of the CRF and the regular data collection process. Final reporting is done within a reasonable time following completion of the study (usually within three months). There are no FDA requirements for expedited reporting of non-serious events.

Investigator Reporting Responsibilities

Investigators are required to collect, assess and report all AEs that occur during a trial. The following information is usually gathered for each event: onset (date/time), duration, severity (mild, moderate, severe), relationship to the study drug and whether or not it is serious. All events are to be recorded on the CRF. In addition, if an event is serious, the investigator usually is expected to report it to the sponsor very quickly (e.g., within 24 hours).

Not only must the investigator report AEs to the sponsor, but he or she also is required to report these events to the IRB, in the manner in which the IRB has requested. As with sponsors, some IRBs will want notification of all serious events, while others will want to hear only about events that are serious and related, or only those that are serious, related and unexpected. The IRB will tell the investigator what is expected, as well as the report timing and mechanisms. It is important that the investigator notify the IRB according to the rules the IRB has established.

It is a regulatory requirement that the investigator notify both the sponsor and the IRB of AEs.The investigator may receive IND Safety Reports (discussed in the next section) from the sponsor. Whenever one is received, the investigator must forward the information to the IRB.

Sponsor Responsibilities

Sponsors are required to review safety data throughout a trial, so appropriate adjustments can be made if there are any relevant safety issues. For example, the protocol might be amended, or, if there are serious safety concerns, the trial might be stopped. Remember that the sponsor is the only entity that has access to all the safety data for a drug; investigators and IRBs see safety data only from the site or sites with which they are involved. Therefore, the burden falls on the sponsor for prompt and thorough review of safety information as it is generated.

Sponsors have the responsibility of reporting AEs that are serious, related and unexpected to the FDA within the expedited reporting time frames, as discussed earlier.

Sponsors have an additional reporting requirement for SAEs in clinical trials; they must also inform all investigators who are currently working with the drug of any serious, related, unexpected AE. Investigators need to receive the same information that was sent to the FDA and within the same 15-day time period. These reports are called IND Safety Reports. Note that IND Safety Reports are sent to all investigators working with the compound, not just those doing the same protocol. The requirements for IND Safety Reports are found in 21 CFR 312.32.6.

There may be rare instances in which an adverse finding or a series of AEs indicate that the drug has a safety issue that is so serious that its continued use in clinical trials is unacceptable. If this occurs, the sponsor must notify the FDA and all investigators who ever participated in a clinical trial with

the drug of that decision immediately. This includes all investigators who ever studied the drug, not just those with currently active clinical trials. The investigators of open trials must then, in turn, immediately notify their IRBs of the trials' discontinuation for safety reasons.

In device trials, unanticipated adverse device effects (UADEs) are also collected. An UADE is defined as any SAE on health or safety, or any death or life-threatening problem caused by or associated with a device if that effect was not previously identified in nature, the investigational plan or application (21 CRF 812.3(s)). If an UADE occurs, the sponsor must immediately conduct an evaluation of the effect. If the sponsor determines that the effect presents an unreasonable risk to subjects, it must terminate all of its investigations, or at least the ones that present the risk, as soon as possible, but at least within five days after making the determination, and within 15 days of receiving notice of the event. (21 CFR 812.46 (b)(2))

Differences Between Clinical Studies and Clinical Practice

One of the most important tasks of a CRA is training and working with investigative sites on AE reporting. One reason AE reporting is fraught with problems stems from the fact that clinical practice and clinical research are not the same thing, and it is easy to get the two confused when it comes to safety reporting. It is often difficult for investigators to understand that the definitions used for AE reporting in trials are regulatory definitions, not clinical definitions. A good CRA understands the definitions and reporting requirements, and takes the time to thoroughly train each site on the requirements before subjects are enrolled. In this section, we will discuss some ways the CRA can help sites with the proper reporting of AEs.

First, the CRA should discuss with his or her sites the differences between clinical practice and clinical research. In studies, the investigator has a dual role as a physician and an investigator. It is a physician's duty to act in the best interest of the patient, while at the same time it is the duty of the investigator to perform good research. These duties are not necessarily in conflict, but there are differences between the roles that must be understood.

Some examples that a CRA may want to discuss with site personnel are:

- Concomitant medications that might normally be prescribed for a patient may not be allowed under the protocol.
- Treatment periods may be longer or shorter under the protocol than are usual in general practice.
- AEs that are "normal" for the disease usually must be reported under study rules.
- A worsening or progression of the disease may or may not be reported as an AE. For example, a worsening of anxiety in an anxiety trial would usually reported, while a progression of Alzheimer's disease in an Alzheimer's trial might not be reported, as it is a progressive disease.

Occasionally, investigators do not understand the importance of reporting AEs if the events do not seem to be connected with the trial or the study medication, or if they are commonly seen with the disease under study. An investigator may say something to the effect of "we see that all the time in this disease" or "it's not connected to the trial" or "that isn't of any importance." These remarks signify a misunderstanding of the differences between clinical practice and research. As a CRA, you will want to be attuned to this type of misunderstanding and be aware of the need for additional explanations and training.

Sometimes it helps to remind the investigator and staff that the study is being conducted to find out about the investigational drug, including safety as well as efficacy. That is why studies are conducted—we never really know what we will learn about a drug or device when it is under investigation.

The investigator also may need to be reminded of his or her regulatory responsibilities with respect to conducting trials. He or she also is bound by the contract with the sponsor, and most contracts require the investigator to report AEs as mandated by the regulations.

Assessing the Relationship of an AE to the Study Drug

Investigators are usually asked to assess the relationship between an AE and the investigational product by picking the term that best characterizes the relationship of the AE to the investigational product: similar to not related, probably not related, possibly related, probably related, definitely related. Not much may be known about the product, so investigators could be uneasy about making a decision. The following are some aids a CRA might use when training investigators to make these decisions. It is always important to confirm that the PI and Sub-Investigators are assessing AE causality, not inappropriately delegated staff.

Temporal Relationship

Does the timing of ingesting the investigational drug strongly correlate to the timing of the event? For example, assume that the subject takes the drug, comes in two days later and is diagnosed with a cancer. The cancer is probably not related because it occurred too soon after taking the study drug. Or, assume that a subject has been taking the study drug without issue, but develops an AE just after the dose was titrated upward; in this case, the event might well be related to the drug.

Known Patterns of Reaction

Assume that the study drug causes a distinctive rash and a study subject develops that type of rash. Chances are good that the rash is related to the study drug.

Other Potential Cause

Is there something else that would explain the occurrence of the event? For example, assume that the subject is allergic to chocolate, but couldn't resist

that piece of devil's food birthday cake last night. He ate some and ended up with hives. The hives are probably not related to the study drug, but to the chocolate.

Does it Make Sense?
Assume that a study subject suffers from regular migraines, takes the study drug and has a migraine. It's probably not related. Since starting the study drug, migraines have occurred every two-to-three days whereas before taking the study drug, they occurred once or twice a month. They are probably related to the study drug. This might, in fact, be reported as an exacerbation of a previously existing medical condition, e.g., a change in severity.

Dechallenge/Rechallenge
In this scenario, the subject has an AE. The study drug is stopped (dechallenge) and the event stops. The study drug is restarted (rechallenge) and the event occurs again. It is probably related to the drug under study. This is a very definitive test, but it may not be done unless it is allowed in the protocol. Although an investigator may stop a study drug (dechallenge) at any time deemed appropriate, he or she may not restart it (rechallenge) unless it is allowed by the protocol or after discussion with and agreement by the sponsor.

It is important for CRAs to review all documentation related to AEs and causality during monitoring visits to ensure the appropriate individual (PI or Sub-Investigator) is completing the causality.

Common Reporting Problems

There are a number of common misunderstandings that result in incorrect AE reporting. Many of these errors can be avoided if the CRA takes the time to explain them to site personnel in advance. One of these misunderstandings involves symptoms vs. a syndrome. Usually sponsors would like a syndrome to be reported rather than individual symptoms, for example, flu versus cough, sniffles and sore throat all reported separately.

Another common error is the reporting of a procedure, as opposed to reporting the disease/condition that resulted in the procedure. An example of this is reporting a coronary bypass as the event, instead of reporting the heart condition that necessitated the bypass.

Changes in severity are frequently reported incorrectly, or not at all. The general convention is that if an event worsens in severity, it is reported as a new event, even if the event is in the pre-study history for the subject. Some protocols also require the reporting of changes in events when the change is for the better.

Although mentioned earlier in this chapter, it is critical for the CRA to ensure that his or her sites understand the distinction between the terms "serious" and "severe," where "severe" refers to the intensity of an event with no regard to whether or not it meets the criteria for being classified as "serious."

In case of exposure in utero, it is a good idea for a CRA to make a note to

follow up with the investigator on any cases of pregnancy. It is easy to forget to do this when the subject is not being seen on a regular basis.

Dealing with Problems

If a CRA is having trouble with appropriate AE reporting at a site, the first step is to discuss the situation with the site personnel and conduct additional training, including a discussion of both the protocol and the regulations as they pertain to AEs. If training and retraining do not help the situation, the CRA should discuss the situation with his or her supervisor and/or the study medical monitor.

At times, the sponsor will send people from the quality assurance/auditing group to assess the problem. This will usually get the attention of the investigator, as audits can tend to be somewhat frightening. If the problems are not resolved, the sponsor may need to take more drastic action and actually stop the trial at the problem site. (Note: In this case, you will not want to use the site again for another trial.) Stopping the trial for this reason is quite rare, as investigators usually become compliant earlier in the process. Most like to perform well when conducting a study and simply need the help of a knowledgeable CRA to keep things running smoothly.

Everyone involved in clinical trials must recognize that clinical trials differ from clinical practice and that subject safety is paramount. A CRA must have expert knowledge of the AE rules and regulations in order to help study sites remain compliant in this endeavor. Helping sites report AEs appropriately is one of the most difficult and important tasks.

Key Takeaways

- Subject safety is paramount in clinical trials.
- There are differences between clinical practice and clinical trials when it comes to reporting AEs.
- The definitions used in AE reporting are regulatory definitions, not clinical definitions.
- AEs that are serious, related and unexpected require expedited reporting to the FDA.
- All investigators working with an investigational drug must be informed of any event with the drug that is serious, related and unexpected. The sponsor sends an IND Safety Report to each investigator for any AE meeting these criteria.
- The investigator must inform his or her IRB of any IND Safety Report's received from a sponsor.
- Serious AEs must be reported to the sponsor of the study within a very short time period (usually 24 or 48 hours).

- Protocols should contain explicit directions for collecting, assessing and reporting AEs.
- CRAs must train their sites in proper reporting of AEs.

CHAPTER SIXTEEN

Recruitment, Retention and Compliance

This chapter covers three of the most difficult aspects of conducting clinical trials: recruitment of subjects into the trial, retention of subjects after they have been entered and subject compliance with the protocol throughout the study.

Recruitment of Study Subjects

Finding, enrolling and retaining study subjects are some of the largest and costliest challenges facing clinical research professionals today. Given the enormous development costs, it is obvious that companies want to speed up the process as much as possible, allowing for more marketing time before their patent protection for the product expires. The timely enrollment of appropriate subjects into trials is critical to managing the timelines for a development program.

Estimating Enrollment Potential at Sites

Knowing the patient population and being able to accurately estimate the number of subjects that can be enrolled are critical to completing a trial within the given time period. Investigators frequently overestimate the number of potential subjects they have, often because they are looking only at the number of potential subjects who match the overall diagnosis, for example, depression. However, there are a number of other factors that must be weighed and taken into account, including the protocol inclusion criteria and the subjects themselves.

Protocol considerations include the inclusion and exclusion criteria, activities and logistics. The largest constraints on enrollment usually are the

inclusion and exclusion criteria for study entry. These criteria delineate the specific characteristics of the population to be enrolled. They will include demographic parameters, such as age, sex, disease and diagnostic criteria and study-specific requirements. In a study of depression, for example, the following (simplified) inclusion/exclusion criteria might be found:

- Age 18 to 65 years.
- Men and women who are post-menopausal, surgically sterile or using acceptable birth control.
- Depression lasting at least six months, but no longer than one year.
- No previous depressive episodes before current episode.
- No previous treatment with anti-depressive medications.
- Not taking any other medications that might interfere with the study medication (list provided).
- Able to read and comprehend the informed consent document.
- Willing to sign the informed consent.
- Able to swallow pills.
- Able to make weekly visits to the clinic site for three months.

Let's look at how these criteria might affect the ability of a site to enroll subjects.

The upper age limit of 65 may restrict enrollment from sites that treat a large geriatric population. Depression is a disease that tends to recur in people over time, so the criterion that disallows previous depressive episodes would be a problem. The criterion disallowing previous treatment with antidepressants will be a big factor, because if these subjects are already in the care of the investigator many of them already will be on anti-depressive therapies. Willingness and ability to make weekly clinic visits are apt to interfere with a potential subject's life situation, especially when working. On top of these problems, many people just are not willing to participate in research, especially if the protocol requirements are burdensome and they do not see much potential value to themselves for participation.

How can these factors influence the ability to enroll? If a CRA takes the number of subjects a physician has in his or her practice who meet the diagnosis for the study (depression), then halves that number for each major inclusion/exclusion criteria, the number that remains is apt to be close to the number of subjects who will be enrolled. If we assume in our example that the site does not see many geriatric patients, then the four main criteria we need to be concerned with are: no previous episode, no previous treatment, no current medications for depression and willingness to sign a consent form. Let us also assume that the investigator says there are about 400 patients in the practice that suffer from depression. Take 400 and divide it in

half for each of four major inclusion/exclusion criteria.

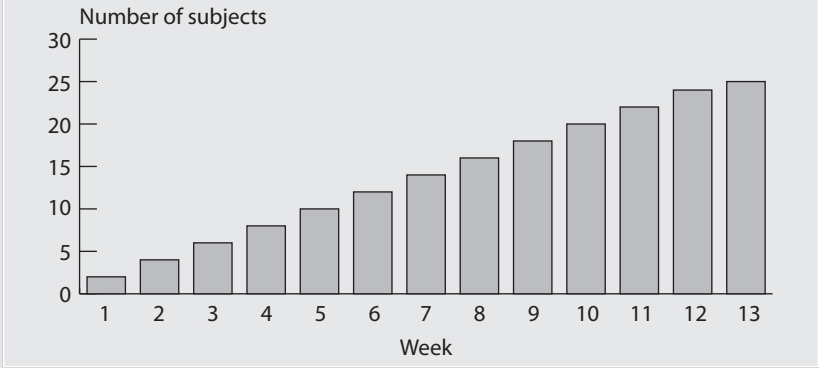
$$400 \rightarrow 200 \rightarrow 100 \rightarrow 50 \rightarrow 25$$

The CRA can assume the site probably will be able to enroll about 25 subjects into the study, in total. This number may be acceptable, but the rate of enrollment needs to be factored in as well. [Note that if a site regularly does research similar to the protocol in question, it may be able to estimate enrollment much more accurately based on its recent experience. In this case, there should be hard data about recent trials, including the inclusion and exclusion criteria, numbers of subjects enrolled and rates of enrollment to back up the estimate.]

The CRA must help the investigator analyze the requirements for the rate of enrollment. The sponsor may expect, for example, two patients to be enrolled every week, for the total of 25. Two patients a week does not seem too onerous, but remember that the study is three months in length and subjects are seen on a weekly basis.

Let's look at what happens as the site begins enrolling. (See Figure 1.) At week one, it enrolls two subjects. During the second week, it enrolls two more, for a total of four subjects on study. By week six, it is up to 12 subjects, and by week 10, it has 20 subjects on study. Since this is a three-month study, all of these subjects are still being seen on a weekly basis, and there are still five more to enroll. (It can be assumed that there are no dropouts for the purpose of this example.) The site must determine, with the CRA's help, if it is able to see and manage that many study subjects within a given week. The investigator's available staff and space must be assessed, along with the ancillary help needed for such things as scheduling visits and calling or emailing the subjects to remind them of their visits and other study responsibilities. Unfortunately, most sponsors and investigators do not look at the cumulative workload as the study progresses. This is an area in which a good CRA can make a significant difference in accurate assessments of enrollment and

Figure 1: Total subjects enrolled



study load capacities. Before starting a study, the investigator should feel confident that his or her site could manage the enrollment rate and number of subjects appropriately.

It is especially important for a CRA to help new sites, those with very little or no study experience, to estimate the potential workload. Understanding what will be required in terms of time, staff and space throughout the trial will add to the overall chance of success.

Other Factors that Influence Enrollment

Another major factor influencing enrollment is competing studies. CRAs need to be aware of the enrollment problems that can result from having a competing study at an investigative site. Competing studies automatically reduce the resources available to your study, including the pool of available subjects. If an investigative site discloses during the feasibility or pre-study visit process that they have a competing study, the CRA must address this during the pre-study visit and obtain honest feedback from the investigator/site about how they will identify subjects for both studies. The type and transparency of the answer can impact site selection.

Even if the study is not competing for the same subject population, too many studies at a site can be a problem; they will compete for the other resources, including coordinator and investigator time and space.

There also can be a significant impact from other studies within the same community. These studies may be trying to enroll the same type of subjects and will draw from the same community pool of potential subjects. For example, in the early 1990s there were more than 150 different AIDS study sites in San Francisco. AIDS activists had a website and a toll-free number that listed all of the studies, plus the main inclusion/exclusion criteria for each as well as contact names and numbers. The people interested in these studies were very well informed and knew which had the most to offer in terms of potential benefit to subjects. Those studies with the newest and potentially best drug were meeting enrollment targets. Enrollment in the others languished. If a sponsor did not have an exciting compound, it was almost impossible to enroll sufficient numbers of subjects.

General interest in the trial, both on the part of the potential subjects and the investigator and staff, can have a major impact on enrollment. CRAs will want to remember that both investigators and subjects have a choice when it comes to participating in a clinical trial; the more exciting the trial and the compound, the more interest there will be in participating. It also helps if the CRA keeps the trial in the forefront of the investigator's and coordinator's minds; if they are thinking about the trial, they will be looking for potential subjects when they see patients in their regular practice. Consistent emails, phone calls and visits from a CRA can help encourage enrollment.

It is important for a CRA to consider the available staff and space at a site, even if there are no competing studies. If the coordinator and other involved personnel do not have sufficient time to conduct study activities, or if there

is no room to store study supplies and carry out study activities, they may be loath to enroll subjects. Sites sometimes underestimate the staff, space and time requirements for conducting a study; the CRA can help them realize what is involved and needs to be done to complete a successful study. The best way for a CRA to assess these things is to look around—check for organization, a relaxed attitude and happy employees. Think about what you see, and make an assessment of whether it appears that an additional study would create a workload problem.

Some sponsor companies require investigational sites to complete and sign a recruitment plan with their site CRA. This is usually done when study enrollment timelines are tight, and the overall subject enrollment numbers are high. Or it is required of sites with poor or non-existent patient enrollment. The purpose of the enrollment plan is to strategize effective enrollment tactics, to devise a plan to enroll a specific number of patients at specific timeframes (per week, per month) and obtain site assurance in writing that they will do their utmost to comply with the requirements of the recruitment plan.

Advertising for Study Subjects

Sometimes advertising for study subjects is planned right from the start of a study. In general, advertising planned from the start is used when it is expected that subjects will be difficult to find and enroll, when the timeline for enrollment is extremely ambitious or when a site routinely advertises for all its studies. In other cases, it becomes necessary to advertise for study subjects when enrollment targets are not being met as the study progresses, i.e., there is already an enrollment problem. However, the goal of advertising is the same no matter when it begins—to find and enroll suitable subjects into a trial.

The FDA has deemed that advertising for potential study subjects is not objectionable. In general, advertising is anything that is directed toward potential study subjects with the goal of recruiting them into the study. It may consist of radio or television spots, newspaper ads, posters on bulletin boards, flyers, internet postings or any other items intended to directly reach prospective subjects. For example, a large general practice that conducts studies has multiple copies of a notebook in its waiting room that contains a brief explanatory page for each study it is conducting, with basic details about the study and whom to contact for further information. These notebooks are considered advertising.

The FDA considers advertising for study subjects to be the start of the informed consent process. Consequently, all advertising must be reviewed and approved by the IRB before use. Note that advertising may not be needed until later in the study, when it becomes apparent that enrollment goals are not being met. It does not matter that advertising materials were not submitted to the IRB when the study was first reviewed and approved; they simply must be approved before they can be used.

There are some items that do not count as advertising under FDA rules. Not included as advertising, according to the FDA information sheet on Recruiting Study Subjects from July, 2018, are:

> *(1) communications intended to be seen or heard by health professionals, such as "dear doctor" letters and doctor-to-doctor letters (even when soliciting for study subjects), (2) news stories and (3) publicity intended for other audiences, such as financial page advertisements directed toward prospective investors.*

Investigators must keep in mind that ads written like news stories are still not news stories, but are more akin to "infomercials" or "advertorials"—ads with a newsy feel or element. They are still ads. All ads need to be approved by the IRB.

Somewhat confusing is the fact that there is a certain class of internet advertising that also does not need prior IRB review. Quoting from the same information sheet above:

> *IRB review and approval of listings of clinical trials on the internet would provide no additional safeguard and is not required when the system format limits the information provided to basic trial information, such as: the title; purpose of the study; protocol summary; basic eligibility criteria; study site location(s); and how to contact the site for further information. Examples of clinical trial listing services that do not require prospective IRB approval include the National Cancer Institute's cancer clinical trial listing (PDQ) and the government-sponsored AIDS Clinical Trials Information Service (ACTIS). However, when the opportunity to add additional descriptive information is not precluded by the data base system, IRB review and approval may assure that the additional information does not promise or imply a certainty of cure or other benefit beyond what is contained in the protocol and the informed consent document.*

Submitting all advertising to the IRB for review and approval is the best course of action. That eliminates all doubt and the need to make the determination of what is and is not appropriate material for the general public.

Advertising is reviewed by the IRB to ensure that it is not coercive and does not make promises about a cure or favorable outcome, or promise things other than what appears in the protocol or the consent. This is especially important if the study involves subjects who are likely to be vulnerable to undue influence, such as children, prisoners and economically or educationally disadvantaged people.

For written advertisements, such as those designed for use in newspapers, the IRB will want to see finished copy to evaluate the whole ad, including type size and any visual effects. For audio and video advertising (radio, television, social media), the IRB will review both the written text and the audio version. Most IRBs will advise the investigator to submit the text first to be sure it is acceptable before the actual audio- or videotaping is done.

Advertising must not make any explicit or implicit claims that the investigational drug, biologic or device is safe and effective or that it is equivalent or superior to any other product. Remember that the reason for the trial is to determine these things; they are not yet known. The ads must explain that the test article is investigational or experimental. Using a term such as "new treatment" implies it is a proven and approved product and is not appropriate.

New Treatment ForThe Common Cold!!!

Cut your sniffle time in half!!!
Get paid $1,000 after only 7 days

Study subjects needed. Three shots a day for 4 days.
Call Success Clinical at 1-800-999-9999

Advertisements may say subjects will be paid for participating in the study, but the payments should not be emphasized by big, bold type or other methods.

Above is an example of an unacceptable advertisement. Note that it says "new treatment," promises to cut the time of the cold in half and emphasizes the overly high payment amount.

A more appropriate advertisement might be:

Research Study

Subjects needed for a study to investigate the effects
of an experimental medicine on lessening
the symptoms of the common cold.

Subjects must be seen by the second day of the cold and must be at least 18 years old. For details, contact Shirley Williams at Eastside Clinic. (222) 222-2000

What information should go into an advertisement? In general, the information should be limited to what prospective subjects need to know to determine if they might be interested in and eligible for the study. These may include the following items, according to the FDA information sheet:

> *Generally, FDA believes that any advertisement to recruit subjects should be limited to the information the prospective subjects need to determine their eligibility and interest. When appropriately worded, the following items may be included in advertisements. It should be noted, however, that FDA does not require inclusion of all of the listed items.*

1. *the name and address of the clinical investigator and/or research facility;*
2. *the condition under study and/or the purpose of the research;*
3. *in summary form, the criteria that will be used to determine eligibility for the study;*
4. *a brief list of participation benefits, if any (e.g., a no-cost health examination);*
5. *the time or other commitment required of the subjects; and*
6. *the location of the research and the person or office to contact for further information.*

CRAs should be familiar with the information in the FDA information sheet, noted above, so they may better assist investigators in the proper development and use of advertising materials. The CRA should review all ads to make sure they are IRB-approved prior to use.

New Strategies for Subject Recruitment

Google

It is very common for potential study subjects to conduct Google searches on their medical condition, or even to look for possible clinical trials in which they might participate. If you want your web page to be available to potential trial subjects, there are two ways to make this happen on the Google search page. The first is in the unpaid section, called the "organic search" section. The other is in the paid section, "sponsored links." The sponsored links section is the list that shows up on the right-hand side of the page, or in the top section.

The sponsored links are based on using Google "adwords," which link your ad to a specific page on a website. This is based on a system that allows you to set one or more search terms. If the term is typed in by a Google user, the ad will show up, and if the user clicks on the ad he or she will be directed to the specified web page.

Whether your ad actually shows up or not depends on how much you are willing to pay to direct a user to your website. This is called "cost per click" (CPC) and is paid only when the user clicks the ad and is directed to your web page. The CPC determines how often and how high your ad will appear in the sponsored links—the more you pay, the more often this will happen. The more specific your search term, the less competition there will be, so your term will cost less and show up more often. For example, a general term like "clinical trial" will require a higher CPC to outrank competition, while a term like "transcranial electronic stimulation" could show up high in the sponsored links with a relatively low CPC. In fact, if there were no other company using the search term, you could end up at the top of the sponsored links list at a small CPC. It's important that your web page is carefully

and professionally designed for each trial, with the appropriate keywords and information to both attract potential subjects and aid in achieving a higher level in the organic search section. Remember, all advertising, including internet advertising, must be approved by an IRB before use.

Note that many people may not trust ads, so a listing in the organic search section will usually result in a much higher click rate than a listing in the paid section. On the other hand, if a subject is searching for a new treatment for a disease, he or she might also click on an ad.

When you set up an adwords system on Google, you have the option of indicating a geographical region from which you want to attract searchers. This is called "geo-targeting" to indicate areas near your study site's locations. For example, if you had a study site in Chicago (or in Madrid), you could indicate that if a searcher in the Chicago area (or Madrid) is looking for information on transcranial electronic stimulation, you will pay the CPC amount to Google if your ad is shown and the searcher clicks on it. This could be especially useful for global trials.

The major benefits of using geo-targeting with adwords are that it allows directing a potential subject to your web page, and if you have no presence in a certain region there is no need to spend adword costs on that region. This is an interesting technology for enhancing subject recruitment, especially in more difficult or esoteric trials for which enrollment is expected to be difficult.

Although Google is currently the largest search engine, others also might be worth using, such as MSN's BING. Note that different search engines may be more popular in countries other than the U.S., e.g., Baidu in China.

Social Networks

There has been an explosion in the growth and use of social networks, such as Facebook, Twitter and Instagram, which has created new opportunities for the recruitment of subjects into clinical trials. Used correctly, social networking can be an effective method for generating pre-qualified patient referrals.

According to the website Marketwired.com, February 09, 2017–"A study of clinical development teams reveals that 57% of surveyed contract research organizations (CROs) and only 33% of pharmaceutical and medical device firms incorporate social media platforms into clinical trial patient recruitment strategy."[2]

Ads can run on social networks, as well as on Google. Since people have chosen to belong to these networks, they are more inclined to accept and act on messages received on these sites than compared to unsolicited advertising. Messages are also shared exponentially, without huge cost to the messenger.

Social networking sites have the ability to target ads to individual user pages based on information in the user profile, including location. Because these networks are global in scope, geo-targeting can be used to specify areas for desired recruitment of study subjects.

A new trend is a Facebook page for study sites. Social media-savvy sites generate a large number of "likes" for their Facebook pages, which increases

exposure and potential study-patient identification.

Study sites also use Instagram to showcase pictures of their facilities or staff to further promote services.

YouTube videos might also be used to disseminate information about a trial. A YouTube video can also have a link to a web page, so it could connect a viewer directly to your web page with additional information about a clinical trial.

There is a website, clinicaltrials.gov, that is often used by investigational sites where clinical studies are listed by company. Potential subjects then find the studies and sign up. This is an emerging and effective means to identify patients.

Many trial sponsors have questions about the value and legality of reaching potential participants online. However, when it comes to using these networks for clinical trial recruitment, sponsors are not selling products or making any claims about treatment. They are only presenting clinical trials, in IRB-approved advertising, as an option to potential participants. This is really no different than any IRB-approved ads that might be used, i.e. newspaper or radio ads. It is just the location of the ad that is different (online). Using social networks is simply a new tool to reach a broader population and to help with the always difficult task of recruiting enough subjects for a clinical trial.

Other Recruitment Methods

Although advertising comes immediately to mind when discussing recruitment for study subjects, there are several other methods for finding subjects. The starting place for most sites is their own clinical/medical records. Many sites keep their patient information in a computer database that allows them to search based on diagnostic criteria. After they have found patients with an appropriate diagnosis, they are able to contact them to ascertain their interest and suitability for the trial. Contact made via telephone or email to database patients is an effective means of follow-up. In the case of studies in chronic diseases, such as diabetes or hypertension, most subjects will probably come from the investigator's own practice. In the case of acute diseases, such as pneumonia and other infectious diseases, searching the investigative site's records may not be particularly useful.

Many potential subjects hear about a trial by word-of-mouth, perhaps from a friend who is in the trial. Sites that conduct a number of trials often gain "free advertising" from current or past study subjects spreading the word. Subjects also find clinical trials by talking to people, searching the web and contacting organizations, including disease-related support groups and pharmaceutical companies.

There are many websites available to potential study subjects that list trials that are in progress or about to start. CenterWatch, for example, has an online database listing of clinical trials that is easily accessible (centerwatch.com/clinical-trials/listings/).

Advocacy groups for various diseases, such as AIDS, are sources of information about trials; sites may receive interested subjects from these groups or from people who have been in contact with them.

There are also dedicated clinical trial recruitment companies that provide expertise on advertisement and targeted recruitment campaigns, and strategies to identify and recruit patients for clinical trials.

Additionally, there are specific websites for clinical trials advertisement purposes.

Frequently, other physicians or healthcare professionals will refer potential subjects to a trial. Investigators often contact other physicians in the community to inform them of the trial, and ask that it be mentioned to suitable subjects. The investigator may make these contacts by phone or may send letters to other healthcare professionals in the community.

Usually, finding subjects for a trial is accomplished by a combination of methods. The more difficult it is to enroll, the more variety there will be in the methods used to attract potential subjects. It is important for a CRA to monitor enrollment and enrollment rates right from the start of each study and make suggestions for ways to enhance enrollment before it becomes a major problem. It is much easier to help when it begins to look like there may be trouble than to wait until there is a major problem. The way to fix enrollment problems is often by implementing several small ideas and suggestions. Not everything works in each case, and a single change is frequently not sufficient.

I once monitored a trial for a rare genetic mutation. Several investigators informed me that they were contacted by their patients about the trial, which is how the investigators became involved with the study and the sponsor. An example of patient centricity at its most admirable.

— Elizabeth

Payments to Research Subjects

It is quite common for subjects to be paid for participating in clinical trials, especially in the early phases of development. When subjects are paid, however, it is viewed by the FDA as a recruitment incentive, not as a study benefit. All payment schedules must be approved by the IRB in advance of the study, or in advance of being used. The IRB will look at both the payment amounts and the timing of the payments to be sure they are not coercive and would not present an undue influence on the subject's trial-related decisions. The payment amount must be included in the informed consent.

Subjects are usually paid on a regular basis throughout the trial, most commonly for each completed visit. It is rarely appropriate to pay subjects only if they complete the entire trial; this might encourage them to continue with the trial even if they otherwise would have discontinued due to side ef-

fects or other reasons. The FDA does allow a small payment as an incentive to finish the study, as long as it is not coercive. However, the IRB must determine that this bonus payment is reasonable and not so large that it would influence subjects to stay in the trial if they otherwise would withdraw.

The amount of the payments to subjects varies with respect to the complexity of the study and the involvement of the subjects. Payments are usually designed to cover any costs the subjects might incur by participating, such as transportation costs, parking, lunch and childcare. Payments must not be so large as to be coercive; that is, the subjects should not be entering a trial only because of the compensation. Before approving subject payments, the IRB will also take into account where the study is being conducted and the patient population. Payments of $25 per visit may be no enticement at all to people in some neighborhoods, but may constitute a great deal of money and enticement to subjects in other areas.

The exception for payments is in phase I trials, in which healthy volunteers are the subjects. In this case, there are no real benefits for participating in the trial, so subjects are usually paid more. The amounts are not exorbitant, but are higher than in other trials and generally compensate the subjects for the greater amount of time required, such as overnight stays in the testing facility. Note that in the FDA's Information Sheet on Payment and Reimbursement to Research Subjects, July, 2018, it states "Paying research subjects in exchange for their participation is a common and, in general, acceptable practice. Payment to research subjects for participation in studies is not considered a benefit that would be part of the weighing of benefits or risks; it is a recruitment incentive. FDA recognizes that payment for participation may raise difficult questions that should be addressed by the IRB. For example, how much money should research subjects receive, and for what should subjects receive payment, such as their time, inconvenience, discomfort or some other consideration. In contrast to payment for participation, FDA does not consider reimbursement for travel expenses to and from the clinical trial site and associated costs such as airfare, parking and lodging to raise issues regarding undue influence. Other than reimbursement for reasonable travel and lodging expenses, IRBs should be sensitive to whether other aspects of proposed payment for participation could present an undue influence, thus interfering with the potential subjects' ability to give voluntary informed consent. Payment for participation in research should be just and fair. The amount and schedule of all payments should be presented to the IRB at the time of initial review. The IRB should review both the amount of payment and the proposed method and timing of disbursement to assure that neither are coercive or present undue influence [21 CFR 50.20]."

Some sites routinely pay subjects for participating in trials, while others never pay study subjects at all. Either is acceptable. What is important to remember about payments to study subjects is that they must not be coercive or present undue influence, and that they must be pre-approved by the IRB.

Incentive Payments to Healthcare Professionals

There are two types of incentive payments: those paid by the investigator to other professionals to encourage them to find study subjects, and bonus payments by study sponsors to investigators and their respective staff to enhance enrollment.

Incentive payments to healthcare professionals by an investigator for the referral of study subjects are known as referral fees or finder's fees, examples of which are payments made to a coordinator or nurse, resident or intern physicians or other local physicians for each subject that is referred and entered into a study. These payments are usually not acceptable and may compromise the integrity of a trial. They may also be in violation of regulations or institutional policies.

Some states have laws that prohibit referral fees. For example, the California Health and Safety Code § 445 clearly prohibits referral fees. It states:

> *No person, firm, partnership, association or corporation, or agent or employee thereof, shall for profit refer or recommend a person to a physician, hospital, health-related facility or dispensary for any form of medical care or treatment of any ailment or medical condition.*

Also, the American Medical Association has stated in its Code of Medical Ethics that referral fees for research studies are unethical. Section 6.03 of the code, Fee Splitting: Referrals to Health Care Facilities, states:

> *Offering or accepting payment for referring patients to research studies (finder's fees) is also unethical.*

Many IRBs have taken a firm stand on the issue of finder's fees and will not permit them.

Incentive payments to healthcare professionals also include bonus payments by the study sponsor to investigators and coordinators for enhanced (faster or more) enrollment. True bonus payments are usually not acceptable because they may encourage the enrollment of "borderline" subjects, those that the investigator otherwise would not recruit. This creates a conflict of interest and should be avoided.

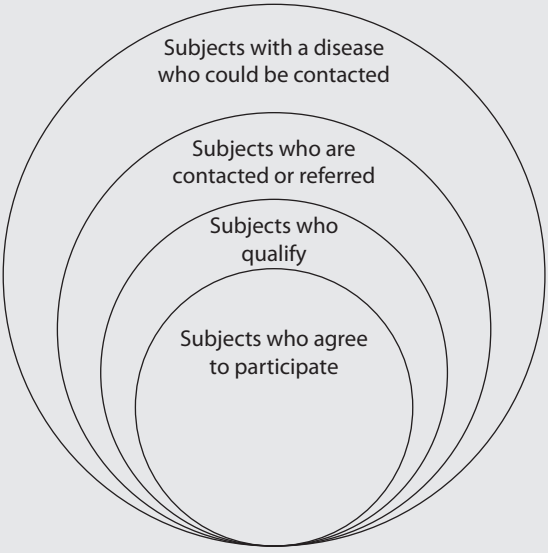
There is no problem, however, with a sponsor covering true extra costs for enrollment procedures. These payments might be for additional people to help with the screening of potential subjects, advertising costs or other direct costs borne by the investigative site. This is frequently decided upon before the study begins, even though not implemented unless necessary to increase enrollment or speed the rate of enrollment. For example, a sponsor may be willing to pay a per-screen amount for the pre-screening of study candidates. In this case, there is usually a limit on the number of pre-screens allowed in relation to the number of subjects actually entered into the trial. This ensures that the site is actually looking for and pre-screening suitable candidates. The CRA will usually act as the liaison between the site and the sponsor on questions of appropriate support for enrollment.

If site personnel are not sure whether or not a payment plan is appropriate, they should contact their IRB for an opinion before implementation.

Summary

Timely and appropriate recruitment and enrollment of subjects into clinical trials are essential for a drug, biologic or device development program. CRAs must be aware of the regulations regarding recruitment and have an understanding of the potential problems and solutions for enrollment. It is important to remember that at each step, from potential patient identification, through prescreening, screening and eligibility, the number of potential subjects decreases. The Venn diagram in Figure 2, patterned after one developed by Bert Spilker,[3] shows this in graphic form.

Figure 2: Venn diagram showing stages of enrollment for a clinical trial



The CRA plays a significant role in subject enrollment by acting as an advisor to sites, by being aware of the rules and regulations regarding recruitment and by being the liaison between the sponsor and the site for managing enrollment concerns.

Retention of Study Subjects

Once subjects are enrolled in a trial, it is important that they stay in the trial until it is complete, if at all possible. CRAs should be familiar with both the

reasons subjects drop out and how retention can be enhanced. The CRA should be the expert for helping sites with retention problems. In this section, we will explore the reasons that subjects leave trials and what can be done to increase retention.

Reasons Investigators or Sponsors Discontinue Subjects

Investigators and sponsors may discontinue a subject for a number of reasons. Some are medical, some are based on the patient's compliance and cooperation and some are trial-related. Some of the more common reasons for discontinuing a subject are listed below.

Medical Reasons for Discontinuation:

- Failure of the investigational drug to be effective.
- Intolerable adverse events.
- Patient's condition deteriorates.
- Patient's condition improves (eliminates need to continue).
- Patient develops an intercurrent illness (an illness other than the one under study but occurs during the course of the trial).
- Pregnancy.
- Abnormal laboratory values.
- Did not meet original entry criteria (discovered after study entry).

Patient Compliance and Cooperation Reasons:

- Unacceptable compliance with protocol activities.
- Unacceptable compliance in taking the study medication.
- Not keeping appointments.
- Not cooperating with study staff and/or study procedures.
- Use of non-approved concomitant medications.
- Moved out of the area.

Trial-related Reasons:

- Trial was terminated by the sponsor due to safety concerns.
- Benefit so great trial is no longer ethical.
- Business reasons.
- Investigator no longer to continue the trial (retired, died, moved).
- Investigator did not meet enrollment targets in a timely fashion or did not comply with the protocol.

- Investigator had other problems or was put on the debarred list by the FDA. Since it was either the investigator or the sponsor who decided to discontinue patients or the trial for these reasons, there would be no further discussion.

The main concern for CRAs is helping sites retain subjects who would have decided to drop out of the study on their own.

Reasons Subjects Drop Out of Trials

It is important to differentiate between those subjects who choose to drop out on their own and those who are discontinued by the investigator or sponsor. There are many reasons study subjects decide to stop participating in a trial. Some of them are valid medical reasons, such as intolerable adverse reactions or a worsening of the disease. These cases are usually discussed with and agreed to by the investigator.

There are, however, other reasons that subjects drop out, that are not so compelling and could perhaps be avoided. This is when the CRA can help site personnel understand what causes some of the problems and how they might prevent them from occurring. The key for the CRA is catching problems, or patterns of problems, early so they can be fixed. The CRA wants to ensure that losses do not become the standard and that they do not exceed what normally would be expected during a study. Some reasons subjects drop out are:

- The subject does not understand the importance of remaining in the trial even when the disease condition has improved.
- The study requirements are too burdensome.
- The subject loses interest in the trial.
- The medication is unpleasant to take.
- The subject does not like some of the study staff or finds people at the investigative site unfriendly (which could be anyone, including the receptionist).
- The subject has to spend too much time at the clinic.
- Transportation, childcare or time off from work difficulties.
- The subject is upset about some aspect of the trial.
- Friends or family are unhappy about the subject's participation.
- The subject has a change in his or her personal life.

Maximizing Retention in Clinical Trials

The secret to subject retention in clinical trials is easy. It's not really a secret at all, but is just plain common sense. All site personnel have to do is be nice,

treat subjects well, spend time with them, listen carefully to what they are saying and communicate openly and often.

Investigators and study coordinators are very busy people. They get rushed and behind on things, have good and bad days and experience the same problems as the rest of us. Nevertheless, if a study is to go well, they must be able to set aside their concerns and problems when study subjects arrive for their visits. Study subjects want to feel that their contribution is important, and during their time with the investigator and/or coordinator want to be the sole focus of attention.

When a study subject comes in for a clinic visit, he or she wants to be able to discuss what has happened since the last visit, to have any study concerns allayed, to be praised for doing well, to have questions answered and to be treated like an important partner in the study venture. In short, a study subject wants to be appreciated. After all, there are risks in becoming part of a study, there is no guaranteed outcome and it is voluntary. No one has to participate at all. People who volunteer for studies are special people, and they should be treated that way.

Given the premise of wanting to be treated well, there are many, frequently small, things that can make subjects decide that trial participation may not be worth the effort. Some of these things are:

- Having to wait when coming in for an appointment.
- Not being treated nicely and with respect.
- Not seeing the investigator or the coordinator, but being seen by a "substitute" they don't know.
- Not seeing the same person at each visit (developing a one-on-one relationship).
- Being rushed and hurried through the appointment.
- Feeling that the investigator/coordinator doesn't really want to see them.
- Not being asked about how they feel and how the study is going for them.
- Not having the opportunity to ask questions.
- Being afraid to ask study-related questions.
- Being made to feel dumb or silly when asking questions.
- Being berated for doing something wrong.
- Having the investigator or coordinator disparage the study.

There are also situations in which a subject does not return and is lost to follow-up, or in which a subject drops out but refuses to give a reason, other than personal choice, which is the subject's right—he or she doesn't have to

give a reason. But that doesn't help site personnel understand if there is a more pervasive, underlying problem. These situations are difficult to prevent, so the investigative site cannot do much about them.

If there are many of these cases at a center, however, they should serve as a wake-up call. Chances are the real reasons are in the list above, but the subject doesn't want to say anything about them to site personnel.

These problems can all be fixed, but they first need to be recognized and acknowledged. It's critical to catch them early. Some problems are easy to fix. For example, if a subject has a logistics problem, such as transportation to the investigative site, a solution may be to pay for a taxi or other transportation vendor to transport the subject back and forth. If childcare is a problem, perhaps the visit time can be adjusted to an evening or weekend time so the subject can make appropriate arrangements. Questioning the subject about problems and being willing to help with arrangements or adjustments may allow the subject to continue participation. Subject payments in any form (cash, goods or services) should be reviewed by the IRB. It is fine to vary payments according to subjects' needs (taxi fare for one, but not another), but it would usually be stated as "payment for (actual) transportation costs," for example. Since these are actual costs to subjects, they would not be considered coercive. Coercion normally implies a sum of money above costs, with no purpose other than to entice people to enter the trial.

Some successful investigative sites have very clever ways of making their study subjects feel happy, important and wanted. Some of the ideas and little things that have added to retention success for sites are:

- Giving each volunteer a special study t-shirt.
- Giving them mugs, tote bags or gym bags for a study where there was exercise testing.
- Separate waiting room with coffee, tea and doughnuts—and current magazines and newspapers.
- Internet access while they wait for a study visit, or during a study visit that requires timed testing with long waiting intervals.
- Reminder calls, texts or emails the day before each visit.
- Sending a cab to pick someone up if transportation is a problem.
- Thank you notes from the coordinator after a few weeks on a study.
- Thank you notes at the end of the subject's participation (leads to repeat volunteering).
- Balloons.
- Birthday cards.

For new investigative sites especially, though beneficial for most sites, it helps if the CRA meets with the investigator and coordinator at the begin-

ning of the trial and plans out a strategy to help retain subjects. Many sponsors are willing to foot the bill for little extras (mugs, t-shirts) that might encourage subjects to feel good about their participation and remain in the trial until completion.

Any time there is a pattern of more-than-expected dropouts at an investigative site, the CRA should discuss the situation with the investigator and coordinator. Each case should be analyzed. Perhaps the reasons are clear-cut and recognizable, but perhaps they are not. It may be time to reflect on the atmosphere at the site and take a hard look at how subjects are being treated. The site personnel might even want to talk with subjects about their perceptions of how the study is going, how they feel when they come in for visits and if there are ways in which the investigative site could improve the study process.

Difficult as it is, site personnel must also take an honest look at their interactions with study subjects. Sometimes it helps to think about how you would feel if you were in the study, or how you would feel about having one of your loved ones participating.

Summary

Retention of subjects in clinical trials is critical to the completion of an informative, sound clinical trial. Site personnel should help subjects understand that a successful trial is a partnership between the subjects and the investigative staff. Respect, courtesy, honesty and open communication on the part of both subjects and investigators will increase the chances of successfully completing a study.

Subject Compliance

Clinical trials are conducted to assess the safety and efficacy of an investigational drug. To be able to accurately assess safety and efficacy, however, study subjects must take the medication as it is prescribed. Unfortunately, subjects do not always do this. In this section, we will look at compliance, what can go wrong and how to increase the probability of good compliance.

Undetected poor compliance can lead to invalid study results. Lack of compliance in one subject may affect only that particular subject; if several subjects are noncompliant, however, it can invalidate the entire study. Noncompliance can have the following results:

- An effective medication may look ineffective. This can mean that a medication that would be effective, and that would be of benefit to patients, never makes it to the marketplace. This is an unfortunate result for the sponsor that has made the investment in the investigational drug, and even more unfortunate for those people who would have received benefit from it.

- An ineffective medication looks effective. This result is worse than the one above because, once marketed, the medication will be relied on to effect a cure and will not be effective in doing so.
- Failure to detect serious adverse events.
- Inappropriate dosage labeling. Depending on the noncompliance, the drug labeling could recommend either too high or too low a dose. This is not good in either direction—patients could be taking too little to be an effective treatment or more than they need, which could lead to an excess of adverse reactions.
- The effects of the investigational drug in noncompliant subjects cannot be extrapolated to compliant subjects. It is very important that all study subjects are as compliant as possible during their involvement in clinical trials.

Reasons for Noncompliance

Sometimes study subjects are noncompliant for disease-related reasons. One reason is a lack of symptoms, or what can be called the "antibiotic effect." As many of us know from personal experience, it is hard to remember to take medications when you feel better and have very few or no remaining disease symptoms. A prime example of this is the standard 10-day course of treatment with many antibiotics. After five or six days, when the patient appears to be better, it is very common to stop taking the pills. The subject has become noncompliant with the medication schedule; this happens in trials as well as in general practice.

There are also compliance problems with people suffering from terminal diseases. When a person knows he or she is going to die soon anyway, he does not have the same incentive to take a course of medications that he might otherwise have.

There are many other reasons subjects are not compliant when it comes to taking medication. Sometimes they just forget to take their pills. Sometimes there is a lack of belief in the treatment—"it isn't going to work anyway, I'm sure I'm on the placebo." If the medication is unpleasant to take, such as having a bad taste or pills so big they are hard to swallow, compliance may be poor.

Noncompliance can result from the way the drug is packaged. Think about using safety containers (childproof lids) in an arthritis study, for example. The subjects may not be able to open the containers without help, which will surely affect compliance. Sometimes a study drug is packaged in large blister packs containing several days' worth of the drug and with each day's drug clearly marked as to when it should be taken. At first glance, it appears this would help compliance, but think about it a bit more. What happens when a subject has to go to work? Most people do not want to carry a large blister pack to work with them and have other people asking about it.

Consequently, subjects might take the day's drug out of the package and just carry it in a pocket, not knowing that the ordering of the pills for the day is important. They then become noncompliant.

Sometimes subjects just do not understand the dosing scheme, especially if it is complicated. "Oh, it's two white ones and one pink one? I thought it was two pink ones and one white one. That's why I ran out of pink ones last week." Sometimes it is the regimen that is confusing, with too many pills, too many different times per day to take them or confusion about the times and/or doses. It also can be the duration of the study, as subjects can lose interest over time.

Subjects may also become noncompliant because of adverse reactions. If a subject becomes nauseated after taking the medication, or thinks it is causing headaches, he or she may not take it as often as required, if at all. A subject may not take medication appropriately because of mistrust, either in the medication or in the physician. A subject may be influenced by family or friends in ways that affect compliance; if people important to the subject do not want him or her to take the pills, or be in the study, this may affect compliance.

Other ways in which subjects may be noncompliant related to the study medication are by prematurely discontinuing the drug or by sharing the drug with other people. Some of the other reasons subjects may become noncompliant include:

- Taking other medications at the same time, when the other medications are not allowed by the protocol.
- Using alcohol or other disallowed substances such as marijuana while in the study.
- Changes in a living situation that has an impact on when and how the study drug is taken.
- A mental condition that has an unfavorable effect on the ability to follow protocol instructions.

There are other compliance issues in studies that are not related directly to the medication. Subjects may also be noncompliant by missing visits or not coming in within the visit windows. They may not adhere to other study requirements, such as special tests (eye exams, for example), dietary requirements or keeping diaries.

Sometimes compliance problems stem from investigator-related reasons. Subjects will be less compliant if it is difficult to schedule study visits, or if they are kept waiting when they arrive for a visit. If study staff do not keep appointments, subjects are apt to do the same. Worst of all is a poor physician-patient relationship. In general, subjects want to please the physician and do things correctly, but if the relationship is poor, the subject is not as likely to care about complying with study requirements.

Unfortunately, there are many ways to be noncompliant, both on purpose

and by mistake. The key is discovering them and fixing the problem before it has a negative impact on the study.

Managing Compliance

Study protocols should be designed to enhance compliance as much as possible. They should also make it possible to monitor compliance.

CRAs should discuss compliance with site personnel and help them understand not only why it is important, but also how they can help to ensure compliance during the study. First of all, the CRA must help the investigator and coordinator understand that they need to work with their patients, both before and during the trial. There are certain things study patients must be aware of and do during the study. Just as clinical trials are different than clinical practice for investigators, they also are different for study subjects. The investigator and coordinator must ensure that potential study subjects are aware that if they are in the study, they must:

- Come in for all study visits on time and within the visit windows.
- Answer the questions truthfully, especially with respect to their medical histories and disease history.
- Cooperate fully with study procedures. This is one reason it is critical that the investigator fully explains the study to potential subjects.
- Allow tests to be done as appropriate, and on time.
- Take study medications as prescribed.
- Follow all study directions.
- Ask if something is not clear and inform the site of any problems.
- Report any new medications (OTC or Rx) before they take them or as soon as possible afterward.

The CRA should emphasize to the site that patients must be told how important it is to answer questions truthfully, especially about their compliance during the study. Patients need to know that it is better to let the investigator/coordinator know that they missed some doses than say nothing about it, and that they will skew the results of the study if they are not forthcoming with this information. A CRA should remind the site personnel that they must thoroughly question each subject about compliance at each visit. They should be sure to let subjects know that they should call if they are having any problems complying with study activities or are confused about what needs to be done.

There are a variety of ways of testing for compliance in studies. Every study will have some way of asking about and maintaining drug accountability. Usually a record is kept for each subject of the amounts and dates study drug is dispensed, and the amounts and dates of study drug returned.

Subjects are told to bring back any unused medications at each visit. The returned study drug is counted and recorded by the coordinator. This is a reasonable way to assess compliance, but, unless the subject admits a problem, there is no way to know about the pill that fell down the drain or was swallowed by the vacuum. The person seeing the subject should also question him or her about whether or not all doses were taken.

Watching subjects take the pills in person would encourage good compliance, but studies are not usually set up in such a way that the subject is at the site each time a dose needs to be taken. This would work only if there is a single dose of medication being given, an IV drug is being administered or something similar.

Subjects are sometimes asked to keep diaries and record when each medication dose is taken. This is probably a good solution for very compliant subjects, but for others it is as easy to forget writing in the diary as it is to forget to take the medication.

The "gold standard" for testing for compliance is to check blood levels. This is done in some studies, but mostly only the very early (phase I) studies. It is expensive and not feasible to do most of the time.

What can site personnel do to maximize compliance? First, it helps to know the subjects they enrolled. If an investigator and coordinator have worked with a subject before, they should have an idea of whether or not the person will be compliant. They should question subjects before entering the study on their willingness to comply with study activities, if they can swallow the pills, if they can come in for visits, etc.

The investigator and coordinator must pay attention to the signs of potential noncompliance. Does the patient show up for visits? Is the patient punctual? Did the subject complete all necessary pre-study activities? Is the person really interested in the study and aware of the requirements?

The coordinator should ask the subject about anything that may interfere with completing the study. Does the subject have a vacation planned during the time of the study? Does he or she understand what is involved in participating? Does the patient's lifestyle allow for complying with the study rules and activities? Does the distance the patient lives from the site preclude efficient and timely transportation to the study site for visits?

In short, if site personnel know or think a subject will not be a good, compliant patient, he or she should not be enrolled in the study.

When Noncompliance Happens

If the site is aware that a subject has been noncompliant, either in taking the medication or other study activities, the site should inform the sponsor of the noncompliance issue. Details of any noncompliance situations should be documented both in the CRF and in a note to the investigator's study file. The coordinator should discuss the situation with the subject and do some retraining in study procedures. If the subject continues to be noncompliant, he or she may need to be dropped from the trial. Keeping subjects who are not

compliant in a trial is not good for the subject or for the trial. When subjects are dropped from a study for noncompliance, the relevant information must be recorded both in the CRF and in the subject's office chart or with a note in the investigator's study file.

By working closely with each potential subject before enrollment into a trial, and by working closely with subjects throughout the trial, compliance can be maximized and study results will be more reliable than if there had been major compliance problems.

Good study designs and protocols will anticipate noncompliance and give instructions for minimizing it and for handling it, should it occur. If the CRA and the investigator do their jobs, both to minimize noncompliance and to detect and report it, the study should remain valid.

Table 1: Impact on clinical trial performance

All therapeutic areas, phases II-III

	Less complex protocols	More complex protocols	Difference
Number of case report form pages per protocol (median)	55	180	+227%
Study volunteer enrollment rates	75%	59%	-16%
Study volunteer retention rates	69%	48%	-21%
Time from protocol ready to FPFV (median)	115 days	129 days	+12%
Time from protocol ready to LPLV (median)	413 days	714 days	+73%
Number of amendments	1.9	3.2	+68%

Source: Tufts CSDD

The Impact of Protocol Complexity on Subject Enrollment, Retention and Compliance

Not surprisingly, the complexity of the protocol has an effect on subject enrollment and retention in a trial, as well as on subject compliance. Tufts CSDD looked at the impact of protocol complexity on clinical trial performance, with some interesting results. (See Table 1.)

Notice that the enrollment rate goes down when protocol complexity goes up. This makes sense, of course; the more difficult a study will be for a potential subject, the less likely subjects are to volunteer and be involved. Complex studies require more time and effort from subjects.

Similarly, subject retention declines when complexity increases. This, too,

is easy to understand; the more procedures subjects have to adhere to, the less likely they will want to remain in the trial. If the trial becomes too burdensome, in terms of time and/or activities, people will drop out rather than try to complete it.

Compliance is also an issue as trial complexity increases. More procedures mean more chances for something to go wrong. It's more difficult for subjects to remember and adhere to everything, as well as for site personnel to remember everything that needs to be done throughout the study.

This interrelatedness of all of the factors of a clinical trial should be addressed when the study is being planned. Thinking about the effect of complexity on study subjects in advance can lessen problems as the study progresses.

Key Takeaways

Recruitment

- Timely enrollment of subjects is critical to a drug, biologic or device development program.
- CRAs must help investigative sites accurately estimate the number of subjects they can expect to enroll in a study.
- Sites need to have the necessary personnel, time and space to handle the enrollment needed for each trial.
- Protocol requirements, especially the inclusion and exclusion criteria, are the primary limiting factors for enrollment.
- Assessment of the rate of enrollment is critical to managing a trial at the investigative site.
- Competing studies, both at the site and in the community, can have a significant impact on enrollment.
- Advertising for study subjects is allowed by the FDA, but must not be coercive or exert undue influence on potential subjects.
- All advertising must be approved by the IRB before use.
- Modern recruitment strategies include online search engines, such as Google, and social networks including Facebook and YouTube.
- Most study subjects refer themselves to clinical trials.
- Payments to study subjects must be approved by the IRB and must not be coercive or exert undue influence.
- Finder's fees or referral fees are not acceptable and in some states are illegal.

- Sponsors will usually pay true extra costs for enrollment procedures.
- CRAs must be able to monitor enrollment and to suggest methods to increase enrollment if it lags behind expectations.
- The more complex the study, the harder it will be to enroll subjects.

Retention of Study Subjects

- Investigators may discontinue subjects from a trial for medical reasons, compliance or cooperation issues or because the sponsor is stopping the trial.
- Subjects have many reasons for dropping out of a trial, including medical reasons and logistics problems.
- Determining problems as early as possible is the first step to retaining subjects in trials.
- Respect and open communication are the biggest factors in subject retention.
- CRAs can help their sites achieve good retention.
- The complexity of the protocol has an impact on subject retention.

Subject Compliance

- Good compliance is critical for valid conclusions from clinical trials.
- Subjects need to be aware of the importance of compliance.
- Sites need to determine if potential study subjects are likely to be compliant, and not enroll subjects who probably will not be compliant.
- There are many different ways in which subjects may be noncompliant with study procedures.
- Site personnel need to be alert to compliance problems throughout the study.
- If noncompliance occurs, the site should notify the sponsor.
- Compliance decreases as study complexity increases.

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CHAPTER SEVENTEEN

Study Closeout

When a study has been completed at an investigative site, it must be officially closed. This is almost always the responsibility of the CRA. This chapter looks at the reasons studies are closed and what must be done officially to do so.

Reasons for Study Closeout

The primary reason to close a study that has been completed: enrollment has stopped, all subjects have completed their study-related activities and the data are complete and correct. This is, of course, the best and most desired outcome. There are also reasons for closing a study before it is complete. Studies may be terminated early for both positive and negative reasons. Some of the reasons are listed below.

Positive Reasons for Early Study Termination:

- The investigational treatment is so beneficial that it would not be ethical to conduct a trial during which subjects might not receive the active treatment.
- Overall enrollment is met in the trial, so all sites are being closed even if they did not complete the site enrollment goal.
- Statistical stopping criteria were set up in advance (in the protocol) and those criteria are met. This means that the endpoint is reached (either positive for the investigational treatment or not) and the trial will end. Whether or not the outcome is the one anticipated, there is no reason to expend additional resources on the trial.

Negative Reasons for Prematurely Ending a Trial:

- The investigational treatment is found to be unsafe.
- The investigational treatment is not effective.
- It is not possible to find and enroll sufficient study subjects.
- The sponsor decides that the potential product was not viable for marketing.
- The sponsor terminates the program for another reason.
- The company runs out of funds. (This is being seen more frequently in small startup companies that rely heavily on venture capital.)
- The protocol is too difficult to execute.
- An investigator loses interest in the trial.
- An investigator dies, retires, moves, etc., and there is no replacement investigator.
- Problems arise in the manufacturing or stability of the compound.
- Compliance or other problems arise at the site.

As might be suspected from the length of the two lists, more studies are terminated early for negative reasons than for positive ones.

A trial may be discontinued at all sites at the same time or at individual sites at different times. Whatever the timing, the activity is essentially a single-site activity, that is, it must be done at each site without regard to activity at the other sites.

One cautionary note: If the study is stopped abruptly while subjects are still taking the study medications, there should be an orderly plan for discontinuing each subject. This plan will be formulated by the sponsor and communicated to each investigator. The CRA should be prepared to explain the plan to the site and ensure that it is followed correctly. The site also must be prepared to notify subjects promptly and assure them of appropriate therapy and follow-up outside of the trial.

The most common reason for closing a study is because it is finished and complete. It is also the easiest to handle. Site personnel are usually pleased that it was finished, hopeful of a favorable outcome and, frequently, hoping for additional studies from the sponsor in the future. In this case, the CRA is welcomed.

If a study was closed for a negative reason, it may affect all sites or just one. In this case, site personnel may not be happy about the closeout. Since the CRA is the sponsor's on-site representative, the CRA may be the recipient of the site's anger or unhappiness. This is the time for the CRA to use tact and interpersonal skills. If at all possible, you should want to leave the investigator and other site personnel on a friendly basis, even if they are unhappy friends.

No matter the reason for closing the study, the same procedures must be followed. In the rest of the chapter, we will discuss what must be done to close a study.

Closeout Procedures

A CRA must be at the site to do a closeout visit. It would be quite unusual to try to close out a site without being there in person. The main items to be addressed during a closeout visit are: CRFs, drug accountability, the investigator's study file and administrative items.

Case Report Forms

If the eCRFs/CRFs have not already been reviewed, submitted and corrected, this must be done now. If the study has come to its natural end, this activity has probably been completed. If the study has been stopped abruptly or early, this may not be complete. It is always better to conduct a final closeout visit after the CRFs have been submitted and reviewed, in the event final corrections need to be made.

The CRA should make sure all CRFs are completed and have been reviewed and submitted, and that any corrections or query forms are complete, in order and ready for storage.

SAE and Protocol Deviation Reporting

The CRA should take the opportunity during the site closeout visit to do a final reconciliation of SAE listings and Protocol Deviation Listings to ensure they have been reported to the sponsor and IRB according to study requirements. Though this should have been an ongoing process during study monitoring visits, especially if a CRA is conducting a closeout visit at a site he or she has not previously visited, the CRA should always conduct a final reconciliation of the SAE and protocol deviation listings with the source documents/CRFs to ensure adequate completion.

Drug Accountability

If study drug supplies remain at the site, the CRA should complete a final inventory at the closeout visit. The study drug should then be packaged for return to the sponsor, in accordance with company policy. A copy of the drug inventory form should be placed in the investigator's study file.

Drug reconciliation should have been done throughout the study, rather than left to the end. In this case, it should be relatively easy for the CRA and the coordinator to finish the reconciliation. Otherwise, drug accounting could be the most time-consuming study closeout activity.

Investigator's Study File

The CRA must thoroughly check the investigator's study document file at this visit. A reconciliation between the investigator study document file and site eTMF at the sponsor/CRO should have been completed prior to the closeout visit to ensure consistency, as well as during the closeout visit for the final reconciliation of documents, if needed.

It is wise to use a checklist (see Appendix C) during review of the investigator study document file, to ensure that nothing is overlooked. All documents must be present, including appropriate reapprovals and correspondence from the IRB. If there were protocol amendments during the study, or amendments to the informed consent form, all versions should be in the file, including their dates of use.

Informed consent forms for each subject must be present. The CRA should double-check to be sure they were all signed and dated appropriately.

There should be documentation for any protocol variations, whether or not they were previously approved. The investigator brochure should be available with all revisions.

If any documents are missing from this file, the CRA should help the investigative site obtain copies. Remember the suggestion that CRAs keep copies of important documents for each site in their own study files? This is a time when they can be very beneficial. When the file is complete and in order, it is ready for storage.

Investigator's Final Report to the Sponsor and the IRB

The investigator is required to make a final study report to the sponsor. This report should include an enrollment summary, including the numbers of subjects entered, those who completed, those who dropped out and their reasons for dropping out. It will also include information about AEs and any other information relative to the trial at that site.

The investigator will also make a final report to the IRB. It will contain the information above, in addition to any other information specifically requested by the IRB.

The investigator must also notify the institution that the study is complete, if appropriate.

The CRA should verify that these reports were completed, collect copies for the sponsor, if appropriate, and ensure that the reports are in the investigator's study file.

Administrative Issues

This may be the last visit the CRA will make to the investigative site for the trial, so any outstanding business or issues should be resolved before the study closeout is complete. Any loose ends should be resolved and taken care of before the site is completely closed.

The CRA should verify that all appropriate grant monies have been paid or requested. Be sure that the monetary amounts are in agreement between the investigator and the sponsor.

If there are unused study materials at the investigative site (CRFs, unused laboratory kits, etc.), they should be returned or disposed of in accordance with direction given by the sponsor.

Any outstanding issues from previous visits, or issues that arose during sponsor review, should be resolved before the study is closed out at the site. If not documented elsewhere, a note detailing the resolution should be put in the investigator's study file.

The CRA should discuss record retention with the investigator. Not only do the records need to be stored and maintained, but there also must be a record of where they are stored. According to the regulations, records must be kept for two years after the NDA is approved for marketing. The same regulations apply if an NDA is not filed or is not approved after the investigation is discontinued and the FDA has been notified. However, most sponsors expect the investigator to retain all study records until notified by the sponsor that they may be disposed of; most often, this is stated in the contract the investigator signed before starting the study. The CRA must be sure that the investigator and site personnel are aware of and understand the retention period.

Investigative sites do not always keep study records as long as they should. Years go by and things happen—there may be a shortage of storage space, a move to a new facility or the erroneous thought that they don't need to "keep all that old stuff" around any longer. Unfortunately, these records may be needed years after the study is over. For example, the sponsor may decide to file a new application based, in part, on old studies; when the FDA visits investigative sites as part of the NDA review process, it will expect to see all the documents in place, even if the study was done many years earlier. It will be an embarrassment to the investigator if he or she has thrown them away, and it may have a negative impact on the sponsor's NDA.

CRAs need to impress upon their sites that record retention is important and not something to be taken lightly, along with the reasons to keep everything. Records must be kept until the sponsor has informed the site in writing that they may be destroyed. It is recommended that the boxes be labeled on the outside "DO NOT DESTROY," with the names of both the investigator and the sponsor as contacts for questions about them. If there is some reason a site can no longer maintain the records, the site should contact the sponsor. In most cases, the sponsor will arrange storage for these materials so that they are not destroyed.

At this time, it may be best to remind the investigator of any publication terms for the study and to notify the sponsor of any impending FDA audit. When everything is complete and accounted for, the CRA should thank the site for its participation, being sure to include everyone who worked on the study. It is nice to follow up with a written letter of thanks.

Final Visit Report

The CRA must complete a visit report after this site visit, as for any other visit. Many companies have a special visit report for the closeout visit. This report documents that the study was officially closed.

In the final report, the CRA should verify that everything was checked, found complete and prepared for storage. If there were any outstanding issues from previous visits, the resolution of those issues should be documented in this visit report. The CRA should be sure that the report is clear and does not leave any unresolved loose ends.

Key Takeaways

- Studies can be stopped because they are complete, or for a variety of other reasons—both positive and negative.
- The CRA is the person who will do a study closeout at an investigative site.
- All study documents, including CRFs, informed consent forms, drug accountability and study regulatory documents, must be complete and filed at the end of the study.
- All study drugs and other supplies must be returned to the sponsor or disposed of at the end of the study.
- The investigator must prepare a final study report for the sponsor and the IRB at the end of the study.
- The investigator must be aware of record retention requirements at the end of the study.
- In a final visit report, the CRA must verify that the study was properly closed.

CHAPTER EIGHTEEN

Quality Management

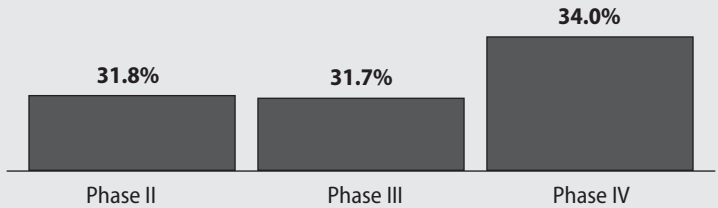
This chapter discusses some activities that can increase quality in clinical trials. Most of the data presented to regulatory agencies when seeking approval for a new drug is collected during clinical trials. If a regulatory agency has concerns or doubts about the integrity of the data, adherence to regulations and GCP, or ethical concerns, this can lead to delays in the approval process. This is very costly for the sponsor. A quality management program that includes continuous monitoring and checking of quality-related measures can help ensure a smooth submission and review process.

There are three inter-related parameters that affect clinical trials and the data resulting from them: time, cost and quality. For example, if a sponsor cuts development time, it may be necessary to add more people or engage a CRO, which would increase cost. At the same time, data quality may decrease because there could be less time to properly collect and review it. There is the possibility that a decrease in available funds for a project might mean that there could be a delay to the start of some trials, or lacking available resources to handle them expeditiously.

One way to manage quality is to be proactive about it from the beginning of the project. Designing good protocols and CRFs, obtaining expert advice and discussing them with site personnel before they are finalized can eliminate problems once the study begins. Some sponsors have even field-tested the protocol and forms with a few subjects before finalizing them. This takes some time and costs money, especially for field testing, but these costs are often much lower than the cost involved in making fixes later on.

Continuous review of the data is another very effective quality management activity. One part of this is the timely review of the data from the first couple of subjects at each investigative site. It may, in fact, be of value to stop enrollment at each site until these first subjects have been reviewed by the

Figure 1: Probability of successful investigative site performance



Probability of selecting sites that will complete ≥ 100% enrollment of patients to goal
Source: RapidTrials, 2011

CRA and data management staff. If this review is done quickly, few potential subjects will be lost and an increase in quality should continue throughout the trial. Receiving feedback from the sponsor early allows misconceptions about processes and procedures to be corrected before they repeat over many subjects and multiple visits. This is also the time to work with any study coordinator (CRC) who is "error prone," whether due to misunderstanding or carelessness.

Continuous review depends not only on the CRA and monitoring visits, but upon data management. Whether the data are entered by an electronic data capture (EDC) system at the site or by data-entry technicians at the sponsor, quality is dependent on computer checks being done in a regular and timely manner, including the transmission of queries to the sites. CRCs will learn from the queries they receive and will be less prone to making the same mistakes in the future. The CRA can also use the query information for specific training at sites.

With a good quality management plan in place, the overall rate of errors and problems at study sites should decrease as the study continues. The time spent upfront to put these activities in place will be more than compensated for by the time saved throughout the study. Stressing the correction process at the beginning and continuing it throughout the study should allow the sponsor to have analysis-ready data very soon after the study is complete. This can result in earlier regulatory filings, which may then result in quicker approvals and additional marketing time for the product.

Site Metrics

A successful study site is one at which the enrollment goals are met, in terms of both numbers of subjects and the time to complete enrollment, and where the data generated are of high quality (accurate, valid and complete; see Chapter 14). Unfortunately, the percentage of successful sites is only slightly over 30%.[4] Therefore, it is critical that a sponsor (or CRO) has systems in place to determine which sites will be good performers for clinical trials.

There are two facets to improve site quality: selecting good sites initially

and helping ongoing sites. The probability of improving study success with both of these activities can be enhanced if sponsors keep some basic metrics on sites as part of their quality management program. To collect and maintain metrics, sponsors and CROs often develop their own in-house databases and analytical systems, or they may purchase available commercial programs.

Performance-based data can be used to identify and select sites with the highest probability for success.[5] For new studies, looking at the metrics for sites used in the past can help when selecting good sites and avoiding sites that have not performed well. Some of the metrics that might be used for site identification are:

- Previous experience (number of studies and therapeutic areas).
- Time it takes for IRB review.
- Past enrollment data.
- Data quality measures from completed studies.

Some of these metrics may not be available for sites that the sponsor or CRO has not worked with in the past, but once a site has been used, this information can be collected. The use of these metrics will not guarantee good sites, but affords an opportunity to add another level of confidence to the selection process. (More information on site selection can be found in Chapter 12.)

For current studies, maintaining "real-time" site metrics can show the sponsor which sites are excelling, as well as which sites might need more training or closer monitoring. Not only is it easier to collect and maintain metrics throughout the study, as opposed to calculating them at the end, but they can be put to good use throughout the study. Once the metrics are set up, they can be calculated based on ongoing data entry from CRFs and on regular input from the CRAs and the sites (e.g. enrollment tracking). Since most metrics can be programmed to be done by computer, this involves very little extra work and is potentially a big advantage.

These programs usually are not maintained by the CRA, but the CRA helps collect the information for them. The metrics should be shared with the CRAs in advance of each monitoring visit; the CRA can subsequently use this tool to help improve quality at the study sites.

A set of basic metrics might include the following:

- Number of subjects enrolled.
- Number of screen failures.
- Recruitment/enrollment time (from study start date to the date enrollment was completed).
- Number of subjects who discontinued the study early (dropouts), by category:

  - Ineffective study medication.
  - AEs.
  - Deaths.
  - Non-compliance.
  - Lost to follow-up.
  - Other categories, as appropriate.
- Number of protocol deviations.
- Number of AEs (or SAEs).

During the trial, the sponsor might want to compare sites based on these metrics. For example, an enrollment rate can be calculated by dividing the days of the enrollment time by the number of subjects enrolled during that time. This can be done before enrollment is complete, and will show which sites are enrolling more rapidly. This allows the sponsor to investigate why some sites are seeing better, or worse, enrollment. Insights gained can be shared to help other sites. If sites are above or below average in any of these categories, the sponsor may want to find out why. Why are there more protocol violations at Site X? Why does Site Y have so many dropouts? Why is Site Z enrolling much more quickly than the average?

Let's look at an example of enrollment rates over a study with 10 sites. Table 1 shows that they did not all start enrollment at the same time, but a rate can be calculated by dividing the number of subjects enrolled to date by the number of days since each site started the study.

Table 1: Enrollment rates

Site number	Start date	Current date	Number of days	Subjects enrolled	Enrollment rate
1	12/5/2018	6/1/2019	178	21	0.118
2	12/16/2018	6/1/2019	167	3	0.018
3	1/4/2019	6/1/2019	148	14	0.095
4	1/23/2019	6/1/2019	129	25	0.194
5	2/3/2019	6/1/2019	118	6	0.051
6	2/3/2019	6/1/2019	118	19	0.161
7	2/25/2019	6/1/2019	96	34	0.354
8	3/21/2019	6/1/2019	72	9	0.125
9	3/24/2019	6/1/2019	69	13	0.188
10	3/28/2019	6/1/2019	65	17	0.262
Totals and overall rate			**1,160**	**161**	**0.139**

There are two sites in the chart that are enrolling much better than average—Site 7 and Site 10. This may be good, or it may not be. Are techniques being used for enrollment that other sites might not have thought to utilize? Or are sites enrolling too quickly and using inappropriate subjects? The CRA might want to visit both sites to see what is happening and why the enrollment is significantly higher than at the other eight sites.

Site 2 shows that enrollment looks very low. It would be a good idea to look into the reasons why enrollment is failing at this site, especially as it was the second site to begin. Site 5 isn't doing well, either.

Enrollment comparison is one tool that can help the sponsor manage the study.

Other site metrics that may be of interest can also be collected. Some to consider are:

- Time from commitment to IRB approval.
- Time to collect and submit study initiation paperwork.
- Number of coordinators.
- Number of sub-investigators.
- Time from subject visit to completion of CRFs.
- Turnaround time for queries.
- Error rate (e.g. queries per subject or queries per CRF page).
- Protocol specific items.

Errors can be costly. The following example shows how this metric might be collected and compared over different investigative sites. Note that error rates could also be compared for different types of studies, or over different clinical programs.

In our example, let's assume we are looking at the same 10 sites we examined for enrollment rates. Although a bit unrealistic in a real situation, we will assume that each CRF page contains about 10 fields. Data management can tell us how many CRF pages have been entered to date for each site and how many queries have been made (each error means one query). Table 2 shows enrollment as well as the number of pages entered, queries sent and the error rate (queries divided by pages).

With enrollment rates, higher is better, but error rates should be as low as possible. Sites 4 and 7 look good here; not only have they enrolled well, but their error rates are low and they have enough pages entered to have confidence in what they are doing. Sites 3 and 9 look pretty good also, but note that there is not a great deal of data entered for them yet. Site 2 looks good, but with so few pages entered, you can't really get a good feel for how this rate will hold up.

On the other hand, Sites 8, 6 and 5 have pretty high rates. It's probably too early to tell about Sites 8 and 5 since there are not many pages entered yet, but

Table 2: Query/error rates

Site number	Start date	Current date	Number of days	Subjects enrolled	Enrollment rate
1	21	314	54	0.172	0.118
2	3	24	2	0.083	0.018
3	14	140	13	0.093	0.095
4	25	450	35	0.078	0.194
5	6	62	15	0.242	0.051
6	19	250	76	0.304	0.161
7	34	342	29	0.085	0.354
8	9	60	24	0.400	0.125
9	13	150	12	0.080	0.188
10	17	235	46	0.196	0.262
Totals and overall rate			**2,027**	**306**	**0.151**

Site 6 could be a problem. It would be good for CRAs to check the sites with higher error rates quickly, so that any misunderstandings can be corrected before the errors are repeated.

The CRA is the sponsor's primary resource for keeping the error rate low at study sites. It is the CRA who trains (and re-trains) study coordinators how to complete the CRFs correctly. It is the CRA who is charged with reviewing the forms for accuracy and completion before they are submitted to the sponsor, with the exception of those eCRFs submitted directly by sites. And it is the CRA who reviews queries with the CRC to be sure they are understood and that errors don't repeat throughout the study. Because of this, CRAs must shoulder some of the responsibility for error rates at their sites. Therefore, an effective CRA will pay close attention to errors found at his or her sites, and will work with the CRCs to ensure an understanding of how to complete the CRFs correctly, as well as the need for carefulness and accuracy. Pointing out the cost of errors and the amount of the cost borne by sites can help to reinforce the importance of doing things right the first time.

The collection of metrics takes some time and effort, but it can have a huge payoff in terms of managing sites for current studies and selecting sites for future studies. Errors are expensive to fix, both in terms of resources and time. Poor sites can make a huge difference in overall data quality. Picking good sites can lessen the time to complete a study.

In summary, initiating a good quality management program can save time and money while increasing data quality, and might, in fact, have a positive impact on the time to regulatory approval of a new product.

Key Takeaways

- The three interrelated parameters that affect clinical trials and the data resulting from them are time, cost and quality.
- Build in quality from the beginning of each project—be proactive.
- Continuous review of the data throughout a study can increase quality and ensure faster completion times.
- There are a number of site metrics that can be kept to help determine which sites might need additional help, as well as which sites might be best to use for future studies.
- CRAs should have regular access to site metrics so they can be used for training.
- The cost of errors is very high.
- Keep the quality up.

CHAPTER NINETEEN

Audits

During the clinical development process, the FDA may conduct audits (also called inspections) of investigative sites. Sponsors and IRBs may also conduct their own audits of investigative sites. The FDA also audits sponsors and IRBs. This chapter discusses these types of audits, as well as the CRA role in each. The chapter begins with audits conducted by sponsors and institutions or IRBs, but will concentrate primarily on those audits conducted by the FDA, as they are the most critical to the drug approval process and to the CRA.

Sponsor Audits of Investigative Sites

There are two main purposes for a sponsor to audit an investigative site. The first, and most common, reason is to ensure that a site is complying with regulations and protocol when conducting a study and that everything is in order in case of an FDA audit. These are referred to as routine audits. The second reason is that there is evidence the site is out of compliance, and the sponsor wants to either verify the problem or be reassured that no problem exists. These are called for-cause audits.

A sponsor's right to audit a site is based on both the regulations and (usually) on the contract between the investigator and the sponsor. The contract will usually state that the investigator agrees that the sponsor may conduct audits of the site. The regulations under which sponsor audits are loosely covered are found in 21 CFR 312.56(a)(b), which states:

> *(a) The sponsor shall monitor the progress of all clinical investigations being conducted under its IND, and (b) A sponsor who discovers that*

> *an investigator is not complying with the signed agreement (Form FDA1572), the general investigational plan, or the requirements of this part or other applicable parts shall promptly either secure compliance or discontinue shipments of the investigational new drug to the investigator and end the investigator's participation in the investigation.*

Sponsor audits are usually carried out by the sponsor's quality assurance (QA) department, if it has one. The CRA may or may not accompany the audit team, but usually does not assist in the actual audit. If the sponsor company is too small to have a QA department, or if the QA department does not have the resources to conduct an audit, the sponsor may contract with a CRO to do the work. In general, a sponsor may contract out routine audits but will usually do for-cause audits itself.

Routine Audits

If the sponsor knows or suspects that a site will be audited by the FDA, a routine audit may be conducted, either while the study is in progress or after it has been completed during the NDA review period. The sponsor knows the FDA will inspect some sites during its review of the NDA, so the sponsor will focus on the sites that are logical for the FDA to pick: those at which enrollment was the highest or at which multiple studies contributed to the NDA.

For a routine audit, the sponsor will send in an audit team, who will follow the same inspection plan used by the FDA. This inspection plan can be found in the FDA Compliance Program Guidance Manual for Clinical Investigators (Program 7348.811) or at www.fda.gov/oc/gcp/compliance.html.

A written report of sponsor audit results usually is not given to the investigator, because FDA inspectors do not have routine access to sponsor audit reports and sponsors do not want to have these reports freely circulating, either at the investigative site or internally. If a written report is sent to an investigator, the sponsor will usually ask that it be destroyed after corrective action is taken.

If any problems are found during the audit, the CRA most likely will be asked to work with the site to remedy them, with the goal being to ensure that the site is ready for an FDA audit. The CRA will report back on the final status at the site; this is sometimes done in a formal audit response, which is kept with the original audit report. Audit reports and responses are usually maintained in and by the QA department, and any other copies are to be destroyed.

For-Cause Audits

For-cause audits of investigative sites by a sponsor may be handled somewhat differently. These are audits conducted because of suspected noncompliance at a site, either with the regulations or with the protocol. They have the potential for being much more serious, both for the sponsor and ultimately for

the investigator. The sponsor is unlikely to tell the investigator it is a for-cause audit; the CRA will probably know, since he or she most likely reported the information about the suspected problems to the sponsor. The audit team will look at most of the things it would inspect for any audit but will pay particular attention to the area of the suspected noncompliance.

Depending on the results of the audit, a number of things could happen:

- If everything appears to be in compliance, the results will be handled in the same way they would for any routine audit.
- If the problem was not found but is still suspected, another group may be sent to look. Or the sponsor might inform the FDA and ask it to inspect the site.
- If problems were found, they will either be rectified or enrollment may be put on hold pending further investigation, or the study may be stopped at the site. In this case the FDA will be informed, if appropriate. If so, this will be done by the QA department, probably in conjunction with the medical monitor for the study and the sponsor's regulatory group.

The CRA is likely to be involved with for-cause audits in some way, especially if problems are found and enrollment is put on hold or the site is closed. These are not pleasant situations to be in, and the CRA will need a lot of tact and diplomacy in working through the problems.

Nightmare audit

I had a nightmare FDA audit two years ago that lasted more than two weeks. The one thing that kept me going was that I had personally done a good job from my end. I had no control over what was done to CRFs or source documents after the study was closed. I learned that, early on, I gave the site too many chances without documenting that there were problems; I had not wanted to "tell on them" without giving them a chance to correct them.

Document, document, document. Having to fax the FDA auditor my visit reports (with my company's blessing) was quite a learning experience. I wished, of course, that there was more on my reports about the problems I was aware of and had addressed with the site. I had communicated all the problems to the project manager on the phone, but not in writing, except too briefly on visit reports. This site had enrolled too quickly—60 patients when the average everywhere else was about eight.

—A CRA Friend

IRB Audits of Investigative Sites

IRBs also visit or audit sites upon occasion. A central or independent IRB may visit sites simply because it is not located nearby, and it wants to be assured the site is managing studies correctly. These are routine audits.

An IRB may also make for-cause visits if there is reason to think the site has ethics or compliance violations. IRBs are required to report to the FDA any instances of unanticipated problems involving risks to human subjects, serious or continuing noncompliance with the regulations or IRB requirements or any suspension or termination of IRB approval.

CRAs will not be involved in IRB audits. Of course, the CRA would be involved in closing the study at a site if approval was withdrawn.

FDA Audits

The FDA's Bioresearch Monitoring Program (BIMO) includes visits to investigators, sponsors, IRBs, CROs and animal labs. All FDA-regulated products are involved, including drugs, biologics, devices, radiological products, foods and veterinary products. Although the BIMO programs vary somewhat from product to product, they all have the same goals:

1. To ensure the quality and integrity of the information submitted to the FDA.
2. To protect human research subjects.

The FDA compliance program has three parts:

1. Clinical Investigators (Program 7348.811)
2. Sponsors, Contract Research Organizations (CROs) and Monitors (Program 7348.810)
3. Institutional Review Boards (IRBs) (Program 7348.809)

Copies of the FDA Compliance Program Guidance Manuals for Inspections (the three programs listed above) are available through the FDA's website: fda.gov. It would be useful for a CRA to read these documents, as they delineate the particular items an FDA inspector will concentrate on.

The FDA can make inspection visits to sponsors and IRBs at any time, with the purpose of determining compliance to the regulations and the organizations' own SOPs. CRAs will not be involved in IRB inspections and only rarely would be involved in sponsor inspections, so there is no need to discuss these any further. However, we will discuss FDA audits of investigative sites in detail, as CRAs have a decided role and impact on this process.

FDA Audits of Investigative Sites

The FDA conducts three types of inspections at clinical investigative sites: study-related, bioequivalence study and investigator-related. Bioequivalence study inspections are conducted when one study is the sole basis for a drug's approval; we will not discuss these here. The two other types are important for a CRA to be aware of. For either study-related or investigator-related audits, the purpose is threefold:

1. To determine the validity and integrity of the data.
2. To assess adherence to regulations and guidelines.
3. To determine that the rights and safety of the human subjects were properly protected.

We will take a detailed look at both study and investigator audits.

Study-Related Audits

Study-related audits/inspections are almost always done on the studies that are important to an NDA or BLA that has been submitted to the FDA. These studies are the primary efficacy studies on which a sponsor relies for showing that the product works and should be approved for marketing.

The sites picked are usually those that contributed the most data to the application, either by high enrollment or by conducting multiple studies. Because of this, sponsors usually have a reasonable idea of which sites have a high probability of being audited. The sponsor also knows that studies will be inspected during the NDA review time, which is currently six months or less for a Track A product, and one year or less for all others, from the date the FDA receives the application.

The primary efficacy studies are closed at this point, as the trials are complete and analyzed before being submitted in the NDA; in fact, they may have been closed for quite a while. Sometime early in the NDA review process, CRAs are often sent to the sites with high probability of being audited to ensure that all study materials are available and organized for FDA review. (Note that a site will usually inform the sponsor of a FDA-scheduled audit, in which case the sponsor may send the CRA in to help the site prepare.) If the CRA finds missing documents or other problems, the site may be able to remedy the situation before an FDA audit occurs.

Investigator-Related Inspections

Investigator-related inspections are initiated for a variety of reasons, many of which are listed below:

- Investigators have done a large number of studies or have done work outside their specialty areas.
- An investigator has done a pivotal study that is critical to a new product application and it merits extra attention.

- The safety or efficacy findings of an investigator are inconsistent with the results from other investigators working with the same test product.
- The sponsor or IRB has notified the FDA about serious problems or concerns at the site.
- A subject has complained about the protocol or subject rights violations at the site.
- There was an unexpectedly high number of subjects with the diagnosis under study, given the location of the study.
- Enrollment at the site was much more rapid than expected.
- The study and investigator were highly publicized in the media.
- Any other reason that piques the curiosity of the agency.

Unless a sponsor alerted the FDA to problems at a site, the sponsor will probably not know in advance about an investigator-related inspection. (If the sponsor did alert the FDA, then it probably has already done its own QA audit.) Consequently, a CRA is rarely, if ever, involved in these audits.

Site Preparation

The best audit preparation is for the site to have done things correctly to begin with, in which case an audit will reveal no problems. However, once an audit is scheduled, the site should prepare by amassing all the study documents in one easily accessible place and reviewing them to be sure everything is accounted for, complete and well organized. The study documents that should be available for review include all informed consent forms, patient charts and other source documents, CRFs and the study regulatory file. When an inspector asks to see a document, the site should be able to retrieve it easily and quickly. Sometimes, although this is seen most often when the FDA audits non-U.S. sites, the FDA may ask the site to send a letter of availability of records; this letter certifies that all study records will be available for FDA review upon its arrival.

If there is time, and travel schedules allow, the CRA often goes to the site and assists in the audit preparation; if not, the CRA should be available at least by telephone to answer any questions the site may have or to send copies from the sponsor study file of any missing documentation. Sometimes a CRA can lend moral support by telling the site what to expect during the audit, how to interact with the inspector and what the process is. No one from the sponsor will be present during the audit; the audit is between the investigator and the FDA.

The Audit Process

The audit process begins with notification to the site. The inspector usually contacts the site by telephone to arrange a mutually acceptable time for the audit visit. Sites are generally given one weeks' notice. If the audit is investigator-related, and if the FDA has concerns about subject safety or compliance, the time between the notification and the visit will probably be very short and delays will not be acceptable. If there are serious concerns, the FDA could just appear at the site without advance notice. Most sponsors ask and expect their investigators to let them know immediately about an impending audit.

The role of the investigator in the audit is to be present, to provide the inspector with a quiet, comfortable place to work, to assemble the necessary documents and to answer questions. The investigator should be polite, courteous, cooperative and reasonable when interacting with the FDA inspector; antagonism is inappropriate and will undoubtedly be regretted later. The investigator should provide all the materials/documents the inspector requests, but should never give the inspector unlimited access to the files. All questions should be answered, but extra information should not be volunteered. The inspector knows what he or she is asking for and will continue to question until the necessary information is obtained. The investigator should not offer the inspector anything beyond a cup of coffee; offering even a meal may be misconstrued. At this time, the FDA is not privy to grant information or to sponsor audit results, so if the inspector asks for this information the investigator should politely refuse to answer. If the inspector is treated politely, the audit will be more pleasant for everyone. The CRA should go over these suggestions on conduct with the investigator and staff before an audit occurs.

When the inspector arrives at a site, he or she will present credentials (a photo ID) and a Notice of Inspections Form (482) to the clinical investigator. If the inspector does not present these credentials, the investigator should ask for them. The investigator should check the date on the inspector's credentials to be sure it is still valid and note the inspector's badge number. During the inspection, the inspector will meet with study staff and review study documents. Two main aspects of the study will be looked at during the inspection: study conduct and study data. According to the FDA Guidance for IRBs and Investigators, the conduct of the study will be considered by reviewing the following items:

- Who did what.
- The degree of delegation of authority.
- Where specific aspects of the study were performed.
- How and where data were recorded.
- How test article accountability was maintained.
- How the monitor communicated with the clinical investigator.
- How the monitor evaluated the study's progress.

Notice that the monitor (CRA) is mentioned in two of these bullets. A CRA must communicate carefully with the investigator throughout the study and may want to make use of written communications to reiterate the points discussed during a monitoring visit. These communications should be kept in the investigator's study file, and copies should also be kept in the sponsor's file. At the very least, the monitor should sign a study visit log at each monitoring visit to verify that the site was actually visited. (There is an example of a study visit log in Appendix C.) This also underscores the need for complete monitoring visit reports, which were discussed in Chapter 14.

When the inspector audits the study data, he or she will compare what were submitted to the FDA with the site records that support the data, i.e., investigator copies of the CRFs and all the available source documents, including patient charts, laboratory reports, other test reports and so forth. Sometimes the inspector will also have copies of the CRFs from the sponsor and will compare all three versions. The inspector will pay close attention to:

- The diagnosis.
- Whether the patients were properly diagnosed based on their past history.
- Whether or not the subjects met the protocol inclusion/exclusion criteria.
- Concomitant medications, especially those that were not allowed.
- Appropriate follow-up of AEs.

The inspector may look at data for only a sampling of subjects, or if there appear to be problems, he or she may look at the data from all of the subjects. All informed consents are usually reviewed.

An FDA audit usually takes one to two weeks, although it depends on the amount of data to review, the findings and the amount of time the inspector has available for the audit. The days may not be consecutive for the entire period, but rather a day or two at a time at the site until the review is complete.

The inspector should meet with the investigator throughout the process to review the audit findings. During this meeting, the investigator may ask questions about anything that is not understood and may clarify anything the inspector has interpreted incorrectly. Sometimes a misunderstanding or negative finding by the inspector can be explained satisfactorily at this point. The inspector can also use this as an opportunity to investigate further. If there are significant findings, the inspector may issue a Form FDA-483 (Notice of Observations) to the investigator. This form will detail the findings from the audit that may constitute compliance violations.

Most sponsors ask that an investigator call them after the inspector leaves and let them know the results of the audit. If the investigator has received a 483 form, the sponsor will help the investigator formulate his or her reply (a written reply is not required but highly recommended).

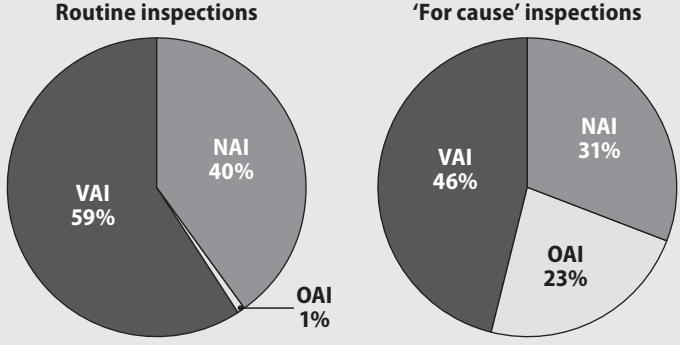
After the Audit

After the audit has been completed, the FDA inspector prepares an Establishment Inspection Report (EIR). This report goes through FDA compliance channels, and a classification is assigned to it. The investigator will receive a copy of the report approximately four months after the audit. The report is also available through the Freedom of Information Act, and most sponsors will request copies for their files.

The Electronic Data Capture are:

- **No Action Indicated (NAI)**. This is the best outcome and means that no significant deviations from the regulations were found. The clinical investigator is not required to respond to this report.
- **Voluntary Action Indicated (VAI)**. This report provides information about findings of deviations from the regulations and GCP. The letter may or may not require a response from the investigator. If a response is required, the letter will specify what is necessary. A contact person also will be listed for any questions.
- **Official Action Indicated (OAI)**. This is the worst result to receive. It identifies serious deviations from the regulations that require prompt action from the investigator. In most cases, the FDA will issue a warning letter that outlines problems the agency expects to be corrected. The FDA may also inform the sponsor if the agency feels that monitoring of the study was deficient (beware, CRAs). In addition to issuing the warning letter the FDA may take other action, such as regulatory and/or administrative sanctions against the investigator. All in all, this is a very unpleasant process and should be avoided at all cost.

Figure 1: FDA inspection results



NAI=No Action Indicated; VAI=Voluntary Action Indicated; OAI=Official Action Indicated

Source: CDER; (reflects multiple years);
Routine inspections, N=6,245; 'For cause' inspections, N=653

Consequences

The consequences of problems found during audits can be significant, especially when they have an impact on a large amount of the data for a pivotal trial. The study at a particular site may be invalidated, especially if sufficient source documents were not available, if there were significant unreported concomitant therapies or if there was a failure to follow the protocol. If the site was a high enroller and generated a significant amount of data in support of the sponsor's NDA, these problems could delay the NDA or result in a disapproved application. A sponsor may even have to repeat a study, which could add years to the drug development cycle.

There are also significant consequences for the investigator in these cases. An investigator may be disqualified or restricted from conducting clinical trials. This puts him or her on the infamous "black list," known more formally as the List of Disqualified and Restricted Investigators. An investigator can be added to the list through a court hearing or through a consent agreement; he or she can be disqualified from ever conducting clinical studies or may have other restrictions placed on him or her, such as conducting studies only as a sub-investigator or conducting not more than one study every two years, etc. Once on the list, the investigator stays on the list forever, even if corrective actions are taken.

It does not happen often, but in the worst cases an investigator can be fined and/or sentenced to prison. For example, look at the case of Dr. Richard Borison, a psychiatrist, and Dr. Bruce Diamond, a pharmacologist. They conducted schizophrenia trials for eight years using resources at the Medical College of Georgia but pocketed the proceeds. They also encouraged psychotic patients to enter trials by giving them money and cigarettes and had untrained staff performing study procedures, including blood draws. These abuses were discovered when a disgruntled employee informed the university. The doctors were fined and jailed in 1997 and were ordered to pay back millions of dollars to the university.

Key Takeaways

- Sponsors audit investigative sites for studies that contribute highly to their development programs. They also audit sites at which it appears there may be compliance problems.
- IRBs can also audit sites, especially if they suspect ethics violations.
- The FDA performs both study-related and investigator-related audits.
- The best preparation for an audit is to perform the study correctly.
- CRAs should help their sites understand the audit process and prepare for them.
- There are three classes of EIRs that result from an FDA inspection: NAI, VAI and OAI.

- The consequences of noncompliance are great and can result in delays in an NDA, and/or in disqualification and other penalties for investigators.
- There has been an increase in compliance problems during the past few years.
- CRAs must be educated about the correct procedures for clinical trials and must watch their sites closely to ensure compliance.

CHAPTER TWENTY

Errors, Misconduct and Fraud

This chapter discusses some serious situations that CRAs face: errors, misconduct and fraud. The discussion will be limited to the occurrence of these unfortunate events at investigative sites, and will focus primarily on the CRA's role in detecting and coping with these problems. The chapter will start by defining each term and then looking at the impact of each on a clinical trial and on the CRA.

Definitions

If you consult a dictionary, you will find the following definitions for error, misconduct and fraud:

> *Error: an act involving an unintentional deviation from truth or accuracy.*
>
> *Misconduct: intentional wrongdoing.*
>
> *Fraud: intentional perversion of truth in order to induce another to part with something of value or to surrender a legal right.*[1]

As you can see, these are listed in increasing severity, and the same is true of their impact on a clinical trial and on the CRA. We'll consider each category in detail.

Errors

If you think about the definition of an error, it contains two key ideas. The first is that an error is a deviation from truth or accuracy, and the second is that it is unintentional. There is no doubt that a CRA will see errors when monitoring studies; in fact, the CRA can expect to see some errors at every study site he or she monitors, assuming the sites enroll any subjects at all. Most commonly the errors CRAs will see are those in case report forms, although these are not the only errors that can occur during a study. Errors may also occur in drug dispensing, study documents, protocol conduct or any other aspect of study performance.

Some of the errors may occur during a study, starting with CRFs. Errors commonly seen on CRFs result from omissions (missing values), inconsistencies, incorrect entries, out-of-range entries, illogical entries and undecipherable entries.

This example uses one of the standard questions that is asked in almost every study. See how it can be answered (on a CRF) to meet the error types listed above. The question is:

Sex: Male ☐ Female ☐

It looks very straightforward and should be easy to answer without making an error. Here is the error of omission:

Sex: Male ☐ Female ☐

Notice that neither box is checked—the question was not answered.

An error of inconsistency would be, in this case, that the subject was listed as a male in one place and as a female in another. Most CRFs will not ask this question directly more than once, but there may be other questions where the sex is implied by the answer. One common question in the inclusion/exclusion criteria asks if the female subject has had a pregnancy test. The answer can be assumed to be "Yes," but then the entry for the example is:

Sex: Male X Female ☐

There is an inconsistency between the two entries. An incorrect entry is easy—the wrong box was checked.

For this question, out-of-range entries would probably not be seen. An out-of-range entry occurs when an answer is supposed to fall between two values and doesn't. For example, when the answer to "Rate the subject's pain on a scale of 1 to 10" is recorded as "12." An illogical entry for this same question would be "Better" or "D." Neither entry makes sense, given the question and the way it is worded.

Undecipherable entries are sometimes illegible answers, those that cannot be read because of poor handwriting. They also may be entries like:

Sex: Male X Female X

Overall, errors run the gamut from small discrepancies to glaring inconsistencies.

Because errors are unintentional, there is hope of eliminating, or at least reducing, their occurrence over the course of a study. Chapter 11 discussed different ways in which the CRA can help lessen or eliminate errors at sites. It also discussed the impact of errors and the cost of errors. It is important to realize that the CRA can make a significant contribution to studies by working with his or her sites to eliminate errors made on CRFs.

In general, errors are relatively easy to find and easy to fix. Although it depends on the parameter, the impact of errors on the study is usually quite low, since they are fixable. If the CRA is doing a good job, the error rate should decrease as the study progresses. The following are some things the CRA can do to help decrease or eliminate errors:

- Review the first patient or two very soon after enrollment. Conduct a very thorough review. Quick feedback to the site can do more than anything else to eliminate future errors. Many errors, especially at the beginning of a study, are due to misunderstandings on the part of the study coordinator and other site personnel. If these problems are found and corrected early, they usually will not occur in the future.
- Look for systematic errors and instruct the site on the correct way to record the data. Systematic errors also usually are due to misunderstandings and can be eliminated by quick feedback. For example, the CRF may have a question that reads: Have there been any changes in concomitant medications since the last visit? The site may be recording only new or stopped medications, rather than including changes in dosage for medication during the study. Once this is clarified, these systematic errors should not continue.
- Train your sites well in the beginning, and re-train them if:
  - There are misunderstandings.
  - New personnel are added.
  - The study or procedures change in any way.
- Demand good work, nicely. This is especially important when there are errors due to carelessness. One of the techniques a CRA may find helpful is to remind the site of the high cost, both timely and monetarily, of correcting errors. An estimate of the cost of each error for a site is about $20 and 15 minutes of time.

The CRA also has a great influence when it comes to eliminating other errors in studies, such as those that occur in drug dispensing, study documents, protocol conduct and other aspects of study performance. Remember that the CRA is the sponsor representative who visits the site most often and may, in fact, be the only sponsor representative who ever visits an investigative site. No one else has a better opportunity to eliminate errors in a study

than the CRA who monitors it. It is the responsibility of the CRA to:

- Be aware of problems that might occur.
- Be aware and vigilant when looking for problems.
- Instruct site personnel to handle problems accordingly if they occur.
- Train site personnel to decrease and/or eliminate problems in the future.

To summarize, most errors are caused by misunderstanding or inattention. The impact of errors on study results is generally low, because they are usually correctable once they are caught. They can be eliminated, or at least reduced in number by training, which includes feedback. The dual role of the CRA is checker and trainer; actual error correction must be done by site personnel.

Misconduct

Misconduct is a degree more serious than error. Misconduct implies that someone knowingly did something that was wrong. In studies, some of the more commonly seen types of misconduct are enrolling subjects who "almost qualify" without permission, guessing at vital signs and easing things into compliance, examples of which can be found later in this section.

Investigators are under enormous pressure to enroll subjects quickly into clinical trials. The pressure has increased even more over the past few years with the widespread use of "competitive enrollment." Sponsors sign more investigators than they expect to need for a trial and allow enrollment of subjects to continue only until the necessary number of subjects is reached. If investigators enroll quickly, they will remain investigators for the trial; if they enroll slowly, they may have very few subjects entered when enrollment is halted, perhaps none, which would result in being dropped from the trial. Some study-related activities must take place at a site before subjects can be enrolled. It is possible that an investigator can even lose money on a study if he or she has no, or low, enrollment when the enrollment period is closed.

Given this enrollment scenario, it is easy to understand why an investigator would use all means available to find suitable subjects. Due to the fact that some of the inclusion and exclusion criteria for studies have measurements that are somewhat imprecise or could lend themselves to differing interpretations, such as blood pressure readings or rating scales such as the Hamilton Rating Scale for Depression (HAM-D), it can be tempting, and fairly easy, to ease these readings or ratings into compliance. For example, if a subject in a hypertension study was supposed to have an initial diastolic blood pressure between 90 and 100 mmHg, and the person being evaluated for the study is perfect in every way except that his initial diastolic blood pressure is 88 mmHg, who would know if the investigator recorded it as 90 or 91? No one

would, as long as the office chart and the CRF match. But if it is incorrect and was done on purpose, it is an example of misconduct.

Another example is a case in which subjects were to read an eye chart from a distance of 15 feet. Each subject did this at every visit. It wasn't until a new and astute CRA measured the distance that it was found to be only 13 feet, rendering the data unusable. The investigator knew he didn't have a 15-foot span to use, but figured it was "close enough" and that no one would measure.

The investigator was aware of the discrepancy, but didn't really think it made any difference, so he never mentioned it and continued to use the shorter span. This is misconduct.

Misconduct can have a more pronounced effect on studies than errors, simply because it may not be discovered or it may be unfixable if it is found. In the eye exam example, the misconduct was discovered but the data for about 25 subjects was unusable. It was in a very difficult study in which every subject enrolled was critical. When misconduct is not discovered it can, depending on the magnitude of the problem, affect the results of a study. It could make an investigational drug look effective or safe when it is not, or vice versa; neither is a good outcome for consumers.

It is much more difficult for a CRA to root out misconduct than errors. A CRA must be vigilant when performing source document review, particularly when it comes to verifying the inclusion and exclusion criteria for a subject. Sometimes site personnel may change things slightly in the CRF to make the subject fit the study, without thinking about past entries in an office chart. The CRA must also be aware of the pressures to enroll and be cognizant of enrollment that seem a little too good to be true. (Things that seem too good to be true often are.)

CRAs also need to think about what is needed in a study and should not be afraid to verify that they are correct. What a difference it could have made if the original CRA on the eye study had measured the 15-foot distance before subjects were enrolled.

Fraud

Fraud is the most serious offense of the three and the most difficult to discover. Fraud is willful deception. The impact of fraud on a study is apt to be very large, but can be measured only if it is discovered. It is a nightmare for the sponsor(s) involved and for the CRA. A CRA will not see cases of fraud often. We will discuss some publicized cases of fraud later in this chapter.

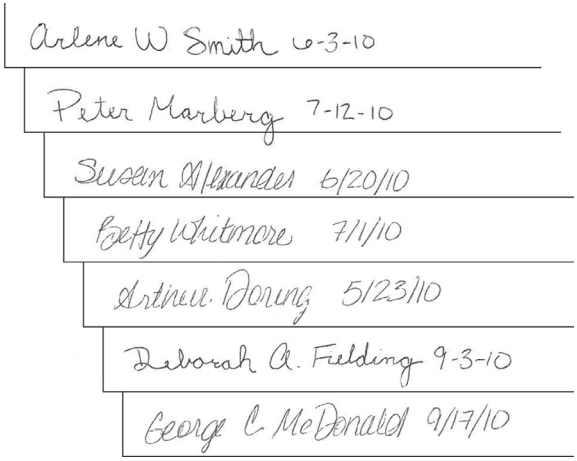
Fraud can manifest itself in various ways. Some of the more common ways are the use of fictitious trial subjects and/or data, faked test results and fraudulent study documents. Fraud is usually committed in order to increase revenue from the trial—either by enrolling more subjects, enrolling more quickly or cutting actual costs. After discussing some examples of fraud, we will talk about what a CRA can do to lessen the chances of fraud, how to look for fraud and what can be done when it is discovered.

Fraud is difficult to discover. The perpetrator of fraud is usually careful to do as much as possible to keep the deception hidden. However, there are some techniques a CRA may find useful when reviewing data that may point to situations that should be investigated further. It is important to keep in mind that the incidence of fraud in clinical trials is very low, and most CRAs will never encounter fraud. Still, it is important for CRAs to remain vigilant and aware of its potential.

Real-life Examples of Fraud

In a study at one investigative site, everything looked fine. The study went well, enrolled well and no one suspected that it was not handled correctly. It was only during a routine FDA inspection during the NDA review that a problem was found. The FDA inspector took all of the informed consents, stacked them up and fanned through them looking at the signatures. What he saw looked something like this:

It became apparent to the inspector as he rifled through them that all of the consent forms were signed by only three different people. The names on the form were different, but the handwriting was the same. As it turned out, in this case, they had been signed by the investigator and two research nurses.



Study subjects did not exist at all, but were part of a carefully laid plan to collect the grant without actually enrolling subjects. The subjects were fictitious, as were the data. It was cleverly done and might not have been discovered at all, except for the savvy inspector who looked at all of the consents together.

Why didn't the CRA find the consent problem? Because the consents were checked individually, as each subject was enrolled. Each one was signed and dated before the subject was entered into the study. The consents were each kept with the individual study chart and CRF, not together in one place. It never occurred to the CRA to pull them out and fan through them. It is a good practice for CRAs to look at all the consents together occasionally,

rather than individually as each subject is enrolled.

This investigator had contributed heavily to the data submitted for approval of this drug, so the sponsor company was required to re-analyze all of the data without including this investigator. It was an enormous job and cost the company dearly in terms of time and resources.

In another case, the investigator had subjects but didn't want to take the time to have their blood drawn. Instead, he drew blood from his own staff in greater quantities, divided it up and labeled it with the initials of each subject.

This way it could be done all at one time and stored ready to ship.

In this study, all of the blood samples were shipped to the sponsor. They were batched and sent every two-to-three months. The problem at this site was discovered when the samples for August and September came in and the vials were marked for October—someone had grabbed them by mistake. The CRA investigated, checked the freezer and there they were, neatly labeled and stored for months in advance. Needless to say, the data were not usable. Would this have been caught during routine monitoring? Probably not, unless the CRA happened to look in the freezer and see them. Had the site known the freezer would be checked, the samples probably would have been moved or disguised. One hint that might have caught the notice of that CRA beforehand was the site's lack of "busyness." If you don't see many subjects during your monitoring visits, it may be time to suspect fraudulent practices.

In 2010, a prominent anesthesiologist researcher on the East Coast was found guilty and sentenced to six months in prison for falsifying data in some clinical trials and inventing other trials entirely. He admitted to faking dozens of studies, and 21 published papers written in support of pain-killing medications had to be retracted. He had never applied for IRB approval at the medical facility where these trials supposedly had been conducted.[2]

When questioned about the incidence of investigator fraud, according to an article in Scrip Clinical Research, an FDA spokesperson stated, "despite concerns that falsification may be difficult to identify, investigator fraud in clinical trials is generally believed to be rare. Published estimates of the proportion of clinical trials affected by fraud range from 1% to 5% of clinical trials, with less than 1% of all investigators involved in engaging in data falsifications."[3]

Do Subjects Really Exist?

People who revert to fraud are usually quite clever at disguising their fraudulent practices, which makes them difficult to discover. However, there are some things a CRA can do when monitoring an investigative site to help uncover signs of potential fraud. First, think about whether or not subjects actually exist. When you are at an investigative site, look for signs that point to the existence of actual subjects/patients being seen. Do you see patients in the waiting room? Is the practice bustling? Are the phones ringing? Do you hear appointments being scheduled?

When the CRA is reviewing source documents, particularly office charts, there are things you would expect to see. Office charts usually contain the patient's name,

address, phone number, social security number, date of birth and insurance information. If it is not there, where is it? Does the chart look like most office charts, with entries done over time, in different handwriting, with different pens? Are lab reports available in the chart? The CRA should think about whether or not the patient charts look like standard office charts in most medical practices.

Look at the dates of study visits and compare them on a calendar. Are people coming in on appropriate days of the week, or are there a lot of weekend and/or holiday visits? Look for things that you would not expect to see. A site may see study patients on a Saturday, or even in the evenings, but you would not expect to see Sunday visits or visits on holidays (Thanksgiving, Easter Sunday, July 4th, etc.).

Think about the accrual rate of subjects into the trial. Is the rate faster than expected? Faster than other sites? How can this site enroll well if others can't? If there is no explanation, a wise CRA will thoroughly check the source documents and look closely at the data and the screen failure rate. Is it similar to other sites' or lower than expected?

Numeric Data

There are also things to consider when reviewing numerical data, such as blood pressure readings. Look at the blood pressure readings listed below:

120/80	120/85	115/80	120/75	110/70
120/80	110/70	115/80	120/90	110/70
120/85	110/80	120/80	120/80	110/65
120/80	110/80	120/80	120/85	115/80

The first thing you should notice about these numbers is that they all end in either 0 or 5. You would not expect all blood pressure readings to end in 0 or 5, when presumably they could end in any digit. Unless the instrument used is calibrated only in increments of five, this will not happen.

With numerical data, look for other digit preferences, as well as 0 and 5. You should expect to see a pretty random distribution of the last digits; you would not expect to see mostly 7 or 3, for example. Look also for other invented patterns of numbers (lots of 77s or 123s, for example), and for more duplicate numbers than you would expect.

Look also for too few or too many outliers (outliers are the data values that lie outside the range you would normally expect to see). If you are dealing with a population of subjects whose blood pressures are "normal," as opposed to a hypertension study, for example, you will expect to see some people with higher than normal pressures and a few with lower than normal pressures. If you are seeing too many that are outside the normal range, you may want to investigate further. The same is true if you see no one outside the normal range. The data may be valid, but it is worth checking the source documents for verification or asking about it.

Commonly Chosen Data for Fabrication

According to Iber, Riley and Murray in their book "Conducting Clinical Trials,"[4] the data points commonly chosen for fabrication, with comments in italics added, are:

Entry Criteria:

- Known disqualifying factors are suppressed, *such as taking a non-allowed medication prior to entry.*
- Birth date altered to meet eligible age range; weight or height altered. *It's more difficult to alter the birth date in source documents, since it appears in many places. Weight is variable and may fluctuate, making it more likely to be changed.*
- Dates of prohibited medication use altered or suppressed. *Example: no previous treatment with an antibiotic was allowed in an infectious disease trial. The subject was treated, but it was not put in his chart or on the CRF.*
- History of drug or alcohol abuse or mental illness suppressed. *If this information already appears in the chart, it is difficult to suppress. If it is a new patient; however, this information can just be omitted from the chart when the history is taken.*

Safety Checks:

- Reports of procedures from previous visits or from other patients are used for the current visit. *Laboratory reports, ECGs, etc. are either from a previous subject visit, or might be from a completely different person as with the blood sample example.*
- Blood and urine samples substituted from other patients. *This can happen when the subject doesn't qualify. A sample from someone who does qualify might be split and relabeled with the subject's identifiers.*

Visit Data:

- Visit dates altered to fit permitted windows. *This keeps the patient in compliance and the visit from being missed.*
- Visits fabricated. *This can be easy to do, especially with phone visits or visits when laboratory tests, ECGs, etc. are not completed.*
- Medication counts falsified, with tablets discarded so inventories match false reports. *This makes it look like they are in compliance when they are not. It can also cover up incorrect dispensing on the part of site personnel.*
- Diaries fabricated. *Note that the handwriting in diaries can be checked*

in the same manner as the writing on consents—look at them all together, both for a single subject and for all subjects.

Suspicion of Misconduct or Fraud

When a CRA suspects that things may not be quite right at a site, there are a number of things that can be done. The first is to thoroughly monitor everything, doing more than you might do under normal circumstances. Be thorough when reviewing source documents, taking the time to check all variables. Check carefully across visits, thinking about whether the new data seems consistent with older data in light of what you know about each subject. Do you see differences in the data that appear odd or unusual?

The CRA can also check the laboratory reports and other test results. Be sure the patient identifiers are consistent (name, age, sex, social security number, date of birth, etc.). If someone is falsifying information, he or she is apt to make mistakes on the small, non-essential information rather than on the primary information. If you notice discrepancies, ask the study coordinator or the investigator about them and listen carefully to the explanations they give you.

If you have checked carefully and your suspicions remain, call someone to help. Ask your supervisor or another (senior) CRA to monitor with you and see what they think. If there still appears to be a cause for concern, ask your Quality Assurance (QA) group to send someone to perform an audit. At this point, the investigative site may not need to know about any concerns involving misconduct or fraud. It may be best not to alert the site, as some may be tempted to cover up the issues. Also if there was no misconduct or fraud, the relationship may be damaged by the accusation. Remember, you need to continue working with them. If your company has determined that there is probably fraud, it must be reported to the FDA. In this case, the FDA most likely will do a for-cause audit of the investigative site, which was discussed in the previous chapter.

Consequences of Fraud

The consequences of fraud can be disastrous for a sponsor. The data from the fraudulent site may not be usable, which may result in losing a complete study. This can delay the NDA or cause the FDA to declare it as "unfileable." This can set a development program back by several years or may cause the program to be completely halted. At the very least, a sponsor will probably need to reanalyze the data, which will eliminate all data from the questionable site.

The consequences for investigators who have participated in fraud are also severe. They may be placed on the FDA List of Disqualified and Restricted Investigators or they may be barred from participating in clinical research. In the worst cases, they also may be fined and/or sent to prison.

There can be consequences for a CRA if fraud has been found at his or her site. If the CRA found the problem through diligence and good monitoring and found it early, he or she will probably be credited with a job well done. Given that fraud can be very difficult to detect, a CRA might not have found it even while doing a superb job of monitoring; in this case, there are not likely to be any tangible repercussions for the CRA. There may be intangible repercussions, however; memories are long when it comes to cases of fraud. Even if the fraud was cleverly perpetrated and disguised and even if there was no blame placed on the CRA, it's not pleasant to have to explain (for years) what happened at "your" site. Of course, if the CRA did not find problems because of improper monitoring, the outcome won't be as rosy. CRAs can be severely reprimanded, or even lose their jobs, in this situation.

The best steps a CRA can take to minimize the potential for fraud at a site, or to detect it if it is present, are:

- Monitor carefully and thoroughly. Don't cut corners. Ask questions if you are seeing discrepancies.
- Think about what you are seeing and doing. Does it make sense?
- Pay attention to small signs and problems. Be aware of what is going on around you. Pay attention to your "gut feelings."
- Listen. Be approachable. Many times fraud is uncovered because an employee tells someone else about it.
- Bring in another set of eyes. The site does not have to know why you have someone else with you—it can just be a joint monitoring visit or a training session.
- If you see potential problems, share them with your supervisor. The problems will not take care of themselves.

Conclusion

Many years ago, the FDA began seeing a large increase in the number of complaints filed against investigators. The FDA's Division of Scientific Investigations (DSI) was promoting the importance of filing complaints, due in part to some of the abuses seen in clinical trials. DSI tracks the complaints they receive closely and has instituted an aggressive follow-up program for investigating them.

Complaint inspections find noncompliance at sites in far greater numbers than unsolicited inspections; in fact, between 1999 and 2000, approximately one in every four complaint inspections resulted in an OAI inspection rating. The complaints to the agency come from many sources, including disgruntled employees, sponsors, IRBs and others. Complaints coming from sponsors often originate with CRAs, as CRAs are in the best position to determine what is occurring at study sites.

It's difficult to prevent all errors, but they are usually fairly easy to find and fix. They may generally decrease in number as the trial progresses.

Once a mistake is fixed, the impact on the overall trial results may not be significant.

The difference between misconduct and fraud is really only one degree since, in both cases, there is intention to do things incorrectly. Both can be difficult to detect, especially fraud, as it is often cleverly perpetrated on a large scale. In general, fraud is committed for personal gain, while misconduct is committed for expediency. Both can have a major impact on a trial.

CRAs are the first line of defense against errors, misconduct and fraud, and they must remain vigilant to these potential problems.

Key Takeaways

- Errors are unintentional, usually due to misunderstanding or carelessness, and can be fixed. They usually have a low impact on a trial.
- Early detection of errors and close cooperation with site personnel will generally reduce errors in a study.
- Misconduct and fraud are classified as intentional wrongdoing, are difficult to detect and can have a major impact on a trial.
- Fraud is usually committed for personal gain, while misconduct is often committed for expediency.
- The CRA is the first line of defense against errors, misconduct and fraud.
- Good monitoring and awareness can help prevent and detect misconduct and fraud.
- The FDA is relying on help from CRAs to discover noncompliance at investigative sites.

References

1. Merriam-Webster's Collegiate Dictionary, Eleventh Edition. Merriam-Webster. Springfield, MA. 2009.
2. "Surviving the Nasty Surprise of Investigator Fraud." Scrip Clinical Research. December 2010.
3. Ibid.
4. Iber, Frank L., Riley, W. Anthony and Patricia J. Murray. Conducting Clinical Trials. Plenum, 1987.

CHAPTER TWENTY-ONE

The Future for CRAs

CRAs, who have long had an essential role in ensuring the quality and integrity of clinical trial data, continue to find their responsibilities changing and expanding beyond traditional monitoring duties. Based on today's trends, it is likely that the CRA job will evolve further.

Impact of Technology

Since the mid-1990s, industry thought leaders have predicted that technology would ultimately replace the role of the study monitor. That may not happen. And technology has helped expand and change the CRA's role in clinical research.

While EDC can improve a monitor's efficiency, it won't eliminate the need for source document verification and general study oversight. A CRA does much more at site visits than review CRFs and source documents; EDC doesn't affect these other activities.

Nevertheless, EDC has changed the nature of site visits. EDC allows field monitors to examine patient enrollment, look at actual data, review queries that have been generated, run reports and make sure the data entry is up-to-date before visiting a site. This technology also gives CRAs the ability to analyze information and to query data directly with the sites, making source verification activities more efficient. Many field monitors say the best things about EDC are the reduced numbers of queries and the shorter time needed at the site for monitoring visits.

As noted in Chapter 14, risk-based monitoring and remote/central monitoring have led to a decrease in some on-site monitoring activities, and a more efficient means of reviewing and transmitting study data. It has also

further contributed to the separate, emerging role of the remote monitor. The author feels that the partnership of the regional CRA and remote monitor will become the accepted process for site management in years to come.

CROs and sponsors are also transitioning to eTMF data files and training programs; a paperless system eliminates the need for brick and mortar office space. Due to this, offices that used to physically house CRAs and paper files are closing due to lack of need. Technology has not replaced the need for CRAs, but rather changed the way CRAs perform their job.

Regulatory portals and shared databases are expediting study start-up and IRB submission activities, which require CRAs to become adept at utilizing a variety of databases to conduct their jobs. CRAs must have experience with computer- and cloud-based systems in the conduct of job responsibilities; gone are the days when a mere "comfort level" was sufficient enough when performing monitoring tasks.

Increased Responsibility

Although specific approaches differ widely by company, drug sponsors are beginning to rely on CRAs to help build stronger relationships with investigative sites. Increasingly, sponsors give study monitors additional responsibility for site management activities, such as evaluating patient enrollment plans, helping to solve patient recruitment problems and participating in site selection. This often means not only monitoring data and ensuring investigator compliance, but also solving day-to-day problems at sites and acting as the liaison between the drug sponsor and the investigator.

More companies are empowering their CRAs to be influential in site selection. The majority of sponsors/CROs already have their monitors conduct pre-study site visits to evaluate the investigator, staff, facility and lab, and then make recommendations about whether the site should participate in a study. This can result in more successful studies because the monitors, who work with investigative sites on a regular basis, know the quality—or lack thereof—of individual sites.

If a CRA has developed a good relationship with an investigator and site personnel, and helps select that site for a study, the investigator is apt to work harder to make the study successful. Working with the same monitor on repeat studies can also help improve communication and expectations between investigators and field monitors. Both sides benefit from these monitor-investigator relationships. Monitors may be able to alert investigators about potential studies in the pipeline, while investigators develop a sense of loyalty that extends to giving that drug sponsor preference when competing studies arise. At the same time, this type of relationship can go a long way toward helping to solve problems that occur during a study.

Regional Monitoring

CRAs have seen their roles shift, in part, due to wide-spread adoption of the regional field monitor structure by major pharmaceutical companies. Many of the top drug companies use this approach as opposed to sending CRAs from a centralized office to far-flung investigative sites. This regional structure has allowed drug companies to cut travel costs and has also led to improved job satisfaction and decreased turnover rates of CRAs.

At the same time, sponsors have realized another benefit of a regional study monitor structure: Regional monitors, who repeatedly visit the same sites and spend many hours with investigators and coordinators, have become an invaluable source of information about site operational issues, such as the professionalism of a site, the efficiency of the coordinator and how staff handle data. Study monitors might notice other factors that could effect the success of a study, such as signs that the coordinator and ancillary staff are overworked or frustrated. They are the eyes and ears of the sponsor.

The demands placed on regional monitors, who work out of their home offices with minimal supervision, require a higher level of skill, experience and education than in the past. Many CRAs not only have degrees in nursing or life sciences, but also have studied business, accounting, sociology or psychology.

CRA training schools

Clinical research and CRA training academies (private standalone training companies or CROs/sponsors providing specific CRA training) are emerging to meet the growing interest of clinical professionals entering the clinical trials industry, requiring preliminary research training.

Conclusion

Pharmaceutical companies have come to value the skills of experienced CRAs. Pay and benefits have increased to reflect this. Because travel requirements have often been reduced and duties have expanded beyond ensuring the quality of data, job satisfaction has improved. The CRA position has become more of a career choice and less of a stepping stone to another position in clinical research.

As their roles and responsibilities continue to grow, CRAs are becoming even more critical to the success of clinical trials. Investigative sites consistently have rated the quality of CRAs as one of the top five most essential factors contributing to study success. For the sponsor or CRO, the study monitor is the person who can make or break a study.

Key Takeaways

- EDC has changed the nature of site visits, which allows monitors to make sure data entry is up-to-date before visiting a site.
- Risk-based and remote monitoring practices have reduced the need for completion of some on-site monitoring tasks.
- Sponsors are delegating more study monitoring responsibilities to CROs.
- Monitors are expanding their duties beyond checking to see that sites comply with regulations and verifying source documents.
- Companies are empowering regional monitors to be influential in site selection and help communication with investigators.

We've covered a great deal of basic material in this book, and we hope you have found it useful and helpful as a CRA. Remember that the little things can make a big difference and can make your job easier. There is no doubt about it—the job of CRA is not for the faint-hearted. It's an enormous amount of work and a lot of responsibility. It requires multiple skills, lots of travel and the ability to keep many different balls in the air at once. It's also fun and challenging, with numerous opportunities to learn new things, meet new people and have new experiences. If you enjoy this job as much as we did, you'll never regret having the chance to do it. We hope you enjoy your CRA adventure. We'll leave you with some final key takeaways that will help you in this job and in your future.

Key Takeaways

- Always know the protocol.
- Don't take job-related problems personally. It's just business.
- Never burn bridges. It's a small world.
- Keep educating yourself.
- Change is coming.
- Treat people as you like to be treated.
- Don't be afraid to admit you were wrong.
- Enjoy yourself.
- Be nice.
- Smile.

APPENDIX A

Resources

Books and Videotapes

Acres of Skin: Human Experiments at Holmesburg Prison—A True Story of Abuse and Exploitation in the Name of Medical Science
Allen M. Hornblum, 1998

Bad Blood—The Tuskegee Syphilis Experiment
James H. Jones, 1981

Code of Medical Ethics
American Medical Association, 150th Anniversary Edition, 1997

Factories of Death—Japanese Biological Warfare, 1932-45, and the American Cover-up
Sheldon H. Harris, 1994

Guide to Clinical Trials
Bert Spilker, Lippincott-Raven, 1996

Human Radiation Experiments—(The) Final Report of the President's Advisory Committee
Advisory Committee, 1996

Nazi Doctors—(The) Medical Killing and the Psychology of Genocide
Robert Jay Lifton, 2000 (reprint)

(The) Placebo Effect
Edited by Anne Harrington, 1997

(The) Plutonium Files—America's Secret Medical Experiments in the Cold War
Eileen Welcome, 1999

Protecting Human Subjects—A Series of Instructional Videotapes—Evolving Concern; Protection for Human Subjects (3 videotapes)
OPRR/OHRP

Protecting Study Volunteers in Research—A Manual for Investigative Sites
Cynthia Dunn,M.D.; Gary Chadwick, Pharm.D. MPH, CIP 2002

Tuskegee's Truths; Rethinking the Tuskegee Syphilis Study
Susan M. Reverby (Editor), 2000

Agencies

Center for Drug Evaluation and Research (CDER)
Clinical Investigator Information
www.fda.gov/AboutFDA/CentersOffices/CDER/default.htm

FDA
www.fda.gov

International Council for Harmonization
www.ich.org

OHRP Site
www.hhs.gov/ohrp

World Medical Association
www.wma.net
The World Medical Association (WMA) is the organization that issued the Declaration of Helsinki and is responsible for its updates.

Bioethics Resources on the Web
http://bioethics.od.nih.gov
This site is maintained by the National Institutes of Health and provides links to a wide variety of bioethics resources on the web.

Human Subjects Research and IRBs
http://bioethics.od.nih.gov/irb.html

ClinicalTrials.gov
www.clinicaltrials.gov
The U.S. National Institutes of Health, through its National Library of Medicine, has developed ClinicalTrials.gov to provide subjects, family members and members of the public current information about clinical research studies.

HIPAA References

Background/Overview

HHS HIPAA implementation process
http://aspe.hhs.gov/admnsimp/kkimpl.htm

Privacy

Summary of the HIPAA Privacy Rule
www.hhs.gov/ocr/privacy/hipaa/understanding/summary/index.html

Other Information

Department of Health and Human Services (HHS) Protection of Human Subjects Regulations
www.hhs.gov/ohrp/humansubjects/index.html

Belmont Report
http://ohsr.od.nih.gov/guidelines/belmont.html

FDA Forms
www.fda.gov/opacom/morechoices/fdaforms/cder.html

FDA Information Sheets
www.fda.gov/oc/ohrt/irbs/default.htm

Declaration of Helsinki
www.wma.net/en/30publications/10policies/b3/

Nuremberg Code
http://ohsr.od.nih.gov/guidelines/nuremberg.html

NIH Required Education in the Protection of Human Research Participants
http://grants.nih.gov/grants/guide/index.html

Sources of Potential Investigators
www.centerwatch.com
www.clinicalinvestigators.com

APPENDIX B

Hints and Tips

Travel Hints

Planning

- Make your travel plans as far in advance as you can. You'll have better luck getting the flights and hotels you want. You will also have a better chance of getting the seat or type of hotel room you prefer. Early bookings are less expensive.
- Make sure you have completed online check-in with your airline, and have your itinerary printed or downloaded before you leave, as it makes the check-in process more efficient at the airport.
- Early morning flights don't have as many delays because the planes are often at the airport overnight.
- Always arrive at the airport 1.5-2 hours ahead of time for domestic flights and 2.5-3 hours ahead of time for international flights.
- Two credit cards, an ATM card and a phone card are essential.
- Have some cash with you, but not an inordinate amount.
- Have some change with you for tolls and parking meters.
- Carry the 800 numbers for all the major airlines, hotels and car rental places with you when traveling.
- Smart phones are essential for traveling, for GPS, voice recognition for calling family members, for calendar entries and reminders, notification of delays or flight cancelations and for calling investigative site personnel. However, they need to be turned to off or to "vibrate" during meetings. Return calls after the meeting.
- Double-check with your sites before leaving for the airport to be sure they are expecting you.

- If you have an important meeting, go the day before to the city or town where it is being held. You can never count on getting there on time the same day.
- Wear comfortable shoes.
- Take all pertinent addresses and phone numbers with you.
- Download a "maps" application to your phone for places you visit regularly.
- Ask your sites for suggestions about handy hotels, restaurants, etc.
- Take advantage of the cheaper fares by staying over Saturday night when you can. This gives you a chance to explore a new part of the country.
- The TSA has pre-qualification access programs for frequent travelers (that qualify) that allow for expedited security screening and entry at participating airports.
- Always ensure that your passport is current for unexpected international business travel.
- Always check the weather forecast for the city to which you are traveling, to ensure you have packed accordingly (winter coat, shoes, layers).
- Hotel chains also have apps downloadable to your smart phone that allow you to make or change reservations, track hotel points and check in online, which may also enable you to pick your room and obtain an upgrade.

Stress and Health

- Travel has the potential for being very stressful—try not to let it let it stress you too much.
- Take some time to relax when you travel. Read a book, watch a movie, do a crossword puzzle or find something else you like to do that will help relieve travel stress.
- Wash your hands frequently when traveling. This will help you avoid colds and other bad bugs. Also, carry some antibacterial hand sanitizer with you. It comes in travel-size containers.
- Don't count on getting a meal on the flight. Take a sandwich with you if you'll miss meals during travel. It's bad enough to be tired from traveling, without being tired and hungry.
- Airplane air is very dry. Avoid getting dehydrated on long trips by drinking plenty of water. Alcohol, coffee and regular tea can further dehydrate you.

- Be careful about eating when traveling—it's easy to rely on fast food with tons of calories and fat. Try to include fruit and salads.
- A leftover bag of airline peanuts is not a meal. If you are arriving late and the hotel does not have room service, have the cab driver stop and let you pick up something on the way. Or, sometimes pizza places will deliver to the hotel, depending on the time of night.
- Almost all hotels have some type of gym or exercise equipment. Always try to fit in time for working out, as it combats stress, promotes health and can counter some negative effects of travel (unhealthy eating, sleep deprivation, etc.).

Luggage

- Pack light. Never take more than you can carry comfortably by yourself. Remember that you may have case report forms to carry back with you, so allow some space for them.
- Find clothes that look professional but travel well. Check out travel catalogs that feature clothes especially made for traveling, comfortable clothes that don't wrinkle. Most hotels provide irons for quick touchups (if one is not in the room, call housekeeping and ask).
- Buy duplicate toiletries for a travel kit and keep your travel kit packed and ready to go. Replenish as needed. This is much easier than trying to remember and pack everything each time you leave.
- Many rooms have a small coffee maker. Pack a few cocoa packets or herbal tea, if you like them, so you can have some when you want.
- Carry a folding umbrella with you. Remember to take gloves if it will be cold at your destination.
- Carry your money, credit cards and important papers in a secure manner. Women: If you have a purse with a shoulder strap, put it across your chest and/or under your coat. Men: Don't carry a wallet in your back pants pocket. Make it difficult for pickpockets to see and acquire your things.
- Keep essential papers in your carry-on luggage/briefcase.
- Never check non-replaceable materials.
- You will lose checked luggage sometime.
- Your checked luggage will be delayed sometime.
- Mark your baggage in a distinctive way. Not only does this make it easier for you to see on the baggage carousel, it makes it less likely that someone else will think it is his or her bag. For example, many people have

black suitcases that all look alike. Tie strands of colorful ribbon around the handle of yours. You'll be able to recognize that it's yours instantly, and others will realize it's not theirs.

- Watch for your suitcase on the carousel to be sure that someone else does not take it.
- If your bag does not appear on the baggage carousel, go as quickly as possible to the baggage place to report it. If you delay, you are apt to have a long wait in line.
- If your luggage does not arrive when you do, ask for an amenity kit from the airline. Many of them have small kits with a toothbrush and toothpaste, deodorant, etc., that can tide you over.
- If you are taking a carry on bag, and checking a bag, always carry a set of clothing and toiletries in your carry on bag, to ensure you have something to wear if your luggage is lost or delayed.

Airlines

- Airline apps are a must for the CRA of today. They hold your frequent flier profile, miles accumulated and required targets for the next level of status, trips taken, drink coupons, flight changes, flight bookings, etc. Their alerts regarding flight delays, arrivals and cancellations are more reliable than the airport board, and sometimes the airline customer service. You can rebook yourself if a flight is delayed or cancelled, much faster than the gate agent or airline customer service.

"It's all in the suit.

In my former life, I was a flight attendant. The flight attendant training included training on public speaking, posture and stance. As a CRA, I prefer to wear dark or black suits or dresses, which has had me mistaken for flight crew several times when traveling for monitoring visits. The funniest incident occurred when I was boarding a flight and organizing my belongings on my seat/under my seat. A middle aged gentleman kept making eye contacting and pointing to his bag in the overhead. I chose to ignore his behavior as safety is of critical importance when traveling alone. The man was clearly frustrated as he approached me and demanded to know why I would not help him load his bag into the overhead. The next six words out of my mouth caused him to walk sheepishly back to his seat.

"Sir, I am not the flight attendant."

It never bothers me when this happens, for I know it will continue to happen as long as I travel for clinical research and wear my requisite dark business attire.

—Elizabeth

- Take advantage of airline, hotel and rental company frequent user programs. You can use the accrued points for vacations.
- Try to use one airline as much as feasible. You may travel enough to get a gold or platinum frequent flyer card, which gives you free upgrades to first class.
- Be very nice to airline counter attendants, hotel personnel, etc. You will deal with some of these people on a regular basis, and they can do nice things for you if they want to.
- Always be nice when problems arise. They are rarely the fault of the person you need to deal with, and these folks can either give you minimal service or go out of their way for you.
- At airline check-in security gates, do not place your bag on the x-ray conveyer until you are able to walk through. This is a common place for bags to be stolen.
- If you carry a laptop, note that you will be asked to take your laptop out of its case and may be asked to turn it on.
- If you travel with a tablet, you will be asked to take that out and place in a bin to go through security screening, in addition to your lap top.
- Grab a pillow (and blanket) when you get on the plane. Better yet, bring your own if you can. These items can carry germs, if they're not individually sealed. Airplane seats do not fit all sizes, and a pillow can help. Plus you have one if you want to nap.
- You can get a lot of work done on a plane if you are in business comfort or first class. It is more difficult in the regular coach cabin. It is usually so crowded it's hard to find space. And if the person in front of you puts his or her seat back, it's almost impossible to use a laptop or to work at the tray table.
- If you experience a lot of delays on a particular trip, ask for a meal voucher when you have a long wait. These are valid in the airport.
- Check the monitors regularly in the airport, as well as your airline app. Flights are often changed to other gates, and you may be hurrying to the wrong gate. Check occasionally even if you are at the gate.
- Be alert to the first signs of a canceled flight. This can put you near the front of the line for rebooking.
- If you are caught in a long line of people waiting to be rebooked from a canceled flight, it can be faster to call the airline's 800 number and make the changes over the phone.
- If your travel plans are flexible and you are caught up in weather delays, it can be easier and more efficient to get a hotel and wait until the

next day to fly. You can get caught up on your paperwork in the hotel and avoid waiting and wondering in the airport.

- Airplanes can be cold. Be prepared with a sweater or jacket.
- If the trip is bumpy, order a club soda or water when the drinks cart comes by. They won't leave you with noticeable drips or stains, if you spill them on yourself.

Transportation at Your Destination

- Check the cab price from the airport to the hotel before you get in. Sometimes a limo service car costs no more but is much nicer.
- Lyft and Uber are very convenient and inexpensive ride share options to cabs but are more difficult to catch at the airport.
- Sometimes it is less expensive to rent a car than to take cabs. Be sure to get a car with a GPS, to know where you are going.
- If you get a good cab (limo) driver, arrange for the same person to transport you while you are there and/or back to the airport.
- If you're taking a shuttle back to the airport, check with the hotel about needing to sign up for it in advance.
- When traveling regularly to the same city, find a rental car company you like and use it regularly. They will appreciate your repeat business, and you will have better service.
- Do the rental car paperwork while you wait for your luggage at the baggage claim.
- Be sure you have your driver's license with you and that it has not expired. You will not get a rental car otherwise.
- Some rental car companies have non-smoking cars.
- Fill up the rental car with gas before you return it—it's much cheaper than if the rental company does it.
- Two hours in a rental car costs as much as a whole day. Get the car back on time (or early) if you can to avoid the extra day charge.

Driving to Your Sites

- Be sure you have good directions to the places you need to visit.
- A Global Positioning System (GPS) with a good map base can be very helpful.
- If you drive a lot, keep an emergency kit in your car for bad weather

or other problems. Include a flashlight, flares, jumper cables, a small tool kit, a first aid kit, a blanket, umbrella, gloves and ice scraper. You can also keep a change of underwear, some toiletries, etc., in a car pack in case you can't make it back home because of bad weather. If the weather might be bad or you expect delays, pack a few granola bars, bottled water, etc.

- Be sure your car is dependable and serviced appropriately and that the tires are in good shape.
- An all-in-one tool is handy to keep in the car. So are pre-moistened wipes and antibacterial hand lotion.
- Never let your gas tank go below half full if you are in the country or not familiar with where the next gas station might be. Or in the winter, in case you get stuck somewhere.
- Keep a gallon of windshield washer fluid in the car.

Hotels

- When traveling regularly to the same city, find a hotel you like and use it regularly. They will appreciate your repeat business, and you will have a familiar, comfortable place to stay. If you book in advance and ask for it, they may give you the same room each time.
- If you use the same hotel, you will build up hotel points, which will elevate your status with the hotel. Many hotel points programs give elite status customers free room upgrades. Those accumulated reward points can be used to cover lodging on vacation; some of these hotel chains have properties in exact locales like Hawaii, French Polynesia, London, Paris, Australia, etc.
- Hotel chains also have apps downloadable to your smart phone that allow you to make or change reservations, track hotel points and check in online, which may also enable you to pick your room and obtain an upgrade.
- Use a hotel with guaranteed late arrival so that you don't lose your room if you are delayed.
- If you get to the hotel and they don't have a room for you, ask them to call another hotel for you. Sometimes they will also have their shuttle take you to the alternate hotel.
- If you don't like your room, ask for a different one.
- If the hotel is dirty, don't go back. And tell them why.
- Use the hotel comment cards—for kudos as well as complaints.
- Check the hours for the hotel restaurant or room service when you

arrive if you will need to depend on it later. Sometimes the hours and services printed in the hotel information in your room have changed.

- Sometimes hotels will allow repeat customers to order room service ahead of time, if they are landing after the restaurant has closed. It is nice to arrive to a hot meal when you have not eaten in many hours.
- Don't be hesitant to dine at the hotel restaurant alone. They are used to having business travelers eat solo and will make you feel welcome. You can watch other people, chat with the waitperson and not feel cooped up in your room.
- On the other hand, room service can be great at the end of a long, tough day. Wearing your pajamas while watching TV and eating a club sandwich might really hit the spot. Most room service has a service charge and a tip already added in, so don't feel that you need to tip even more.
- Hotel breakfasts can be exorbitant, especially with room service. Look for a local breakfast place close to the hotel (ask the bell staff). Besides being much less expensive, a little fresh air is nice in the morning.
- Some hotels provide breakfast (Embassy Suites, for example), and sometimes snacks at night. This is especially useful if you are on a per diem for meals.
- If you are going to be in the same hotel for more than one night, unpack and use the drawers. It's easier than rummaging through your suitcase to find everything and easier to pack up again when you leave.
- If you need to work at the hotel, ask for a room with a desk.
- Many hotels offer wireless internet and printing capabilities.
- If it's too dark to read or work in your room, ask for another lamp or brighter light bulbs.
- If you like to exercise, inquire about the facilities when booking your hotel.
- Check with the hotel staff to be sure that the area is safe before going out to jog, etc., especially at night.
- Many hotels will extend the checkout time by a few hours if you ask.
- If you have to check out before the time you will be leaving, the hotel will hold your bags for you. Ask at the concierge desk or bell stand.
- If you need to meet with people at your hotel, the all suite hotels give you a place to meet that's not in the bedroom.
- Say "Thank you" when someone does something nice for you.

Hints for Independent CRAs

As was mentioned in Chapter 1, many CRAs are currently self-employed as independent contractors. There are advantages and disadvantages to working as an independent contractor. The advantages are that you are essentially your own boss. There will be someone at the sponsor company or CRO to whom you "report" for a specific job, but you are usually on your own as far as planning your schedule and hours. You are also able to work from your home, away from the hustle, noise and politics of a corporate office.

Probably the biggest hurdle for independents is finding work. You have to "market yourself," and this can be difficult and time-consuming to do. Working as an independent also requires a significant amount of personal discipline. Many people prefer to work in an office environment with other people around to have coffee and lunch with, and with whom to discuss problems and job situations.

Because there are special considerations when working as an independent CRA, here are some helpful hints that may be of value.

- The IRS considers an independent CRA as a small business. Consequently, you must maintain your records and tax documents appropriately.
- Find yourself a good tax accountant/CPA. You will probably gain more than you spend to pay for this service.
- Always have a contract for the services you provide.
- You may want to discuss your company organization with an attorney.
- There are many kinds of small business organizations, and the appropriateness of each type varies according to personal situations and desires.
- You may also want the services of an attorney if you are not comfortable dealing with contracts.
- Build some structure into your workday, including break times for coffee and lunch.
- Save your household chores for the non-working times of the day.
- Keep yourself organized.
- Set up a good filing system and keep current on your filing.
- Have a separate credit card that you use only for business.
- Keep a separate checking account only for business.
- Invest in a good computer program for tracking your financial information. There are several on the market. (Ask your accountant or CPA for advice.)
- Have business cards made. Since you may work for multiple companies, you might want to have a "generic" card that lists only your name and contact information.

- Develop a system for keeping track of your expenses. Be sure to write them down as they occur. This is important if you are being reimbursed, or for tax purposes if you are not reimbursed.
- Keep your receipts. File them in such a way that you can retrieve them when needed.
- Pay for most things using your credit card. This helps to track expenses.
- If you take someone out for a business meal, jot on the back or bottom of your receipt who was present and the reason.
- Maintain confidentiality. Never discuss one sponsor's program with another sponsor.
- If you are able to combine travel for multiple sponsors, let each sponsor know, and split the expenses appropriately.
- Many independent CRAs work on an hourly basis. Record your time honestly.
- Repeat business is critical. Do not do anything to jeopardize your reputation with a company.

Maintaining Ties With Sites Between Studies

- Telephone them every couple of months to say hello.
- Know the coordinator's birthday and send him or her a card.
- If you see something written about the site (or any of the staff) in the paper, etc., drop them a note.
- If you happen to be in the vicinity and have time, drop by for just a minute to say hello. Keep the visit short so that it's not disruptive.
- When the drug they worked on is approved, drop them a note to tell them.
- Send a card (with a personal note) at the holidays.

Home Office Work

- Make a separate folder for each protocol you are monitoring (hard copy or computer folders; whatever works for you).
- Make a separate folder for each site you are monitoring (hard copy or computer folders; whatever works for you).
- On the inside of the front folder cover, put the names and contact information for the site. Update it as soon as you become aware of a change.

- File the site folders in an order that works for you. Possibilities are by investigator name, city or protocol. You might file them by protocol during the trial and by investigator name when the trial is complete.
- Color code your investigator files by city. Then when you are preparing for a visit to Omaha, for example, you just pull all the yellow folders.
- Organize each folder in the same way so you can easily find what you need.
- Label each folder clearly.
- File them. Don't let the filing pile up.
- File them in an organized manner.
- If you are primarily computer-based with files and study information, don't forget to frequently back up your hard drive. Maintain file copies in a cloud-based system, zip file or hard drive in case your computer crashes.
- Always keep basic office supplies on hand—pens, paper, file folders, paper clips, labels, staples, mail supplies, etc. Get more before you run out.
- Keep an extra printer cartridge on hand.
- Use an uninterrupted power supply (UPS) with your computer. Don't forget to protect your computer's phone or network connection also; this is where the power problems frequently occur. A regular "surge suppresser" is practically worthless.
- Keep your calendar up to date.
- Don't forget to add regularly scheduled meetings, phone calls and reports to your calendar.
- Set aside some time each week to catch up on your paperwork.
- Complete your visit reports as soon as possible after each site visit, preferably on the same day that you make the visit.
- Use a tickler file or outlook calendar reminders so you won't forget important dates, etc.
- Clean your desk regularly. You'll be surprised at what you find at the bottom of a pile.
- Block out time and be on time for conference calls or other meetings.
- Keep basic office supplies for traveling in your briefcase.

Hints for Monitoring

- If you aren't sure where the site is, scope it out the night before.
- Some computer sites that help you locate addresses are google maps, mapquest.com and expedia.com. Most smart phones have a maps option, or you can download a map application.
- Don't be late.
- If you are going to be late, call the site to let them know.
- Do not expect site personnel to stay late for you because you were late in arriving. They have other commitments also.
- Don't spend your time at the site on the phone to other sites.
- Be polite. Good manners are important.
- Know the study you are monitoring. Be very familiar with the protocol. Never visit a site without reading the protocol first. Be sure you understand it—don't embarrass yourself by not being able to discuss it intelligently.
- Always use checklists.
- Carry a "Pocket Pharmacopoeia" by Tarascon with you.
- Remember that your smart phone has the ability provide internet access via the hot spot, but be aware of your company data plan and any additional charges
- Use your own supplies. Don't expect them to be provided for you.
- Be careful about the language and phrasing in your monitoring reports, especially if they go to the site.
- If there is a problem to be dealt with, discuss it with the appropriate people while you are at the site. Don't hit them with it later.
- Document problems, but do it in a professional manner. Be sure to document the resolution to the problem.
- Be sure when you gather your papers to leave that you are not taking the site's copies of documents with you by mistake.
- Do not discuss grants and other financial information with anyone except the investigator without the investigator's permission.
- Be careful to leave things at a site in the same way you found them.
- Take some doughnuts or fruit in with you occasionally.
- Take the coordinator out for lunch once in awhile—especially if he or she is doing a wonderful job.
- Say thank you when someone makes your job easier.

Tips for Keeping the Home Fires Burning (for Travelers)

- Leave your itinerary, including flights and hotel information, where it can be seen (probably on the refrigerator), or email your spouse, partner or child your itinerary.
- Call home every day—at least once and try to use Skype or facetime video calling to see your loved ones and children. Even a simple text message to let them know they are in your thoughts. Take home a little present. It doesn't have to be much, but shows your family they were in your thoughts. (Food works—a special pound of coffee, a loaf of sourdough bread, some salt-water taffy.)
- Try to schedule so that you can be home for important events—birthdays, the big soccer game, the school play.
- Don't plan to arrive just minutes before the big event—your plane will probably be delayed.
- If you're going somewhere interesting, and it's possible, take your family with you on occasion. Maybe you can stay over a weekend for a mini vacation.
- Try to get home before bedtime.
- Remember that your travel is stressful for the ones left at home, too.
- Send the kids a postcard or a letter when you travel. Carry a packet of stamps in your wallet.
- One traveler takes her daughter's small stuffed bear with her every time she travels. When the bear comes home, it reports everything about the trip to the daughter.
- Leave something special in the refrigerator for dinner. Suggest they order pizza one night for a treat.
- If you are in charge of groceries, don't leave the cupboard bare.
- Leave a treat once in awhile as a surprise.
- Leave notes (not instructions) to indicate you are thinking about them.
- If you are in charge of laundry, be sure it's done (or at least under control) when you leave.
- Put your travel dates on the family calendar.
- Don't forget important dates.
- Be sure your bills are paid on time.
- Don't forget dentist appointments, etc.
- Say "Thank you.

APPENDIX C

Sample Forms, Checklists and Logs

Site Information Sheet

Elements of Consent

Activities for Preparation, Monitoring and Closeout of a Clinical Trial

Site Evaluation

Study Documents (based on ICH GCPs)

Study Closeout

Error Query/Correction

Query Resolution

Study Monitor Visit Log

Study Personnel Log

Study Subject Visit Tracking Log

Study Document File Verification Log

Site Visit Report

Investigational Drug Dispensing Record

Inventory of Returned Investigational Material

Performance Evaluation Visit Report - Monitoring

Site Information Sheet

Protocol _____

Investigator _____

Address _____

_____

_____

Telephone _____ **Fax** _____

Email _____

Directions to the site _____

_____

Coordinator _____

Telephone _____

Pharmacist _____

Telephone _____

Other personnel _____

Best days, times for monitoring visits _____

Other pertinent information _____

_____

_____

Elements of Consent

Required elements

- ☐ Statement that the study involves research.
  - ☐ Explanation of the purpose of the research.
  - ☐ Expected duration of subject's participation.
  - ☐ Description of procedures to be followed.
  - ☐ Identification of any procedures that are experimental.

- ☐ Description of reasonably foreseeable risks and discomforts to subject.
- ☐ Description of benefits which may be reasonably expected.
- ☐ Disclosure of alternate procedures or treatment.
- ☐ Statement re: confidentiality of reports
  - ☐ Statement that FDA may inspect the records.

- ☐ Statement re: compensation for any research-related injury.
- ☐ Contact person for questions about the research and subject rights.
- ☐ Contact person in the event of research-related injury.
- ☐ Statement that participation is voluntary.
- ☐ Statement that refusal to participate will not result in the penalty or loss of any benefits to which the subject is otherwise entitled.
- ☐ Statement that the subject may discontinue at any time without penalty or loss of any benefits to which the subject is otherwise entitled.

Additional elements (include as appropriate)

- ☐ Statement that the treatment may involve risks to the subject (or embryo or fetus) which are currently unforeseeable.
- ☐ Circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.
- ☐ Any additional costs to the subject.
- ☐ Consequences for withdrawal and procedures for orderly termination.
- ☐ Statement that significant new findings will be provided to the subject.
- ☐ Approximate number of subjects involved in the study.

Activities for Preparation, Monitoring and Closeout of a Clinical Trial

Following is a list of activities from which personal checklists can be developed. Activities shown are generic and may vary from company to company.

Study Planning Activities

In-house

- ☐ Develop study timelines (IRB Approval, FDA-mandated waiting periods, bulk drug manufacturing, etc.)
- ☐ Update Investigator Brochure, when necessary (yearly or when changes are appropriate) Chemistry, Path/Tox, Pharmacology, and Clinical. (Date of last update _____)
- ☐ Obtain or assign unique protocol numbers.
- ☐ Evaluate and finalize study budget(s).
- ☐ Determine if or which studies will be contracted to outside vendor and initiate, contract, or coordinate with CRO or company personnel according to company policy.
- ☐ Provide CRAs or CRO with protocol summary to help identify potential investigators.
- ☐ Order bulk drug supplies.
- ☐ Prepare initial IND submission (if appropriate).
- ☐ Determine laboratory needs (central vs local).

Field

- ☐ Interview potential investigators.

Pre-Study Activities

In-house

- ☐ Circulate draft protocol for review or through review process.
- ☐ Finalize and approve protocol (date of approval: _____).
- ☐ Update IND.
- ☐ Get release from path/tox (e.g., all required pre-clinical activities are complete and no safety concerns exist).
- ☐ Submit request for investigational drug supplies.
- ☐ Write informed consents.
- ☐ Obtain investigator identifier numbers (if necessary).
- ☐ Request or design CRFs.
- ☐ Send draft CRFs for review.
- ☐ Finalize and order CRFs/EDC system.
- ☐ Obtain Use Patent Review.
- ☐ Prepare Investigator/Study Coordinator Training Manuals, if appropriate.

- ☐ Plan Investigator meeting, if appropriate.
- ☐ Prepare randomization list.
- ☐ Coordinate investigator meeting/start-up dates with field monitors.
- ☐ Establish study files.
- ☐ Design/set-up logs, tracking systems etc.

Field

- ☐ Evaluate and select investigators.
- ☐ Final site evaluations (pre-study visit).
- ☐ Collect and submit all regulatory-/company-required documents.
  - ☐ Signed protocol
  - ☐ 1572
  - ☐ Lab normal ranges and certification
  - ☐ CVs
  - ☐ IRB approval(s)
  - ☐ Informed consent approval
  - ☐ Letter of agreement/contracts
  - ☐ Ancillary Personnel/ Signature Form
  - ☐ Financial Disclosure information

Study Initiation

In-house

- ☐ Send study package(s) to field monitors (Protocol, Brochures, Consents, 1572, contracts/agreement letters, etc.)
- ☐ Submit appropriate documents to Regulatory Affairs and/or place in study file.
- ☐ Submit initial grant payment request, if appropriate.
- ☐ Send laboratory normal ranges to Biostatistician/Data Management.
- ☐ Ship clinical supplies (notify field monitor (CRA) when drug is shipped).

Field

- ☐ Conduct site initiation visits.
  - ☐ Confirm receipt of clinical supplies with each site
  - ☐ Review protocol requirements
  - ☐ Review sponsor policy on CRF/EDC completion and correction
  - ☐ Confirm presence of all required documents
  - ☐ Ensure establishment of study files
- ☐ Establish monitoring visit frequency and communicate to site.

Study Monitoring

In-house

- ☐ Assure all amendments or deviations are approved and filed with regulatory affairs, the investigators and internal study files.
- ☐ Assure IRB approval was received for changes/amendments.
- ☐ Monitor grant payments/adjustments.
- ☐ Document and file annual IRB approvals.
- ☐ Assure receipt and filing of CVs for investigators/subinvestigators added after study initiation.
- ☐ Assure 1572s are updated as required.
- ☐ Assure annual IND update is completed.
- ☐ Assure Investigator Brochure is updated annually or as needed and that revisions are sent to all investigators.
- ☐ Monitor site visit reports for any required action.
- ☐ Maintain current study enrollment and progress data according to company SOPs.
- ☐ Assure all adverse events are reported according to regulation and company policy.
- ☐ Provide field monitors with current study status prior to site visits.

Field

- ☐ Check with in-house colleagues to review site status prior to visit.
- ☐ Visit sites as scheduled/required.
- ☐ Review protocol compliance, especially inclusion/exclusion requirements.
- ☐ Assure required corrections are made.
- ☐ Review CRFs and compare to source documents.
- ☐ Ensure all protocol deviations are documented and reported appropriately.
- ☐ Review drug accounting, storage, dispensing.
- ☐ Check for new adverse events.
- ☐ Collect any outstanding data from previously reported adverse events.
- ☐ Assure that any safety update letters sent to site have been sent to the IRB.
- ☐ Review study files for extraneous documents and to ensure required documents are present.
- ☐ Meet with investigator and study coordinator to review study status, answer questions, etc.
- ☐ Document visit on written report.
- ☐ Confirm date of next visit with site.
- ☐ Written report of visit findings to investigation (optional).

Study Termination

In-house

- ☐ Notify regulatory department when all patients are off drug and study is terminated.
- ☐ Send randomization sheets to investigators, if appropriate (only after all

study documents are in-house).
☐ Send clinical data and statistical summary to investigators, if appropriate.
☐ Prepare final study reports.

Field
☐ All CRFs collected, corrected and in-house.
☐ No outstanding data for serious adverse events, protocol deviations, deaths or pregnancies.
☐ Drug collected, inventoried and returned to sponsor.
☐ Investigator files complete and investigator instructed regarding storage.
☐ Drug reconciled from inventory and shipping invoices.
☐ Investigator briefed on procedure if notified of FDA audit.
☐ IRB notified of termination.
☐ Study file complete and ready for audit.

Site Evaluation

CRA should evaluate each item below, making notes.

Investigator

- ☐ Qualifications
- ☐ Licensure
- ☐ Specialty
- ☐ Clinical trial experience
  - ☐ Number of previous trials
  - ☐ Number of similar trials
  - ☐ Enrollment in previous trials (numbers, time to enroll)
- ☐ FDA audits
- ☐ Number of trials assigned and status

Staff

- ☐ Study coordinator
- ☐ Other specialized personnel
- ☐ Training and licensure
- ☐ Experience
- ☐ Turnover
- ☐ General interest and attitude
- ☐ Number of trials assigned and status

Facility

- ☐ Appropriate for trials
- ☐ Ample storage for study supplies
- ☐ Appropriate drug storage
- ☐ Special storage equipment available (freezer, centrifuge, refrigerator, etc.)
- ☐ Special equipment available
- ☐ Active practice
- ☐ Facilities tour taken
- ☐ Study records storage, study records format (electronic or paper based), study records access
- ☐ Staff working areas
- ☐ Monitoring area
- ☐ Patient treatment areas

IRB

- ☐ Local IRB available
  - ☐ Frequency and timing of meetings
  - ☐ Average time to approval
  - ☐ Responsiveness
- ☐ Use central IRB

Laboratory/Tests

- ☐ Local lab available
- ☐ Necessary tests can be done
- ☐ Timeliness
- ☐ Certification
- ☐ Have experience with central lab

Protocol feasibility

- ☐ Experience with similar studies
- ☐ Interest level
- ☐ Availability of potential subjects
- ☐ Competing studies (in practice and in community)
- ☐ Timing appropriate
- ☐ Study coordinator availability
- ☐ Can attend investigator meeting

Study Documents
(based on ICH GCPs)

Protocol _____

Investigator _____

Pre-Study

- ☐ Investigator Brochure
- ☐ Signed protocol and amendments (if any)
- ☐ Informed consent form
  - ☐ Any other information to be given to subjects
  - ☐ Any advertising materials for recruitment
- ☐ Dated, written IRB approvals for:
  - ☐ Protocol [Date:]
  - ☐ Amendments, if any [Date:]
  - ☐ Consent and any other material to be given to subjects [Date:]
  - ☐ Advertising, if any [Date:]
  - ☐ Subject compensation, if any [Date:]
- ☐ CVs for investigator, subinvestigators
- ☐ Laboratory certification and normal ranges
- ☐ Study manual, if available
- ☐ Shipping records
- ☐ Decoding procedures for blinded trials
- ☐ Financial disclosure sheets
- ☐ Contract
- ☐ Sponsor-specific documents

During the conduct of the trial

- ☐ Investigator Brochure updates
- ☐ Protocol amendments and/or revisions
- ☐ Consent revisions
- ☐ Dated, written IRB approvals of:
  - ☐ Protocol amendments [Dates:]
  - ☐ Revised consents [Dates:]
  - ☐ New or revised subject materials [Dates:]
  - ☐ New or revised advertising [Dates:]
- ☐ CVs for new investigators and/or subinvestigators
- ☐ Laboratory updates of certification and/or normal ranges
- ☐ Shipping documentation (receipt of trial materials)
- ☐ Monitoring visit log
- ☐ Communications with sponsor (letters, telephone reports, etc.)
- ☐ Signed consent forms
- ☐ Source documents

- ☐ Signed, dated, completed case report forms (CRFs)
- ☐ Documentation of CRF corrections
- ☐ Notification to sponsors and IRB of serious adverse events and related reports
- ☐ IND safety reports received from the sponsor
- ☐ Interim and/or annual reports to the IRB
- ☐ Subject screening log
- ☐ Subject identification code list
- ☐ Subject enrollment log
- ☐ Investigational product accountability
- ☐ Signature sheet (all persons making CRF entries or corrections)
- ☐ Record of retained body fluids and/or tissue samples, if any

After study completion or termination

- ☐ Drug (device) accountability
- ☐ Documentation of drug/device return or disposal
- ☐ Completed subject identification code list
- ☐ Final report to the IRB [Date:]

Comments _____

_____

_____

Checklist should be kept in front of study file and updated as appropriate.

Study Closeout

Protocol _____

Sponsor _____

Investigator _____

Date _____

- ☐ Study documents file is complete (refer to Checklist: Study Documents).
- ☐ Final report has been made to the IRB and the sponsor.
- ☐ All case report forms (CRFs) are complete and have been submitted to the sponsor.
  - ☐ All CRF corrections/queries have been addressed.
  - ☐ Any patient diaries, etc. have been submitted, as required.
  - ☐ All adverse event follow-up is complete.
- ☐ All source documentation is in order.
  - ☐ If not with study files, location of materials is noted in the document file.
- ☐ Study personnel form is complete.
- ☐ Subjects' signed informed consent forms are filed.
- ☐ Drug dispensing and disposition forms are complete.
- ☐ Study drug has been returned as per sponsor instructions.
- ☐ All other study materials (extra CRFs, etc.) have been returned to the sponsor.
- ☐ Investigator Brochure is filed with other study materials.
- ☐ All study materials are filed together as per archival procedures.
  - ☐ Location of materials is noted in site records.

Error Query/Correction

Protocol_____ **Protocol date** _____ **Sponsor** _____

Patient	Visit	Page	Field	Problem	Correction	Initials

Query Resolution

Protocol_____ **Investigator** _____ **Subject Number** _____

Page No.	Field	Issue	Resolution	Date	Initial

Study Monitor Visit Log

Protocol_____ **Protocol date** _____ **Sponsor** _____

Name	Job Title	Date(s) of Visit	Signature	Study Coordinator Initials

Use addional sheets as needed. Keep with study documents file.

Study Personnel Log

Protocol_____ **Protocol date** _____ **Sponsor** _____

Name	Job Title	Initials	Start Date of Study Responsibility	End Date of Study Responsibility	Signature

Use additional sheets as needed. Update when personnel changes occur.
Keep with study documents file.

Study Subject Visit Tracking Log

Protocol _____ **Sponsor** _____

Subject	Consent Date	Baseline	Week 1	Week 2	Week 4	Final Status	Comments

Study Document File Verification Log

Study Document File Review	**Initial / /**	**Initial / /**	**Initial / /**	**Initial / /**
Signed, IRB-approved protocol or cover sheet				
Signed, IRB-approved amendments ■ Amendment #, date ■ Amendment #, date ■ Amendment #, date				
IRB-approved informed consent document				
Signed, completed FDA 1572 form (Statement of Investigator)				
IRB approval letter, verifying approval of both the protocol and consent document				
IRB approval of advertising and subject recruitment materials, including any subject compensation				
Investigator Brochure (or package insert, for marketed products)				
Verification of laboratory certification and laboratory normal ranges				
Study Manual, if available				
Shipping records for investigation product				
Decoding procedures for blinded trials				
Financial disclosure forms				
CVs/licenses				
Sponsor-specific documents and communications				
Reviewer initials				

Attach a separate sheet with comments if any problems found.

Site Visit Report

Person Making Report_____ **Title**_____

Reason for Contact _____

Method of Contact ☐ **Phone** ☐ **Visit Date of Contact** _____

Study (Protocol) Identification_____

Site (Investigator) ID_____

Site Persons Contacted_____

Facilities/Staff	**Yes**	**No**	**N/A**	**Comments**
Changes in Staff?	*			
Are the investigator and staff fulfilling study obligations?		*		
Changes in facilities/ Equipment?	*			
Adverse Events	**Yes**	**No**	**N/A**	**Comments**
Have any serious medical events occurred since last visit?	*			
If yes, were required forms completed and submitted?		*		
Any outstanding data or forms for this or previous events?	*			
Was the IRB informed, if required?		*		

Study Conduct	**Yes**	**No**	**N/A**	**Comments**
Are protocol requirements being followed?		*		
Consent for all patients available and signed prior to enrollment?		*		
Site Conduct	**Yes**	**No**	**N/A**	**Comments**
Were CRFs reviewed?		*		
Source documents reviewed?		*		
Were CRF problems discussed w/staff?		*		
Was patient eligibility confirmed?		*		
Is recruitment on schedule?		*		
Were corrections made?		*		
Were any protocol deviations noted?	*			
Is the investigator accessible during visits?		*		
Are changes, events, etc. being communicated to the IRB?		*		
Were all completed CRFs collected?		*		
Drug Supplies	**Yes**	**No**	**N/A**	**Comments**
Is investigational product stored properly?		*		

Drug Supplies	**Yes**	**No**	**N/A**	**Comments**
Are dispensing procedures satisfactory?		*		
Is investigational product being accounted for properly?		*		
Are study supplies adequate?		*		
Documentation	**Yes**	**No**	**N/A**	**Comments**
Signed protocol		*		
1572		*		
CVs for PI and sub-investigators		*		
Approved consent		*		
IRB approvals		*		
Agreements/contracts?		*		
Signed amendments		*		
Lab normals/ accreditation?		*		
Current Investigator Brochure		*		
All pertinent correspondence on file?		*		
IRB Correspondence-Annual, SAEs?		*		
Any unresolved issues from previous visits?	*			

Administration	Yes	No	N/A	Comments
Were results of visit discussed with investigator and staff?		*		
Will findings be provided to site in writing?				
Was appointment made for next visit?		*		

* Requires a comment. Add additional pages if necessary.

Comments _____

_____

_____

_____

Signed_____

Investigational Drug Dispensing Record

Protocol Number _____

Protocol Title _____

Investigator _____

Subject Number/Initials _____

Treatment Code (if applicable) _____

Complete the following information using a new line each time medication is dispensed or returned. Use a separate sheet for each subject.

Date Medication Dispensed or Returned	Lot Number and Identification Code	Quantity Dispensed (Number of tablets)	Quantity Returned (Number of tablets)	Initials	Comments

Inventory of Returned Investigational Material

Sponsor/Address_____

_____

Protocol Number _____

Protocol Title _____

Investigator/Address _____

_____

Contact Person/Telephone Number _____

The following investigational material is being returned.

Drug	Lot Number	Code Number	Full Containers	Partial Containers	Empty Containers	Total Containers

Comments _____

_____

Performance Evaluation Visit Report - Monitoring

Name of Clinical Research Associate (CRA)	
Accompanied by (please print)	
Date of Visit	
Investigator/Protocol Identifier	
Project Manager	
Location (City, State/Province, Country)	
Purpose of Visit	Performance Evaluation Visit

CRA Demographics			
CRA experience level	0-2 years	2-5 years	>5 years
CRA experience in therapeutic area under study	Low	Medium	High
Complexity of the project	Simple	Average	Complex
Site Factors			
Investigator clinical research skill level	Low	Medium	High
Study Coordinator clinical research skill level	Low	Medium	High
Pharmacist* clinical research skill level	Low	Medium	High
Total patient enrollment	Low	Average	High
Rate of enrollment	Slow	On schedule	Fast
Comments on Demographics and Site factors			

*Pharmacist or designated investigational product (IP) dispenser

0. Visit Review – Preparation	Yes	No	NA
0.1 Was a visit confirmation letter sent to the site?			
0.2 Did the CRA send all appropriate documentation to the accompanying Evaluator prior to the visit?			
0.3 Were the Project Manager (PM), Sponsor and site informed of the accompanied visit?			
0.4 Was the site adequately informed as to what would be required of them during the visit?			
0.5 Was the CRA knowledgeable regarding site staff?			
0.6 Was the CRA's knowledge of the protocol/therapeutic area adequate?			
0.7 Was the last visit report reviewed prior to this visit?			
0.8 Did the CRA have a plan for the visit?			
0.9 Was the visit scheduled per sponsor contract?			
0.10 Did the CRA prepare for the visit by bringing study-related monitoring tools such as monitoring notes, tracking logs, forms, etc.?			
0.11 Were there any outstanding items from the previous site visit?			
If Yes, please specify:			
Comments on Visit Preparation			

1. Informed Consent Forms (ICF), Assent and HIPAA/EU Directive Authorization	Yes	No	NA
Did the CRA:			
1.1 Check that all previously unreviewed HIPAA/EU Directive authorizations were completed according to applicable regulations?			
1.2 Verify that the correct version of the ICF was being used?			

1. Informed Consent Forms (ICF), Assent and HIPAA/EU Directive Authorization (Continued)	Yes	No	NA
1.3 Verify that all versions of the ICF/assent were properly completed and present for all subjects?			
1.4 Verify that the consenting process at this site meets regulatory requirements?			
Comments on ICF, Assent and HIPAA/EU Directive Authorization			

2. Case Report Form (CRF), Source Document (SD) Review and Serious Adverse Events (SAEs/SUSARs)	Yes	No	NA
Did the CRA :			
2.1 Review CRFs and source documents in a thorough, organized manner?			
2.2 Verify complete and consistent documentation for AEs, concomitant medications, physical examinations and functional tests?			
2.3 Check that subject eligibility, visit dates and procedures met protocol requirements?			
2.4 Identify issues with ICHGCP compliance?			
2.5 Report protocol waivers/violations/deviations as per the study procedures?			
2.6 Review documentation for date and time of laboratory specimen collection and investigator review/signature?			
2.7 Issue appropriate queries?			
2.8 Verify all outstanding data queries as resolved?			
2.9 Communicate all the issues appropriately with the site staff?			
2.10 Verify completion of all required CRFs?			
2.11 Transmit CRFs according to the monitoring plan?			

Comments on Comments on CRF, SD Review & SAE's/SUSARs

3. Serious Adverse Events (SAEs) and Serious Unexpected Suspected Adverse Drug Reactions (SUSARs)	Yes	No	NA
Did the CRA:			
3.1 Identify any unreported SAEs during this visit?			
3.2 Verify that all previously reported SAEs and SUSARs were submitted as required by Local Regulatory and Ethics committee requirements?			
3.3 Verify complete and consistent documentation for SAEs/SUSARs?			
Comments on SAEs and SUSARs			

4. Investigational Product (IP) Accountability and Supply Management	Yes	No	NA
Did the CRA:			
4.1 Request access to Pharmacy/IP records prior to the visit?			
4.2 Use the IP Accountability process as outlined in the checklist?			
4.3 Verify that all required documents for IP release were on file?			
4.4 Verify that the blinding information was intact and that it was stored appropriately?			
4.5 Assess subject's compliance by comparing logs/labels to the CRF and source data?			
4.6 Verify that receipt records, accountability logs (including a Master IP Accountability log) and/or destruction records were completed, up-to-date and accurate?			

4.7 Verify that general study supplies and IP supplies are adequate, found to be unexpired and being checked at each visit?			
4.8 Verify that proper storage, handling and transporting methods are being employed at this study site?			
4.9 Confirm that the appropriate temperature logs were completed and adequate?			
4.10 Conduct an organized, thorough review of the IP, document all discrepancies and communicate these to the site?			
4.11 Follow up on discrepancies recorded during the previous visit(s)?			
Comments on IP Accountability and Supply Management			

5. Regulatory File Review	**Yes**	**No**	**NA**
Did the CRA:			
5.1 Sign the Site Visit Signature log?			
5.2 Review the regulatory file?			
5.3 Check that regulatory documents were filed and up to date?			
5.4 Copy appropriate documents for the sponsor/central files?			
5.5 Review regulatory documents in a complete and organized manner?			
5.6 Identify outstanding issues?			
5.7 Resolve the issues identified?			
5.8 Give the site staff a method for rectifying outstanding issues?			
Comments on Regulatory File Review			

6. Laboratory and Specimen Handling Procedure	Yes	No	NA
Did the CRA:			
6.1 Check that handling, storage and shipment of samples was in accordance with the requirements of the laboratory manual?			
6.2 Check and confirm that laboratory reference ranges and certifications were on file and current?			
6.3 Check the supply of all laboratory materials and kits?			
6.4 Check expiration dates for laboratory kits?			
Comments onLaboratory and Specimen Handling Procedure			

7. Study Staff, Patient Enrollment and General Conduct	Yes	No	NA
Did the CRA:			
7.1 Meet and discuss the findings of this visit and any required follow-up actions with the Principal Investigator?			
7.2 Meet and discuss the findings of this visit and any required follow-up actions with other appropriate site staff?			
7.3 Answer questions from study site staff?			
7.4 Discuss site recruitment?			
7.5 Communicate clearly and concisely?			
7.6 Behave in a professional and courteous manner during the visit?			
Comments on Study Staff, Patient Enrollment and General Conduct			

8. Post Visit activities	Yes	No	NA
Did the CRA:			
8.1 Conduct the visit to an acceptable standard?			
8.2 Accomplish objectives for the visit?			
8.3 Write the visit report within appropriate time-lines?			
8.4 Write the visit report to an adequate standard?			
8.5 Document all required follow-up actions and resolutions?			
Comments on Post Visit Activities			

Overall Performance/Achievement of Objectives:		
Exceeds Expectations	Meets Expectations	Needs Improvement

Training Given on the Day:

Areas For Development /Further Training Needed/Actions Agreed:

CRA Comments:

CRA **Date**

Regional Manager or designee **Date**

APPENDIX D

Job Descriptions and Academic Programs

CRA Job Summary

This document describes two levels of CRA responsibilities. For simplicity, they are called CRA 1 (entry level) and CRA 2 (advanced).

CRA 1	CRA 2
Investigator Selection	
■ Will not be involved in this activity. Will work with Investigators/ CROs selected by the Sponsor.	■ In consultation with the Sponsor/CRO select investigators appropriate for the therapeutic area and protocol. Note: May also be involved in CRO evaluation/selection.
Pre-Study	
■ Meet with Investigator and staff and review study requirements (protocol, CRFs, sponsor policy and procedures, investigator responsibilities, staffing and patient recruitment). ■ Conduct study initiation visit. ■ Confirm appropriateness of the IRB. ■ Collect and forward all required study documentation to Sponsor. ■ Document visit.	■ Assess study site to ensure facility, patient population and staff are sufficient to support the protocol. ■ Negotiate study budget and/or indemnification agreement. ■ Assist in planning and conducting Investigator Meeting and/or Start-up Meeting. ■ Meet with PI and staff and review study requirements (protocol, CRFs, Sponsor policy and procedures, investigator responsibilities, staffing and patient recruitment. ■ Conduct study initiation visit. ■ Confirm appropriateness of the IRB. ■ Collect and forward all required study documentation to Sponsor. ■ Document visit.

CRA 1	CRA 2
Study Monitoring	
■ Conduct routine monitoring visits to include: – Review protocol compliance – Review CRF/source documents – Resolve questions/issues with Investigator/Staff – Check/inventory clinical supplies – Review communication with the IRB – Review drug accountability ■ Confirm Informed Consent. ■ Correct previous errors. ■ Submit all collected documents and site visit report to Sponsor. ■ Log and track study progress.	■ Conduct routine monitoring visits to include: – Review protocol compliance – Review CRF/source docments – Resolve questions/issues with Investigator Staff – Check/inventory clinical supplies – Review communication with the IRB – Review drug accountability ■ Confirm Informed Consent. ■ Correct previous errors. ■ Submit all collected documents and site visit report to Sponsor. ■ Log and track study progress.
Study Close Out	
■ Review and collect remaining CRFs. ■ Retrieve clinical supplies and any other study materials. ■ Review investigator's study file to insure that all documents are in order and ready for audit or inspection. ■ Review file (document) retention schedule/policy. ■ Submit documentation for study closeout. ■ Arrange any final payments. ■ Review publication policy/procedure. ■ Review any follow-up requirements that may be required (IRB notification, ongoing medical events).	■ Review and collect remaining CRFs. ■ Retrieve clinical supplies and any other study materials. ■ Review investigator's study file to insure that all documents are in order and ready for audit or inspection. ■ Review file (document) retention schedule/policy. ■ Submit documentation for study closeout. ■ Arrange any final payments. ■ Review publication policy/procedure. ■ Review any follow-up requirements that may be required (IRB notification, ongoing medical events).

Clinical Research Associate (CRA)

Entry Level

Position Description

The Clinical Research Associate will perform the following activities as directed by the Sponsor/CRO:

- Meet with Clinical Investigators and staff prior to study initiation to ensure all aspects of the study are understood by the investigator and staff, confirm the appropriateness of the IRB and ensure that all documentation required to initiate the study is complete.
- Monitor study progress to assure compliance with protocol requirements, FDA regulations and Good Clinical Practice by conducting site visits as directed by the Sponsor/CRO.
- Monitor and track patient enrollment and study progress.
- Perform site audits to include source document review.
- Ensure the timely, accurate and complete collection and submission of study data.
- Identify, address, and resolve issues and problems as they might occur.
- At study completion:
- Ensure collection of all data and remaining study supplies for return to the Sponsor/CRO.
- Ensure that appropriate study documents are complete and properly filed.
- Prepare the site for possible FDA inspection.
- Assist the Sponsor/CRO in problem solving and provide consultation on monitoring and study related activities.

This position requires 70% travel.

Educational Requirements

Must have a minimum of a Bachelors Degree in relevant biological or health science.

Experience Requirements

This position requires a minimum of two years relevant clinical research experience that includes at least one year as a field monitor. Experience will include work in a clinical laboratory, clinic or pharmacy or as a member of a drug development team, or experience as a Study Coordinator or Research Nurse.

Specialized Skills, Knowledge, Abilities

Excellent oral and written communication skills, interpersonal relationship skills, knowledge of scientific method, GCPs and regulations relating to clinical research. Must have a working knowledge of computer technology and its application to the clinical environment.

Clinical Research Associate (CRA)

Advanced Level

Position Description

The Clinical Research Associate, independently or in consultation with the Sponsor/CRO will:

- Locate and select clinical investigators appropriate to the therapeutic area and phase of the study.
- Assess potential study sites to ensure the facility, staff and patient population are sufficient for study conduct.
- Negotiate the study budget (grant) and any other contract agreements required by the Sponsor/CRO, if required.
- Plan or assist in conducting study start-up meetings.
- Meet with Clinical Investigators and their staff prior to study initiation to insure all aspects of the study are understood by the investigator and staff, confirm the appropriateness of the IRB and insure that all documentation required to initiate the study is complete.
- Monitor study progress to assure compliance with protocol requirements, FDA regulations and Good Clinical Practice by conducting site visits as directed by the Sponsor/CRO.
- Monitor and track patient enrollment and study progress.
- Perform site audits to include source document review.
- Ensure the timely, accurate and complete collection and submission of study data.
- Identify, address, and resolve issues and problems as they might occur.

At study completion:

- Ensure collection of all data and remaining study supplies for return to the Sponsor/CRO.
- Ensure that appropriate study documents are complete and properly filed.
- Prepare the site for possible FDA inspection.
- Assist the Sponsor/CRO in problem solving and provide consultation on monitoring and study related activities.

This position requires 70% travel.

Educational Requirements

Must have a minimum of a Bachelors Degree, preferably in a relevant biological or health science.

Experience Requirements

This position requires a minimum of eight years of relevant clinical research experience, five years of which must have been as a working CRA or equivalent. Experience will include study design and field monitoring experience in drug/device development, or as a Study Coordinator or Research Nurse.

Specialized Skills, Knowledge, Abilities

Excellent oral and written communication skills, interpersonal relationship skills, negotiating skills, knowledge of scientific method, GCPs and regulations relating to clinical research. Must have a working knowledge of computer technology and its application to the clinical environment.

List of Academic Programs That Train Clinical Research Professionals*

United States

Ph.D. Programs
Baylor College of Medicine, Houston, Texas
University of Colorado, Denver CO

M.S. Programs
Albert Einstein College of Medicine, Yeshiva University, New York, NY
American Institute of Health Sciences, Los Angeles, CA
Campbell University, Research Triangle Park, NC
Duke University, Durham, NC
Massachusetts General Hospital, Institute of Health Professions, Boston, MA
Mayo Clinic, Rochester, MN
New York Medical College, Valhalla, NY
University of Louisville, Louisville, KY
University of North Carolina Wilmington, Wilmington, NC
University of Pittsburgh, Pittsburgh, PA
Virginia Commonwealth University, Richmond, VA

Post-baccalaureate Certificate Programs
American Institute of Health Sciences, Los Angeles, CA
Boston University, Boston, MA
Duke University, Durham, NC
Eastern Michigan University, Ypsilanti, MI
Jefferson Medical College, Philadelphia, PA
LaSalle University, Philadelphia, PA
Massachusetts General Hospital, Institute of Health Professions, Boston, MA
Mayo Clinic, Rochester, MN
Medical College of Pennsylvania/Hahnemann University, Philadelphia, PA
Mercer County Community College, Trenton, NJ
University of California—San Diego, LaJolla, CA
University of California—Santa Cruz, Santa Cruz, CA
University of Chicago, Chicago, IL
University of Cincinnati, Cincinnati, OH
University of Louisville, Louisville, KY
Western Michigan University, Kalamazoo, MI

B.S. Programs
George Washington University, Washington, DC
Campbell University, Buies Creek, NC
University of North Carolina Wilmington, Wilmington, NC

Associate Degree Programs
Durham Community Technical College, Durham, NC
George Washington University, Washington, DC

Outside the United States

Australia
Monash University, Sydney
University of Canberra, Canberra

Canada
British Columbia Institute of Technology, Burnaby, British Columbia
Humber College, Toronto, Ontario
University of Western Ontario, London, Ontario

United Kingdom
Institute of Clinical Research, Maidenhead, UK
John Moores University, Liverpool, UK
University of Leeds, Leeds, UK
University of Oxford, Oxford, UK

*Does not include K30 Programs designed for individuals with MD or PhD degree

APPENDIX E

ICH-FDA Comparison

Activity	ICH Guidelines	21 CFR
IRB	Requires the Investigator to furnish the IRB with a copy of the Investigator Brochure. (4.4.2)	Requires the Sponsor to provide each Investigator with a copy of the Investigator Brochure. (312.55a)
	Requires the Sponsor to obtain a statement from the IRB confirming that it is organized and operates according to GCPs and applicable laws and regulations. (5.11.1b)	FDA does not require this statement.
	Requires that the Subject be given a signed and dated copy of the consent form. (4.8.11)	

Activity	ICH Guidelines	21 CFR
Informed Consent	Requires the person administering the consent to sign the consent. (4.8.8)	Requires a copy of the consent be given the subject. A signed copy is not required. (50.27)
	Elements of consent differ between ICH and FDA. Does not have "optional" elements. (4.8.10)	Requires only the Subjects signature and date. (50.27)
	Does not provide the option of using a "Short Form" and "Summary" for subjects who cannot read and are orally consented. (4.8.9)	Has "additional" elements that are optional. (50.25)
		Provides the option of using a "Short Form" and "Summary" for orally consented subjects. (50.27)
Investigator Files/Records	Requires "all trial related records" be made available to the monitor, auditor, IRB/IEC or regulatory authority. (4.9.7) This includes financial records. (8.2.4)	Does not require financial records be maintained in study files.
Protocol Deviations	ICH requires the investigator to document and explain all deviations.	US regulations do not address this issue.
Protocol Signatures	ICH requires the sponsor and investigator to sign the protocol. (5.6.3) 21 CFR	Is not required by regulation. Most sponsors require it.

Activity	ICH Guidelines	21 CFR
Investigational Medication	ICH places responsibility for maintaining drug dispensing records and reconciliation of drug supplies with the clinical investigator. (5.14.2)	FDA requires the return of unused supplies.
Study Documents	ICH places responsibility for ensuring that all study documents are available at the site (Study file) with the CRA. ICH also requires the CRA to confirm the availability of the documents prior to closing the site. (8)	FDA holds the Investigator responsible for complete, accurate study records.
Curriculum Vitae	ICH requires a CV for both the PI and any sub investigators. (8.2.10)	FDA only requires CVs for principal investigators.
Signature Sheets	ICH requires documentation of signatures and initials of all personnel authorized to enter and correct data on CRFs in both investigator and sponsor files. (8.3.24)	FDA does not have this requirement. (Most sponsors, however, require it.)
Site Visit (Monitoring) Reports	ICH requires the sponsor to document the review and follow-up of the site visit report filed by the CRA. (5.18.6d)	FDA does not have this requirement.

Activity	ICH Guidelines	21 CFR
Site Visit (Monitoring) Reports (continued)	ICH also requires a copy of the site visit report be placed in the investigator's study file. (8.2.20)	
Case Report Forms	ICH requires the CRA (study monitor) to ensure that all changes to CRFs are made properly (initialed, dated and explained, if necessary) by the investigator or an authorized member of the site staff. The authorization must be documented. (5.18.4n)	FDA does not require that the authorization to make CRF changes be documented.
Notification of Subjects Physician	ICH recommends that the clinical investigator notify each study subject's primary care physician of his or her involvement in the study. (4.3.3)	FDA regulations do not address this issue.

APPENDIX F

Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2)

Current *Step 4* version dated 9 November 2016

Introduction

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

The objective of this ICH GCP Guideline is to provide a unified standard for the European Union (EU), Japan and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions.

The guideline was developed with consideration of the current good clinical practices of the European Union, Japan, and the United States, as well as those of Australia, Canada, the Nordic countries and the World Health Organization (WHO).

This guideline should be followed when generating clinical trial data that are intended to be submitted to regulatory authorities.

The principles established in this guideline may also be applied to other clinical investigations that may have an impact on the safety and well-being of human subjects.

Addendum

Since the development of the ICH GCP Guideline, the scale, complexity, and cost of clinical trials have increased. Evolutions in technology and risk management processes offer new opportunities to increase efficiency and focus on relevant activities. When the original ICH E6(R1) text was prepared, clinical trials were performed in a largely paper-based process. Advances in use of electronic data recording and reporting facilitate implementation of other approaches. For example, centralized monitoring can now offer a greater advantage, to a broader range of trials than is suggested

in the original text. Therefore, this guideline has been amended to encourage implementation of improved and more efficient approaches to clinical trial design, conduct, oversight, recording and reporting while continuing to ensure human subject protection and reliability of trial results. Standards regarding electronic records and essential documents intended to increase clinical trial quality and efficiency have also been updated.

This guideline should be read in conjunction with other ICH guidelines relevant to the conduct of clinical trials (e.g., E2A (clinical safety data management), E3 (clinical study reporting), E7 (geriatric populations), E8 (general considerations for clinical trials), E9 (statistical principles), and E11 (pediatric populations)).

This ICH GCP Guideline Integrated Addendum provides a unified standard for the European Union, Japan, the United States, Canada, and Switzerland to facilitate the mutual acceptance of data from clinical trials by the regulatory authorities in these jurisdictions. In the event of any conflict between the E6(R1) text and the E6(R2) addendum text, the E6(R2) addendum text should take priority.

1. GLOSSARY

1.1 Adverse Drug Reaction (ADR)

In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Regarding marketed medicinal products: a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

1.2 Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

1.3 Amendment (to the protocol)

See Protocol Amendment.

1.4 Applicable Regulatory Requirement(s)

Any law(s) and regulation(s) addressing the conduct of clinical trials of investigational products.

1.5 Approval (in relation to Institutional Review Boards)

The affirmative decision of the IRB that the clinical trial has been reviewed and may be conducted at the institution site within the constraints set forth by the IRB, the institution, Good Clinical Practice (GCP), and the applicable regulatory requirements.

1.6 Audit

A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analyzed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

1.7 Audit Certificate

A declaration of confirmation by the auditor that an audit has taken place.

1.8 Audit Report

A written evaluation by the sponsor's auditor of the results of the audit.

1.9 Audit Trail

Documentation that allows reconstruction of the course of events.

1.10 Blinding/Masking

A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the subject(s) being unaware, and double-blinding usually refers to the subject(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s).

1.11 Case Report Form (CRF)

A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject.

1.12 Clinical Trial/Study

Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.

1.13 Clinical Trial/Study Report

A written description of a trial/study of any therapeutic, prophylactic, or diagnostic agent conducted in human subjects, in which the clinical and statistical description, presentations, and analyses are fully integrated into a single report (see the ICH Guideline for Structure and Content of Clinical Study Reports).

1.14 Comparator (Product)

An investigational or marketed product (i.e., active control), or placebo, used as a reference in a clinical trial.

1.15 Compliance (in relation to trials)

Adherence to all the trial-related requirements, Good Clinical Practice (GCP) requirements, and the applicable regulatory requirements.

1.16 Confidentiality

Prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity.

1.17 Contract

A written, dated, and signed agreement between two or more involved parties that sets out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. The protocol may serve as the basis of a contract.

1.18 Coordinating Committee
A committee that a sponsor may organize to coordinate the conduct of a multicentre trial.

1.19 Coordinating Investigator
An investigator assigned the responsibility for the coordination of investigators at different centres participating in a multicentre trial.

1.20 Contract Research Organization (CRO)
A person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions.

1.21 Direct Access
Permission to examine, analyze, verify, and reproduce any records and reports that are important to evaluation of a clinical trial. Any party (e.g., domestic and foreign regulatory authorities, sponsor's monitors and auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subjects' identities and sponsor's proprietary information.

1.22 Documentation
All records, in any form (including, but not limited to, written, electronic, magnetic, and optical records, and scans, x-rays, and electrocardiograms) that describe or record the methods, conduct, and/or results of a trial, the factors affecting a trial, and the actions taken.

1.23 Essential Documents
Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced (see 8. Essential Documents for the Conduct of a Clinical Trial).

1.24 Good Clinical Practice (GCP)
A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

1.25 Independent Data-Monitoring Committee (IDMC) (Data and Safety Monitoring Board, Monitoring Committee, Data Monitoring Committee)
An independent data-monitoring committee that may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial.

1.26 Impartial Witness
A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the subject or the subject's legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject.

1.27 Independent Ethics Committee (IEC)
An independent body (a review board or a committee, institutional, regional, national, or suprana-

tional), constituted of medical professionals and non-medical members, whose responsibility it is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving/providing favourable opinion on, the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

The legal status, composition, function, operations and regulatory requirements pertaining to Independent Ethics Committees may differ among countries, but should allow the Independent Ethics Committee to act in agreement with GCP as described in this guideline.

1.28 Informed Consent

A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

1.29 Inspection

The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organization's (CRO's) facilities, or at other establishments deemed appropriate by the regulatory authority(ies).

1.30 Institution (medical)

Any public or private entity or agency or medical or dental facility where clinical trials are conducted.

1.31 Institutional Review Board (IRB)

An independent body constituted of medical, scientific, and non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trial protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

1.32 Interim Clinical Trial/Study Report

A report of intermediate results and their evaluation based on analyses performed during the course of a trial.

1.33 Investigational Product

A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

1.34 Investigator

A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator. See also Subinvestigator.

1.35 Investigator/Institution
An expression meaning "the investigator and/or institution, where required by the applicable regulatory requirements".

1.36 Investigator's Brochure
A compilation of the clinical and nonclinical data on the investigational product(s) which is relevant to the study of the investigational product(s) in human subjects (see 7. Investigator's Brochure).

1.37 Legally Acceptable Representative
An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial.

1.38 Monitoring
The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

1.39 Monitoring Report
A written report from the monitor to the sponsor after each site visit and/or other trial-related communication according to the sponsor's SOPs.

1.40 Multicentre Trial
A clinical trial conducted according to a single protocol but at more than one site, and therefore, carried out by more than one investigator.

1.41 Nonclinical Study
Biomedical studies not performed on human subjects.

1.42 Opinion (in relation to Independent Ethics Committee)
The judgement and/or the advice provided by an Independent Ethics Committee (IEC).

1.43 Original Medical Record
See Source Documents.

1.44 Protocol
A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. Throughout the ICH GCP Guideline the term protocol refers to protocol and protocol amendments.

1.45 Protocol Amendment
A written description of a change(s) to or formal clarification of a protocol.

1.46 Quality Assurance (QA)
All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirement(s).

1.47 Quality Control (QC)
The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled.

1.48 Randomization

The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

1.49 Regulatory Authorities

Bodies having the power to regulate. In the ICH GCP Guideline the expression Regulatory Authorities includes the authorities that review submitted clinical data and those that conduct inspections (see 1.29). These bodies are sometimes referred to as competent authorities.

1.50 Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR)

Any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,

or

- is a congenital anomaly/birth defect

(see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

1.51 Source Data

All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

1.52 Source Documents

Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

1.53 Sponsor

An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.

1.54 Sponsor-Investigator

An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g., it does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator.

1.55 Standard Operating Procedures (SOPs)

Detailed, written instructions to achieve uniformity of the performance of a specific function.

1.56 Subinvestigator

Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions

(e.g., associates, residents, research fellows). See also Investigator.

1.57 Subject/Trial Subject
An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.

1.58 Subject Identification Code
A unique identifier assigned by the investigator to each trial subject to protect the subject's identity and used in lieu of the subject's name when the investigator reports adverse events and/or other trial related data.

1.59 Trial Site
The location(s) where trial-related activities are actually conducted.

1.60 Unexpected Adverse Drug Reaction
An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product) (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

1.61 Vulnerable Subjects
Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent.

1.62 Well-being (of the trial subjects)
The physical and mental integrity of the subjects participating in a clinical trial.

ADDENDUM

1.63 Certified Copy
A copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.

1.64 Monitoring Plan
A document that describes the strategy, methods, responsibilities, and requirements for monitoring the trial.

1.65 Validation of Computerized Systems
A process of establishing and documenting that the specified requirements of a computerized system can be consistently fulfilled from design until decommissioning of the system or transition to a new system. The approach to validation should be based on a risk assessment that takes into consideration the intended use of the system and the potential of the system to affect human subject

protection and reliability of trial results.

2. THE PRINCIPLES OF ICH GCP

2.1 Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).

2.2 Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.

2.3 The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

2.4 The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.

2.5 Clinical trials should be scientifically sound, and described in a clear, detailed protocol.

2.6 A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion.

2.7 The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.

2.8 Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).

2.9 Freely given informed consent should be obtained from every subject prior to clinical trial participation.

2.10 All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.

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This principle applies to all records referenced in this guideline, irrespective of the type of media used.

2.11 The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

2.12 Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.

2.13 Systems with procedures that assure the quality of every aspect of the trial should be implemented.

ADDENDUM

Aspects of the trial that are essential to ensure human subject protection and reliability of trial results should be the focus of such systems.

3. INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

3.1 Responsibilities

3.1.1 An IRB/IEC should safeguard the rights, safety, and well-being of all trial subjects. Special attention should be paid to trials that may include vulnerable subjects.

3.1.2 The IRB/IEC should obtain the following documents:
trial protocol(s)/amendment(s), written informed consent form(s) and consent form updates that the investigator proposes for use in the trial, subject recruitment procedures (e.g., advertisements), written information to be provided to subjects, Investigator's Brochure (IB), available safety information, information about payments and compensation available to subjects, the investigator's current curriculum vitae and/or other documentation evidencing qualifications, and any other documents that the IRB/IEC may need to fulfil its responsibilities.

The IRB/IEC should review a proposed clinical trial within a reasonable time and document its views in writing, clearly identifying the trial, the documents reviewed and the dates for the following:

- approval/favourable opinion;
- modifications required prior to its approval/favourable opinion;
- disapproval / negative opinion; and
- termination/suspension of any prior approval/favourable opinion.

3.1.3 The IRB/IEC should consider the qualifications of the investigator for the proposed trial, as documented by a current curriculum vitae and/or by any other relevant documentation the IRB/IEC requests.

3.1.4 The IRB/IEC should conduct continuing review of each ongoing trial at intervals appropriate to the degree of risk to human subjects, but at least once per year.

3.1.5 The IRB/IEC may request more information than is outlined in paragraph 4.8.10 be given to subjects when, in the judgement of the IRB/IEC, the additional information would add meaningfully to the protection of the rights, safety and/or well-being of the subjects.

3.1.6 When a non-therapeutic trial is to be carried out with the consent of the subject's legally acceptable representative (see 4.8.12, 4.8.14), the IRB/IEC should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials.

3.1.7 Where the protocol indicates that prior consent of the trial subject or the subject's legally acceptable representative is not possible (see 4.8.15), the IRB/IEC should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials (i.e., in emergency situations).

3.1.8 The IRB/IEC should review both the amount and method of payment to subjects to assure that neither presents problems of coercion or undue influence on the trial subjects. Payments to a subject should be prorated and not wholly contingent on completion of the trial by the subject.

3.1.9 The IRB/IEC should ensure that information regarding payment to subjects, including the methods, amounts, and schedule of payment to trial subjects, is set forth in the written informed consent form and any other written information to be provided to subjects. The way payment will

be prorated should be specified.

3.2 Composition, Functions and Operations

3.2.1 The IRB/IEC should consist of a reasonable number of members, who collectively have the qualifications and experience to review and evaluate the science, medical aspects, and ethics of the proposed trial. It is recommended that the IRB/IEC should include:

A. At least five members.

B. At least one member whose primary area of interest is in a nonscientific area.

C. At least one member who is independent of the institution/trial site.

Only those IRB/IEC members who are independent of the investigator and the sponsor of the trial should vote/provide opinion on a trial-related matter.

A list of IRB/IEC members and their qualifications should be maintained.

3.2.2 The IRB/IEC should perform its functions according to written operating procedures, should maintain written records of its activities and minutes of its meetings, and should comply with GCP and with the applicable regulatory requirement(s).

3.2.3 An IRB/IEC should make its decisions at announced meetings at which at least a quorum, as stipulated in its written operating procedures, is present.

3.2.4 Only members who participate in the IRB/IEC review and discussion should vote/provide their opinion and/or advise.

3.2.5 The investigator may provide information on any aspect of the trial, but should not participate in the deliberations of the IRB/IEC or in the vote/opinion of the IRB/IEC.

3.2.6 An IRB/IEC may invite nonmembers with expertise in special areas for assistance.

3.3 Procedures

The IRB/IEC should establish, document in writing, and follow its procedures, which should include:

3.3.1 Determining its composition (names and qualifications of the members) and the authority under which it is established.

3.3.2 Scheduling, notifying its members of, and conducting its meetings.

3.3.3 Conducting initial and continuing review of trials.

3.3.4 Determining the frequency of continuing review, as appropriate.

3.3.5 Providing, according to the applicable regulatory requirements, expedited review and approval/favourable opinion of minor change(s) in ongoing trials that have the approval/favourable opinion of the IRB/IEC.

3.3.6 Specifying that no subject should be admitted to a trial before the IRB/IEC issues its written approval/favourable opinion of the trial.

3.3.7 Specifying that no deviations from, or changes of, the protocol should be initiated without prior written IRB/IEC approval/favourable opinion of an appropriate amendment, except when

necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), telephone number(s)) (see 4.5.2).

3.3.8 Specifying that the investigator should promptly report to the IRB/IEC:

A. Deviations from, or changes of, the protocol to eliminate immediate hazards to the trial subjects (see 3.3.7, 4.5.2, 4.5.4).

B. Changes increasing the risk to subjects and/or affecting significantly the conduct of the trial (see 4.10.2).

C. All adverse drug reactions (ADRs) that are both serious and unexpected.

D. New information that may affect adversely the safety of the subjects or the conduct of the trial.

3.3.9 Ensuring that the IRB/IEC promptly notify in writing the investigator/institution concerning:

A. Its trial-related decisions/opinions.

B. The reasons for its decisions/opinions.

C. Procedures for appeal of its decisions/opinions.

3.4 Records

The IRB/IEC should retain all relevant records (e.g., written procedures, membership lists, lists of occupations/affiliations of members, submitted documents, minutes of meetings, and correspondence) for a period of at least 3-years after completion of the trial and make them available upon request from the regulatory authority(ies).

The IRB/IEC may be asked by investigators, sponsors or regulatory authorities to provide its written procedures and membership lists.

4. INVESTIGATOR

4.1 Investigator's Qualifications and Agreements

4.1.1 The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB/IEC, and/or the regulatory authority(ies)**.**

4.1.2 The investigator should be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current Investigator's Brochure, in the product information and in other information sources provided by the sponsor.

4.1.3 The investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements.

4.1.4 The investigator/institution should permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authority(ies).

4.1.5 The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.

4.2 Adequate Resources

4.2.1 The investigator should be able to demonstrate (e.g., based on retrospective data) a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

4.2.2 The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.

4.2.3 The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.

4.2.4 The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

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4.2.5 The investigator is responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site.

4.2.6 If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.

4.3 Medical Care of Trial Subjects

4.3.1 A qualified physician (or dentist, when appropriate), who is an investigator or a subinvestigator for the trial, should be responsible for all trial-related medical (or dental) decisions.

4.3.2 During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

4.3.3 It is recommended that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

4.3.4 Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.

4.4 Communication with IRB/IEC

4.4.1 Before initiating a trial, the investigator/institution should have written and dated approval/favourable opinion from the IRB/IEC for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), and any other written

information to be provided to subjects.

4.4.2 As part of the investigator's/institution's written application to the IRB/IEC, the investigator/institution should provide the IRB/IEC with a current copy of the Investigator's Brochure. If the Investigator's Brochure is updated during the trial, the investigator/institution should supply a copy of the updated Investigator's Brochure to the IRB/IEC.

4.4.3 During the trial the investigator/institution should provide to the IRB/IEC all documents subject to review.

4.5 Compliance with Protocol

4.5.1 The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies) and which was given approval/favourable opinion by the IRB/IEC. The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm agreement.

4.5.2 The investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval/favourable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s)).

4.5.3 The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

4.5.4 The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB/IEC approval/favourable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:

A. to the IRB/IEC for review and approval/favourable opinion,

B. to the sponsor for agreement and, if required,

C. to the regulatory authority(ies).

4.6 Investigational Product(s)

4.6.1 Responsibility for investigational product(s) accountability at the trial site(s) rests with the investigator/institution.

4.6.2 Where allowed/required, the investigator/institution may/should assign some or all of the investigator's/institution's duties for investigational product(s) accountability at the trial site(s) to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator/institution..

4.6.3 The investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial subjects. Investigators should maintain records that document

adequately that the subjects were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor.

4.6.4 The investigational product(s) should be stored as specified by the sponsor (see 5.13.2 and 5.14.3) and in accordance with applicable regulatory requirement(s).

4.6.5 The investigator should ensure that the investigational product(s) are used only in accordance with the approved protocol.

4.6.6 The investigator, or a person designated by the investigator/institution, should explain the correct use of the investigational product(s) to each subject and should check, at intervals appropriate for the trial, that each subject is following the instructions properly.

4.7 Randomization Procedures and Unblinding

The investigator should follow the trial's randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the trial is blinded, the investigator should promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s).

4.8 Informed Consent of Trial Subjects

4.8.1 In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the trial, the investigator should have the IRB/IEC's written approval/favourable opinion of the written informed consent form and any other written information to be provided to subjects.

4.8.2 The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written informed consent form, and written information should receive the IRB/IEC's approval/favourable opinion in advance of use. The subject or the subject's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented.

4.8.3 Neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate or to continue to participate in a trial.

4.8.4 None of the oral and written information concerning the trial, including the written informed consent form, should contain any language that causes the subject or the subject's legally acceptable representative to waive or to appear to waive any legal rights, or that releases or appears to release the investigator, the institution, the sponsor, or their agents from liability for negligence.

4.8.5 The investigator, or a person designated by the investigator, should fully inform the subject or, if the subject is unable to provide informed consent, the subject's legally acceptable representative, of all pertinent aspects of the trial including the written information and the approval/favourable opinion by the IRB/IEC.

4.8.6 The language used in the oral and written information about the trial, including the written informed consent form, should be as non-technical as practical and should be understandable to the subject or the subject's legally acceptable representative and the impartial witness, where

applicable.

4.8.7 Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's legally acceptable representative.

4.8.8 Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.

4.8.9 If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to subjects, is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the trial and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative.

4.8.10 Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:

A. That the trial involves research.

B. The purpose of the trial.

C. The trial treatment(s) and the probability for random assignment to each treatment.

D. The trial procedures to be followed, including all invasive procedures.

E. The subject's responsibilities.

F. Those aspects of the trial that are experimental.

G. The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.

H. The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.

I. The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.

J. The compensation and/or treatment available to the subject in the event of trial-related injury.

K. The anticipated prorated payment, if any, to the subject for participating in the trial.

L. The anticipated expenses, if any, to the subject for participating in the trial.

M. That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.

N. That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.

O. That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential.

P. That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.

Q. The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.

R. The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.

S. The expected duration of the subject's participation in the trial.

T. The approximate number of subjects involved in the trial.

4.8.11 Prior to participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects. During a subject's participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.

4.8.12 When a clinical trial (therapeutic or non-therapeutic) includes subjects who can only be enrolled in the trial with the consent of the subject's legally acceptable representative (e.g., minors, or patients with severe dementia), the subject should be informed about the trial to the extent compatible with the subject's understanding and, if capable, the subject should sign and personally date the written informed consent.

4.8.13 Except as described in 4.8.14, a non-therapeutic trial (i.e., a trial in which there is no anticipated direct clinical benefit to the subject), should be conducted in subjects who personally give consent and who sign and date the written informed consent form.

4.8.14 Non-therapeutic trials may be conducted in subjects with consent of a legally acceptable representative provided the following conditions are fulfilled:

A. The objectives of the trial can not be met by means of a trial in subjects who can give informed consent personally.

B. The foreseeable risks to the subjects are low.

C. The negative impact on the subject's well-being is minimized and low.

D. The trial is not prohibited by law.

E. The approval/favourable opinion of the IRB/IEC is expressly sought on the inclusion of such subjects, and the written approval/ favourable opinion covers this aspect.

Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Subjects in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

4.8.15 In emergency situations, when prior consent of the subject is not possible, the consent of the subject's legally acceptable representative, if present, should be requested. When prior consent of the subject is not possible, and the subject's legally acceptable representative is not available, enrolment of the subject should require measures described in the protocol and/or elsewhere, with documented approval/favourable opinion by the IRB/IEC, to protect the rights, safety and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or the subject's legally acceptable representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate (see 4.8.10) should be requested.

4.9 Records and Reports

ADDENDUM

4.9.0 The investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail).

4.9.1 The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.

4.9.2 Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.

4.9.3 Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e., an audit trail should be maintained); this applies to both written and electronic changes or corrections (see 5.18.4 (n)). Sponsors should provide guidance to investigators and/or the investigators' designated representatives on making such corrections. Sponsors should have written procedures to assure that changes or corrections in CRFs made by sponsor's designated representatives are documented, are necessary, and are endorsed by the investigator. The investigator should retain records of the changes and corrections.

4.9.4 The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (see 8.) and as required by the applicable regulatory requirement(s). The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

4.9.5 Essential documents should be retained until at least 2-years after the last approval of a

marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2-years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained (see 5.5.12).

4.9.6 The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.

4.9.7 Upon request of the monitor, auditor, IRB/IEC, or regulatory authority, the investigator/institution should make available for direct access all requested trial-related records.

4.10 Progress Reports

4.10.1 The investigator should submit written summaries of the trial status to the IRB/IEC annually, or more frequently, if requested by the IRB/IEC.

4.10.2 The investigator should promptly provide written reports to the sponsor, the IRB/IEC (see 3.3.8) and, where applicable, the institution on any changes significantly affecting the conduct of the trial, and/or increasing the risk to subjects.

4.11 Safety Reporting

4.11.1 All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify subjects by unique code numbers assigned to the trial subjects rather than by the subjects' names, personal identification numbers, and/or addresses. The investigator should also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the regulatory authority(ies) and the IRB/IEC.

4.11.2 Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.

4.11.3 For reported deaths, the investigator should supply the sponsor and the IRB/IEC with any additional requested information (e.g., autopsy reports and terminal medical reports).

4.12 Premature Termination or Suspension of a Trial

If the trial is prematurely terminated or suspended for any reason, the investigator/institution should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects, and, where required by the applicable regulatory requirement(s), should inform the regulatory authority(ies). In addition:

4.12.1 If the investigator terminates or suspends a trial without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC, and should provide the sponsor and the IRB/IEC a detailed written explanation of the termination or suspension.

4.12.2 If the sponsor terminates or suspends a trial (see 5.21), the investigator should promptly

inform the institution where applicable and the investigator/institution should promptly inform the IRB/IEC and provide the IRB/IEC a detailed written explanation of the termination or suspension.

4.12.3 If the IRB/IEC terminates or suspends its approval/favourable opinion of a trial (see 3.1.2 and 3.3.9), the investigator should inform the institution where applicable and the investigator/institution should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.

4.13 Final Report(s) by Investigator

Upon completion of the trial, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB/IEC with a summary of the trial's outcome, and the regulatory authority(ies) with any reports required.

5. SPONSOR

ADDENDUM

5.0 Quality Management

The sponsor should implement a system to manage quality throughout all stages of the trial process.

Sponsors should focus on trial activities essential to ensuring human subject protection and the reliability of trial results. Quality management includes the design of efficient clinical trial protocols and tools and procedures for data collection and processing, as well as the collection of information that is essential to decision making.

The methods used to assure and control the quality of the trial should be proportionate to the risks inherent in the trial and the importance of the information collected. The sponsor should ensure that all aspects of the trial are operationally feasible and should avoid unnecessary complexity, procedures, and data collection. Protocols, case report forms, and other operational documents should be clear, concise, and consistent.

The quality management system should use a risk-based approach as described below.

5.0.1 Critical Process and Data Identification

During protocol development, the sponsor should identify those processes and data that are critical to ensure human subject protection and the reliability of trial results.

5.0.2 Risk Identification

The sponsor should identify risks to critical trial processes and data. Risks should be considered at both the system level (e.g., standard operating procedures, computerized systems, personnel) and clinical trial level (e.g., trial design, data collection, informed consent process).

5.0.3 Risk Evaluation

The sponsor should evaluate the identified risks, against existing risk controls by considering:

A. The likelihood of errors occurring.

B. The extent to which such errors would be detectable.

C. The impact of such errors on human subject protection and reliability of trial results.

5.0.4 Risk Control

The sponsor should decide which risks to reduce and/or which risks to accept. The approach used

to reduce risk to an acceptable level should be proportionate to the significance of the risk. Risk reduction activities may be incorporated in protocol design and implementation, monitoring plans, agreements between parties defining roles and responsibilities, systematic safeguards to ensure adherence to standard operating procedures, and training in processes and procedures.
Predefined quality tolerance limits should be established, taking into consideration the medical and statistical characteristics of the variables as well as the statistical design of the trial, to identify systematic issues that can impact subject safety or reliability of trial results. Detection of deviations from the predefined quality tolerance limits should trigger an evaluation to determine if action is needed.

5.0.5 Risk Communication
The sponsor should document quality management activities. The sponsor should communicate quality management activities to those who are involved in or affected by such activities, to facilitate risk review and continual improvement during clinical trial execution.

5.0.6 Risk Review
The sponsor should periodically review risk control measures to ascertain whether the implemented quality management activities remain effective and relevant, taking into account emerging knowledge and experience.

5.0.7 Risk Reporting
The sponsor should describe the quality management approach implemented in the trial and summarize important deviations from the predefined quality tolerance limits and remedial actions taken in the clinical study report (ICH E3, Section 9.6 Data Quality Assurance).

5.1 Quality Assurance and Quality Control

5.1.1 The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s).

5.1.2 The sponsor is responsible for securing agreement from all involved parties to ensure direct access (see 1.21) to all trial related sites, source data/documents , and reports for the purpose of monitoring and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities.

5.1.3 Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

5.1.4 Agreements, made by the sponsor with the investigator/institution and any other parties involved with the clinical trial, should be in writing, as part of the protocol or in a separate agreement.

5.2 Contract Research Organization (CRO)

5.2.1 A sponsor may transfer any or all of the sponsor's trial-related duties and functions to a CRO, but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor. The CRO should implement quality assurance and quality control.

5.2.2 Any trial-related duty and function that is transferred to and assumed by a CRO should

be specified in writing.

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The sponsor should ensure oversight of any trial-related duties and functions carried out on its behalf, including trial-related duties and functions that are subcontracted to another party by the sponsor's contracted CRO(s).

5.2.3 Any trial-related duties and functions not specifically transferred to and assumed by a CRO are retained by the sponsor.

5.2.4 All references to a sponsor in this guideline also apply to a CRO to the extent that a CRO has assumed the trial related duties and functions of a sponsor.

5.3 Medical Expertise
The sponsor should designate appropriately qualified medical personnel who will be readily available to advise on trial related medical questions or problems. If necessary, outside consultant(s) may be appointed for this purpose.

5.4 Trial Design

5.4.1 The sponsor should utilize qualified individuals (e.g., biostatisticians, clinical pharmacologists, and physicians) as appropriate, throughout all stages of the trial process, from designing the protocol and CRFs and planning the analyses to analyzing and preparing interim and final clinical trial reports.

5.4.2 For further guidance: Clinical Trial Protocol and Protocol Amendment(s) (see 6.), the ICH Guideline for Structure and Content of Clinical Study Reports, and other appropriate ICH guidance on trial design, protocol and conduct.

5.5 Trial Management, Data Handling, and Record Keeping

5.5.1 The sponsor should utilize appropriately qualified individuals to supervise the overall conduct of the trial, to handle the data, to verify the data, to conduct the statistical analyses, and to prepare the trial reports.

5.5.2 The sponsor may consider establishing an independent data-monitoring committee (IDMC) to assess the progress of a clinical trial, including the safety data and the critical efficacy endpoints at intervals, and to recommend to the sponsor whether to continue, modify, or stop a trial. The IDMC should have written operating procedures and maintain written records of all its meetings.

5.5.3 When using electronic trial data handling and/or remote electronic trial data systems, the sponsor should:

A. Ensure and document that the electronic data processing system(s) conforms to the sponsor's established requirements for completeness, accuracy, reliability, and consistent intended performance (i.e., validation).

ADDENDUM
The sponsor should base their approach to validation of such systems on a risk assessment that takes into consideration the intended use of the system and the potential of the system to affect

human subject protection and reliability of trial results.

B. Maintains SOPs for using these systems.

ADDENDUM

The SOPs should cover system setup, installation, and use. The SOPs should describe system validation and functionality testing, data collection and handling, system maintenance, system security measures, change control, data backup, recovery, contingency planning, and decommissioning. The responsibilities of the sponsor, investigator, and other parties with respect to the use of these computerized systems should be clear, and the users should be provided with training in their use.

C. Ensure that the systems are designed to permit data changes in such a way that the data changes are documented and that there is no deletion of entered data (i.e., maintain an audit trail, data trail, edit trail).

D. Maintain a security system that prevents unauthorized access to the data.

E. Maintain a list of the individuals who are authorized to make data changes (see 4.1.5 and 4.9.3).

F. Maintain adequate backup of the data.

G. Safeguard the blinding, if any (e.g., maintain the blinding during data entry and processing).

ADDENDUM

H. Ensure the integrity of the data including any data that describe the context, content, and structure. This is particularly important when making changes to the computerized systems, such as software upgrades or migration of data.

5.5.4 If data are transformed during processing, it should always be possible to compare the original data and observations with the processed data.

5.5.5 The sponsor should use an unambiguous subject identification code (see 1.58) that allows identification of all the data reported for each subject.

5.5.6 The sponsor, or other owners of the data, should retain all of the sponsor-specific essential documents pertaining to the trial (see 8. Essential Documents for the Conduct of a Clinical Trial).

5.5.7 The sponsor should retain all sponsor-specific essential documents in conformance with the applicable regulatory requirement(s) of the country(ies) where the product is approved, and/or where the sponsor intends to apply for approval(s).

5.5.8 If the sponsor discontinues the clinical development of an investigational product (i.e., for any or all indications, routes of administration, or dosage forms), the sponsor should maintain all sponsor-specific essential documents for at least 2-years after formal discontinuation or in conformance with the applicable regulatory requirement(s).

5.5.9 If the sponsor discontinues the clinical development of an investigational product, the sponsor should notify all the trial investigators/institutions and all the regulatory authorities.

5.5.10 Any transfer of ownership of the data should be reported to the appropriate authority(ies), as required by the applicable regulatory requirement(s).

5.5.11 The sponsor specific essential documents should be retained until at least 2-years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2-years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirement(s) or if needed by the sponsor.

5.5.12 The sponsor should inform the investigator(s)/institution(s) in writing of the need for record retention and should notify the investigator(s)/institution(s) in writing when the trial related records are no longer needed.

5.6 Investigator Selection

5.6.1 The sponsor is responsible for selecting the investigator(s)/institution(s). Each investigator should be qualified by training and experience and should have adequate resources (see 4.1, 4.2) to properly conduct the trial for which the investigator is selected. If organization of a coordinating committee and/or selection of coordinating investigator(s) are to be utilized in multicentre trials, their organization and/or selection are the sponsor's responsibility.

5.6.2 Before entering an agreement with an investigator/institution to conduct a trial, the sponsor should provide the investigator(s)/institution(s) with the protocol and an up-to-date Investigator's Brochure, and should provide sufficient time for the investigator/institution to review the protocol and the information provided.

5.6.3 The sponsor should obtain the investigator's/institution's agreement:

A. to conduct the trial in compliance with GCP, with the applicable regulatory requirement(s) (see 4.1.3), and with the protocol agreed to by the sponsor and given approval/favourable opinion by the IRB/IEC (see 4.5.1);

B. to comply with procedures for data recording/reporting;

C. to permit monitoring, auditing and inspection (see 4.1.4) and

D. to retain the trial related essential documents until the sponsor informs the investigator/institution these documents are no longer needed (see 4.9.4 and 5.5.12).

The sponsor and the investigator/institution should sign the protocol, or an alternative document, to confirm this agreement.

5.7 Allocation of Responsibilities

Prior to initiating a trial, the sponsor should define, establish, and allocate all trial-related duties and functions.

5.8 Compensation to Subjects and Investigators

5.8.1 If required by the applicable regulatory requirement(s), the sponsor should provide insurance or should indemnify (legal and financial coverage) the investigator/the institution against claims arising from the trial, except for claims that arise from malpractice and/or negligence.

5.8.2 The sponsor's policies and procedures should address the costs of treatment of trial subjects in the event of trial-related injuries in accordance with the applicable regulatory requirement(s).

5.8.3 When trial subjects receive compensation, the method and manner of compensation should comply with applicable regulatory requirement(s).

5.9 Financing

The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.

5.10 Notification/Submission to Regulatory Authority(ies)

Before initiating the clinical trial(s), the sponsor (or the sponsor and the investigator, if required by the applicable regulatory requirement(s)) should submit any required application(s) to the appropriate authority(ies) for review, acceptance, and/or permission (as required by the applicable regulatory requirement(s)) to begin the trial(s). Any notification/submission should be dated and contain sufficient information to identify the protocol.

5.11 Confirmation of Review by IRB/IEC

5.11.1 The sponsor should obtain from the investigator/institution:

A. The name and address of the investigator's/institution's IRB/IEC.

B. A statement obtained from the IRB/IEC that it is organized and operates according to GCP and the applicable laws and regulations.

C. Documented IRB/IEC approval/favourable opinion and, if requested by the sponsor, a current copy of protocol, written informed consent form(s) and any other written information to be provided to subjects, subject recruiting procedures, and documents related to payments and compensation available to the subjects, and any other documents that the IRB/IEC may have requested.

5.11.2 If the IRB/IEC conditions its approval/favourable opinion upon change(s) in any aspect of the trial, such as modification(s) of the protocol, written informed consent form and any other written information to be provided to subjects, and/or other procedures, the sponsor should obtain from the investigator/institution a copy of the modification(s) made and the date approval/favourable opinion was given by the IRB/IEC.

5.11.3 The sponsor should obtain from the investigator/institution documentation and dates of any IRB/IEC reapprovals/re-evaluations with favourable opinion, and of any withdrawals or suspensions of approval/favourable opinion.

5.12 Information on Investigational Product(s)

5.12.1 When planning trials, the sponsor should ensure that sufficient safety and efficacy data from nonclinical studies and/or clinical trials are available to support human exposure by the route, at the dosages, for the duration, and in the trial population to be studied.

5.12.2 The sponsor should update the Investigator's Brochure as significant new information becomes available (see 7. Investigator's Brochure).

5.13 Manufacturing, Packaging, Labelling, and Coding Investigational Product(s)

5.13.1 The sponsor should ensure that the investigational product(s) (including active comparator(s) and placebo, if applicable) is characterized as appropriate to the stage of development of the product(s), is manufactured in accordance with any applicable GMP, and is coded and

labelled in a manner that protects the blinding, if applicable. In addition, the labelling should comply with applicable regulatory requirement(s).

5.13.2 The sponsor should determine, for the investigational product(s), acceptable storage temperatures, storage conditions (e.g., protection from light), storage times, reconstitution fluids and procedures, and devices for product infusion, if any. The sponsor should inform all involved parties (e.g., monitors, investigators, pharmacists, storage managers) of these determinations.

5.13.3 The investigational product(s) should be packaged to prevent contamination and unacceptable deterioration during transport and storage.

5.13.4 In blinded trials, the coding system for the investigational product(s) should include a mechanism that permits rapid identification of the product(s) in case of a medical emergency, but does not permit undetectable breaks of the blinding.

5.13.5 If significant formulation changes are made in the investigational or comparator product(s) during the course of clinical development, the results of any additional studies of the formulated product(s) (e.g., stability, dissolution rate, bioavailability) needed to assess whether these changes would significantly alter the pharmacokinetic profile of the product should be available prior to the use of the new formulation in clinical trials.

5.14 Supplying and Handling Investigational Product(s)

5.14.1 The sponsor is responsible for supplying the investigator(s)/institution(s) with the investigational product(s).

5.14.2 The sponsor should not supply an investigator/institution with the investigational product(s) until the sponsor obtains all required documentation (e.g., approval/favourable opinion from IRB/IEC and regulatory authority(ies)).

5.14.3 The sponsor should ensure that written procedures include instructions that the investigator/institution should follow for the handling and storage of investigational product(s) for the trial and documentation thereof. The procedures should address adequate and safe receipt, handling, storage, dispensing, retrieval of unused product from subjects, and return of unused investigational product(s) to the sponsor (or alternative disposition if authorized by the sponsor and in compliance with the applicable regulatory requirement(s)).

5.14.4 The sponsor should:

A. Ensure timely delivery of investigational product(s) to the investigator(s).

B. Maintain records that document shipment, receipt, disposition, return, and destruction of the investigational product(s) (see 8. Essential Documents for the Conduct of a Clinical Trial).

C. Maintain a system for retrieving investigational products and documenting this retrieval (e.g., for deficient product recall, reclaim after trial completion, expired product reclaim).

D. Maintain a system for the disposition of unused investigational product(s) and for the documentation of this disposition.

5.14.5 The sponsor should:

A. Take steps to ensure that the investigational product(s) are stable over the period of use.

B. Maintain sufficient quantities of the investigational product(s) used in the trials to reconfirm specifications, should this become necessary, and maintain records of batch sample analyses and characteristics. To the extent stability permits, samples should be retained either until the analyses of the trial data are complete or as required by the applicable regulatory requirement(s), whichever represents the longer retention period.

5.15 Record Access

5.15.1 The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) provide direct access to source data/documents for trial-related monitoring, audits, IRB/IEC review, and regulatory inspection.

5.15.2 The sponsor should verify that each subject has consented, in writing, to direct access to his/her original medical records for trial-related monitoring, audit, IRB/IEC review, and regulatory inspection.

5.16 Safety Information

5.16.1 The sponsor is responsible for the ongoing safety evaluation of the investigational product(s).

5.16.2 The sponsor should promptly notify all concerned investigator(s)/institution(s) and the regulatory authority(ies) of findings that could affect adversely the safety of subjects, impact the conduct of the trial, or alter the IRB/IEC's approval/favourable opinion to continue the trial.

5.17 Adverse Drug Reaction Reporting

5.17.1 The sponsor should expedite the reporting to all concerned investigator(s)/institutions(s), to the IRB(s)/IEC(s), where required, and to the regulatory authority(ies) of all adverse drug reactions (ADRs) that are both serious and unexpected.

5.17.2 Such expedited reports should comply with the applicable regulatory requirement(s) and with the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

5.17.3 The sponsor should submit to the regulatory authority(ies) all safety updates and periodic reports, as required by applicable regulatory requirement(s).

5.18 Monitoring

5.18.1 Purpose

The purposes of trial monitoring are to verify that:

A. The rights and well-being of human subjects are protected.

B. The reported trial data are accurate, complete, and verifiable from source documents.

C. The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s).

5.18.2 Selection and Qualifications of Monitors

A. Monitors should be appointed by the sponsor.

B. Monitors should be appropriately trained, and should have the scientific and/or clinical knowledge needed to monitor the trial adequately. A monitor's qualifications should be documented.

C. Monitors should be thoroughly familiar with the investigational product(s), the protocol, written informed consent form and any other written information to be provided to subjects, the sponsor's SOPs, GCP, and the applicable regulatory requirement(s).

5.18.3 Extent and Nature of Monitoring

The sponsor should ensure that the trials are adequately monitored. The sponsor should determine the appropriate extent and nature of monitoring. The determination of the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the trial. In general there is a need for on-site monitoring, before, during, and after the trial; however in exceptional circumstances the sponsor may determine that central monitoring in conjunction with procedures such as investigators' training and meetings, and extensive written guidance can assure appropriate conduct of the trial in accordance with GCP. Statistically controlled sampling may be an acceptable method for selecting the data to be verified.

ADDENDUM

The sponsor should develop a systematic, prioritized, risk-based approach to monitoring clinical trials. The flexibility in the extent and nature of monitoring described in this section is intended to permit varied approaches that improve the effectiveness and efficiency of monitoring. The sponsor may choose on-site monitoring, a combination of on-site and centralized monitoring, or, where justified, centralized monitoring. The sponsor should document the rationale for the chosen monitoring strategy (e.g., in the monitoring plan).

On-site monitoring is performed at the sites at which the clinical trial is being conducted. Centralized monitoring is a remote evaluation of accumulating data, performed in a timely manner, supported by appropriately qualified and trained persons (e.g., data managers, biostatisticians).

Centralized monitoring processes provide additional monitoring capabilities that can complement and reduce the extent and/or frequency of on-site monitoring and help distinguish between reliable data and potentially unreliable data.

Review, that may include statistical analyses, of accumulating data from centralized monitoring can be used to:

A. identify missing data, inconsistent data, data outliers, unexpected lack of variability and protocol deviations.

B. examine data trends such as the range, consistency, and variability of data within and across sites.

C. evaluate for systematic or significant errors in data collection and reporting at a site or across sites; or potential data manipulation or data integrity problems.

D. analyze site characteristics and performance metrics.

E. select sites and/or processes for targeted on-site monitoring.

5.18.4 Monitor's Responsibilities

The monitor(s) in accordance with the sponsor's requirements should ensure that the trial is conducted and documented properly by carrying out the following activities when relevant and necessary to the trial and the trial site:

A. Acting as the main line of communication between the sponsor and the investigator.

B. Verifying that the investigator has adequate qualifications and resources (see 4.1, 4.2, 5.6) and remain adequate throughout the trial period, that facilities, including laboratories, equipment, and staff, are adequate to safely and properly conduct the trial and remain adequate throughout the trial period.

C. Verifying, for the investigational product(s):

   I. That storage times and conditions are acceptable, and that supplies are sufficient throughout the trial.

   II. That the investigational product(s) are supplied only to subjects who are eligible to receive it and at the protocol specified dose(s).

   III. That subjects are provided with necessary instruction on properly using, handling, storing, and returning the investigational product(s).

   IV. That the receipt, use, and return of the investigational product(s) at the trial sites are controlled and documented adequately.

   V. That the disposition of unused investigational product(s) at the trial sites complies with applicable regulatory requirement(s) and is in accordance with the sponsor.

D. Verifying that the investigator follows the approved protocol and all approved amendment(s), if any.

E. Verifying that written informed consent was obtained before each subject's participation in the trial.

F. Ensuring that the investigator receives the current Investigator's Brochure, all documents, and all trial supplies needed to conduct the trial properly and to comply with the applicable regulatory requirement(s).

G. Ensuring that the investigator and the investigator's trial staff are adequately informed about the trial.

H. Verifying that the investigator and the investigator's trial staff are performing the specified trial functions, in accordance with the protocol and any other written agreement between the sponsor and the investigator/institution, and have not delegated these functions to unauthorized individuals.

I. Verifying that the investigator is enroling only eligible subjects.

J. Reporting the subject recruitment rate.

K. Verifying that source documents and other trial records are accurate, complete, kept up-to-date and maintained.

L. Verifying that the investigator provides all the required reports, notifications, applications, and submissions, and that these documents are accurate, complete, timely, legible, dated, and identify the trial.

M. Checking the accuracy and completeness of the CRF entries, source documents and other trial-related records against each other. The monitor specifically should verify that:

I. (i) The data required by the protocol are reported accurately on the CRFs and are consistent with the source documents.

II. (ii) Any dose and/or therapy modifications are well documented for each of the trial subjects.

III. (iii) Adverse events, concomitant medications and intercurrent illnesses are reported in accordance with the protocol on the CRFs.

IV. (iv) Visits that the subjects fail to make, tests that are not conducted, and examinations that are not performed are clearly reported as such on the CRFs.

V. (v) All withdrawals and dropouts of enrolled subjects from the trial are reported and explained on the CRFs.

N. Informing the investigator of any CRF entry error, omission, or illegibility. The monitor should ensure that appropriate corrections, additions, or deletions are made, dated, explained (if necessary), and initialled by the investigator or by a member of the investigator's trial staff who is authorized to initial CRF changes for the investigator. This authorization should be documented.

O. Determining whether all adverse events (AEs) are appropriately reported within the time periods required by GCP, the protocol, the IRB/IEC, the sponsor, and the applicable regulatory requirement(s).

P. Determining whether the investigator is maintaining the essential documents (see 8. Essential Documents for the Conduct of a Clinical Trial).

Q. Communicating deviations from the protocol, SOPs, GCP, and the applicable regulatory requirements to the investigator and taking appropriate action designed to prevent recurrence of the detected deviations.

5.18.5 Monitoring Procedures

The monitor(s) should follow the sponsor's established written SOPs as well as those procedures that are specified by the sponsor for monitoring a specific trial.

5.18.6 Monitoring Report

A. The monitor should submit a written report to the sponsor after each trial-site visit or trial-related communication.

B. Reports should include the date, site, name of the monitor, and name of the investigator or other individual(s) contacted.

C. Reports should include a summary of what the monitor reviewed and the monitor's

statements concerning the significant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken and/or actions recommended to secure compliance.

D. The review and follow-up of the monitoring report with the sponsor should be documented by the sponsor's designated representative.

ADDENDUM

E. Reports of on-site and/or centralized monitoring should be provided to the sponsor (including appropriate management and staff responsible for trial and site oversight) in a timely manner for review and follow up. Results of monitoring activities should be documented in sufficient detail to allow verification of compliance with the monitoring plan. Reporting of centralized monitoring activities should be regular and may be independent from site visits.

ADDENDUM

5.18.7 Monitoring Plan

The sponsor should develop a monitoring plan that is tailored to the specific human subject protection and data integrity risks of the trial. The plan should describe the monitoring strategy, the monitoring responsibilities of all the parties involved, the various monitoring methods to be used, and the rationale for their use. The plan should also emphasize the monitoring of critical data and processes. Particular attention should be given to those aspects that are not routine clinical practice and that require additional training. The monitoring plan should reference the applicable policies and procedures.

5.19 Audit

If or when sponsors perform audits, as part of implementing quality assurance, they should consider:

5.19.1 Purpose

The purpose of a sponsor's audit, which is independent of and separate from routine monitoring or quality control functions, should be to evaluate trial conduct and compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements.

5.19.2 Selection and Qualification of Auditors

A. The sponsor should appoint individuals, who are independent of the clinical trials/systems, to conduct audits.

B. The sponsor should ensure that the auditors are qualified by training and experience to conduct audits properly. An auditor's qualifications should be documented.

5.19.3 Auditing Procedures

A. The sponsor should ensure that the auditing of clinical trials/systems is conducted in accordance with the sponsor's written procedures on what to audit, how to audit, the frequency of audits, and the form and content of audit reports.

B. The sponsor's audit plan and procedures for a trial audit should be guided by the im-

portance of the trial to submissions to regulatory authorities, the number of subjects in the trial, the type and complexity of the trial, the level of risks to the trial subjects, and any identified problem(s).

C. The observations and findings of the auditor(s) should be documented.

D. To preserve the independence and value of the audit function, the regulatory authority(ies) should not routinely request the audit reports. Regulatory authority(ies) may seek access to an audit report on a case by case basis when evidence of serious GCP non-compliance exists, or in the course of legal proceedings.

E. When required by applicable law or regulation, the sponsor should provide an audit certificate.

5.20 Noncompliance

5.20.1 Noncompliance with the protocol, SOPs, GCP, and/or applicable regulatory requirement(s) by an investigator/institution, or by member(s) of the sponsor's staff should lead to prompt action by the sponsor to secure compliance.

ADDENDUM

If noncompliance that significantly affects or has the potential to significantly affect human subject protection or reliability of trial results is discovered, the sponsor should perform a root cause analysis and implement appropriate corrective and preventive actions.

5.20.2 If the monitoring and/or auditing identifies serious and/or persistent noncompliance on the part of an investigator/institution, the sponsor should terminate the investiga-tor's/institution's participation in the trial. When an investigator's/institution's parti-cipation is terminated because of noncompliance, the sponsor should notify promptly the regulatory authority(ies).

5.21 Premature Termination or Suspension of a Trial

If a trial is prematurely terminated or suspended, the sponsor should promptly inform the investigators/institutions, and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC should also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

5.22 Clinical Trial/Study Reports

Whether the trial is completed or prematurely terminated, the sponsor should ensure that the clinical trial reports are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor should also ensure that the clinical trial reports in marketing applications meet the standards of the ICH Guideline for Structure and Content of Clinical Study Reports. (NOTE: The ICH Guideline for Structure and Content of Clinical Study Reports specifies that abbreviated study reports may be acceptable in certain cases.)

5.23 Multicentre Trials

For multicentre trials, the sponsor should ensure that:

5.23.1 All investigators conduct the trial in strict compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies), and given approval/favourable opinion by the IRB/IEC.

5.23.2 The CRFs are designed to capture the required data at all multicentre trial sites. For those investigators who are collecting additional data, supplemental CRFs should also be provided that are designed to capture the additional data.

5.23.3 The responsibilities of coordinating investigator(s) and the other participating investigators are documented prior to the start of the trial.

5.23.4 All investigators are given instructions on following the protocol, on complying with a uniform set of standards for the assessment of clinical and laboratory findings, and on completing the CRFs.

5.23.5 Communication between investigators is facilitated.

6. CLINICAL TRIAL PROTOCOL AND PROTOCOL AMENDMENT(S)

The contents of a trial protocol should generally include the following topics. However, site specific information may be provided on separate protocol page(s), or addressed in a separate agreement, and some of the information listed below may be contained in other protocol referenced documents, such as an Investigator's Brochure.

6.1 General Information

6.1.1 Protocol title, protocol identifying number, and date. Any amendment(s) should also bear the amendment number(s) and date(s).

6.1.2 Name and address of the sponsor and monitor (if other than the sponsor).

6.1.3 Name and title of the person(s) authorized to sign the protocol and the protocol amendment(s) for the sponsor.

6.1.4 Name, title, address, and telephone number(s) of the sponsor's medical expert (or dentist when appropriate) for the trial.

6.1.5 Name and title of the investigator(s) who is (are) responsible for conducting the trial, and the address and telephone number(s) of the trial site(s).

6.1.6 Name, title, address, and telephone number(s) of the qualified physician (or dentist, if applicable), who is responsible for all trial-site related medical (or dental) decisions (if other than investigator).

6.1.7 Name(s) and address(es) of the clinical laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in the trial.

6.2 Background Information

6.2.1 Name and description of the investigational product(s).

6.2.2 A summary of findings from nonclinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial.

6.2.3 Summary of the known and potential risks and benefits, if any, to human subjects.

6.2.4 Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s).

6.2.5 A statement that the trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s).

6.2.6 Description of the population to be studied.

6.2.7 References to literature and data that are relevant to the trial, and that provide background for the trial.

6.3 Trial Objectives and Purpose

A detailed description of the objectives and the purpose of the trial.

6.4 Trial Design

The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. A description of the trial design, should include:

6.4.1 A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.

6.4.2 A description of the type/design of trial to be conducted (e.g., double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures and stages.

6.4.3 A description of the measures taken to minimize/avoid bias, including:

A. Randomization.

B. Blinding.

6.4.4 A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s). Also include a description of the dosage form, packaging, and labelling of the investigational product(s).

6.4.5 The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any.

6.4.6 A description of the "stopping rules" or "discontinuation criteria" for individual subjects, parts of trial and entire trial.

6.4.7 Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any.

6.4.8 Maintenance of trial treatment randomization codes and procedures for breaking codes.

6.4.9 The identification of any data to be recorded directly on the CRFs (i.e., no prior written or electronic record of data), and to be considered to be source data.

6.5 Selection and Withdrawal of Subjects

6.5.1 Subject inclusion criteria.

6.5.2 Subject exclusion criteria.

6.5.3 Subject withdrawal criteria (i.e., terminating investigational product treatment/trial treatment) and procedures specifying:

A. When and how to withdraw subjects from the trial/ investigational product treatment.

B. The type and timing of the data to be collected for withdrawn subjects.

C. Whether and how subjects are to be replaced.

D. The follow-up for subjects withdrawn from investigational product treatment/trial treatment.

6.6 Treatment of Subjects

6.6.1 The treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects for each investigational product treatment/trial treatment group/arm of the trial.

6.6.2 Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.

6.6.3 Procedures for monitoring subject compliance.

6.7 Assessment of Efficacy

6.7.1 Specification of the efficacy parameters.

6.7.2 Methods and timing for assessing, recording, and analysing of efficacy parameters.

6.8 Assessment of Safety

6.8.1 Specification of safety parameters.

6.8.2 The methods and timing for assessing, recording, and analysing safety parameters.

6.8.3 Procedures for eliciting reports of and for recording and reporting adverse event and intercurrent illnesses.

6.8.4 The type and duration of the follow-up of subjects after adverse events.

6.9 Statistics

6.9.1 A description of the statistical methods to be employed, including timing of any planned interim analysis(ses).

6.9.2 The number of subjects planned to be enrolled. In multicentre trials, the numbers of enrolled subjects projected for each trial site should be specified. Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.

6.9.3 The level of significance to be used.

6.9.4 Criteria for the termination of the trial.

6.9.5 Procedure for accounting for missing, unused, and spurious data.

6.9.6 Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in protocol and/or in the final report, as appropriate).

6.9.7 The selection of subjects to be included in the analyses (e.g., all randomized subjects, all

dosed subjects, all eligible subjects, evaluable subjects).

6.10 Direct Access to Source Data/Documents

The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents.

6.11 Quality Control and Quality Assurance

6.12 Ethics

Description of ethical considerations relating to the trial.

6.13 Data Handling and Record Keeping

6.14 Financing and Insurance

Financing and insurance if not addressed in a separate agreement.

6.15 Publication Policy

Publication policy, if not addressed in a separate agreement.

6.16 Supplements

(NOTE: Since the protocol and the clinical trial/study report are closely related, further relevant information can be found in the ICH Guideline for Structure and Content of Clinical Study Reports.)

7. INVESTIGATOR'S BROCHURE

7.1 Introduction

The Investigator's Brochure (IB) is a compilation of the clinical and nonclinical data on the investigational product(s) that are relevant to the study of the product(s) in human subjects. Its purpose is to provide the investigators and others involved in the trial with the information to facilitate their understanding of the rationale for, and their compliance with, many key features of the protocol, such as the dose, dose frequency/interval, methods of administration: and safety monitoring procedures. The IB also provides insight to support the clinical management of the study subjects during the course of the clinical trial. The information should be presented in a concise, simple, objective, balanced, and non-promotional form that enables a clinician, or potential investigator, to understand it and make his/her own unbiased risk-benefit assessment of the appropriateness of the proposed trial. For this reason, a medically qualified person should generally participate in the editing of an IB, but the contents of the IB should be approved by the disciplines that generated the described data.

This guideline delineates the minimum information that should be included in an IB and provides suggestions for its layout. It is expected that the type and extent of information available will vary with the stage of development of the investigational product. If the investigational product is marketed and its pharmacology is widely understood by medical practitioners, an extensive IB may not be necessary. Where permitted by regulatory authorities, a basic product information brochure, package leaflet, or labelling may be an appropriate alternative, provided that it includes current, comprehensive, and detailed information on all aspects of the investigational product that might be of importance to the investigator. If a marketed product is being studied for a new use (i.e., a new indication), an IB specific to that new use should be prepared. The IB should be reviewed at least annually and revised as necessary in compliance with a sponsor's written procedures. More frequent revision may be appropriate depending on the stage of development and the generation of relevant new information. However, in accordance with Good Clinical Practice, relevant new

information may be so important that it should be communicated to the investigators, and possibly to the Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) and/or regulatory authorities before it is included in a revised IB.

Generally, the sponsor is responsible for ensuring that an up-to-date IB is made available to the investigator(s) and the investigators are responsible for providing the up-to-date IB to the responsible IRBs/IECs. In the case of an investigator sponsored trial, the sponsor-investigator should determine whether a brochure is available from the commercial manufacturer. If the investigational product is provided by the sponsor-investigator, then he or she should provide the necessary information to the trial personnel. In cases where preparation of a formal IB is impractical, the sponsor-investigator should provide, as a substitute, an expanded background information section in the trial protocol that contains the minimum current information described in this guideline.

7.2 General Considerations

The IB should include:

7.2.1 Title Page

This should provide the sponsor's name, the identity of each investigational product (i.e., research number, chemical or approved generic name, and trade name(s) where legally permissible and desired by the sponsor), and the release date. It is also suggested that an edition number, and a reference to the number and date of the edition it supersedes, be provided. An example is given in Appendix 1.

7.2.2 Confidentiality Statement

The sponsor may wish to include a statement instructing the investigator/recipients to treat the IB as a confidential document for the sole information and use of the investigator's team and the IRB/IEC.

7.3 Contents of the Investigator's Brochure

The IB should contain the following sections, each with literature references where appropriate:

7.3.1 Table of Contents

An example of the Table of Contents is given in Appendix 2

7.3.2 Summary

A brief summary (preferably not exceeding two pages) should be given, highlighting the significant physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic, and clinical information available that is relevant to the stage of clinical development of the investigational product.

7.3.3 Introduction

A brief introductory statement should be provided that contains the chemical name (and generic and trade name(s) when approved) of the investigational product(s), all active ingredients, the investigational product (s) pharmacological class and its expected position within this class (e.g., advantages), the rationale for performing research with the investigational product(s), and the anticipated prophylactic, therapeutic, or diagnostic indication(s). Finally, the introductory statement should provide the general approach to be followed in evaluating the investigational product.

7.3.4 Physical, Chemical, and Pharmaceutical Properties and Formulation

A description should be provided of the investigational product substance(s) (including the chemical and/or structural formula(e)), and a brief summary should be given of the relevant physical, chemical, and pharmaceutical properties.

To permit appropriate safety measures to be taken in the course of the trial, a description of the formulation(s) to be used, including excipients, should be provided and justified if clinically relevant. Instructions for the storage and handling of the dosage form(s) should also be given.

Any structural similarities to other known compounds should be mentioned.

7.3.5 Nonclinical Studies

Introduction:

The results of all relevant nonclinical pharmacology, toxicology, pharmacokinetic, and investigational product metabolism studies should be provided in summary form. This summary should address the methodology used, the results, and a discussion of the relevance of the findings to the investigated therapeutic and the possible unfavourable and unintended effects in humans.

The information provided may include the following, as appropriate, if known/available:

- Species tested
- Number and sex of animals in each group
- Unit dose (e.g., milligram/kilogram (mg/kg))
- Dose interval
- Route of administration
- Duration of dosing
- Information on systemic distribution
- Duration of post-exposure follow-up
- Results, including the following aspects:
    - Nature and frequency of pharmacological or toxic effects
    - Severity or intensity of pharmacological or toxic effects
    - Time to onset of effects
    - Reversibility of effects
    - Duration of effects
    - Dose response

Tabular format/listings should be used whenever possible to enhance the clarity of the presentation.

The following sections should discuss the most important findings from the studies, including the dose response of observed effects, the relevance to humans, and any aspects to be studied in humans. If applicable, the effective and nontoxic dose findings in the same animal species should be compared (i.e., the therapeutic index should be discussed). The relevance of this information to the proposed human dosing should be addressed. Whenever possible, comparisons should be made in terms of blood/tissue levels rather than on a mg/kg basis.

A. Nonclinical Pharmacology

A summary of the pharmacological aspects of the investigational product and, where appropriate, its significant metabolites studied in animals, should be included. Such a sum-

mary should incorporate studies that assess potential therapeutic activity (e.g., efficacy models, receptor binding, and specificity) as well as those that assess safety (e.g., special studies to assess pharmacological actions other than the intended therapeutic effect(s)).

B. Pharmacokinetics and Product Metabolism in Animals

A summary of the pharmacokinetics and biological transformation and disposition of the investigational product in all species studied should be given. The discussion of the findings should address the absorption and the local and systemic bioavailability of the investigational product and its metabolites, and their relationship to the pharmacological and toxicological findings in animal species.

C. Toxicology

A summary of the toxicological effects found in relevant studies conducted in different animal species should be described under the following headings where appropriate:

- Single dose
- Repeated dose
- Carcinogenicity
- Special studies (e.g., irritancy and sensitisation)
- Reproductive toxicity
- Genotoxicity (mutagenicity)

7.3.6 Effects in Humans

Introduction:

A thorough discussion of the known effects of the investigational product(s) in humans should be provided, including information on pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy, and other pharmacological activities. Where possible, a summary of each completed clinical trial should be provided. Information should also be provided regarding results of any use of the investigational product(s) other than from in clinical trials, such as from experience during marketing.

A. Pharmacokinetics and Product Metabolism in Humans

- A summary of information on the pharmacokinetics of the investigational product(s) should be presented, including the following, if available:
- Pharmacokinetics (including metabolism, as appropriate, and absorption, plasma protein binding, distribution, and elimination).
- Bioavailability of the investigational product (absolute, where possible, and/or relative) using a reference dosage form.
- Population subgroups (e.g., gender, age, and impaired organ function).
- Interactions (e.g., product-product interactions and effects of food).
- Other pharmacokinetic data (e.g., results of population studies performed within clinical trial(s).

B. Safety and Efficacy

A summary of information should be provided about the investigational product's/products' (including metabolites, where appropriate) safety, pharmacodynamics, efficacy, and dose response that were obtained from preceding trials in humans (healthy volunteers and/or patients). The implications of this information should be discussed. In cases where a number of clinical trials have been completed, the use of summaries of safety and efficacy across multiple trials by indications in subgroups may provide a clear presentation of the data. Tabular summaries of adverse drug reactions for all the clinical trials (including those for all the studied indications) would be useful. Important differences in adverse drug reaction patterns/incidences across indications or subgroups should be discussed.

The IB should provide a description of the possible risks and adverse drug reactions to be anticipated on the basis of prior experiences with the product under investigation and with related products. A description should also be provided of the precautions or special monitoring to be done as part of the investigational use of the product(s).

C. Marketing Experience

The IB should identify countries where the investigational product has been marketed or approved. Any significant information arising from the marketed use should be summarised (e.g., formulations, dosages, routes of administration, and adverse product reactions). The IB should also identify all the countries where the investigational product did not receive approval/registration for marketing or was withdrawn from marketing/registration.

7.3.7 Summary of Data and Guidance for the Investigator

This section should provide an overall discussion of the nonclinical and clinical data, and should summarise the information from various sources on different aspects of the investigational product(s), wherever possible. In this way, the investigator can be provided with the most informative interpretation of the available data and with an assessment of the implications of the information for future clinical trials.

Where appropriate, the published reports on related products should be discussed. This could help the investigator to anticipate adverse drug reactions or other problems in clinical trials.

The overall aim of this section is to provide the investigator with a clear understanding of the possible risks and adverse reactions, and of the specific tests, observations, and precautions that may be needed for a clinical trial. This understanding should be based on the available physical, chemical, pharmaceutical, pharmacological, toxicological, and clinical information on the investigational product(s). Guidance should also be provided to the clinical investigator on the recognition and treatment of possible overdose and adverse drug reactions that is based on previous human experience and on the pharmacology of the investigational product.

7.4 APPENDIX 1:
TITLE PAGE (Example)
SPONSOR'S NAME
Product:
Research Number:
Name(s): Chemical, Generic (if approved)
Trade Name(s) (if legally permissible and desired by the sponsor)

INVESTIGATOR'S BROCHURE

Edition Number:
Release Date:

Replaces Previous Edition Number:
Date:

7.5 APPENDIX 2:
TABLE OF CONTENTS OF INVESTIGATOR'S BROCHURE (Example)

NB: References on 1. Publications
2. Reports

These references should be found at the end of each chapter
Appendices (if any) 8. ESSENTIAL DOCUMENTS FOR THE CONDUCT OF A CLINICAL TRIAL

8.1 Introduction

Essential Documents are those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor and monitor with the standards of Good Clinical Practice and with all applicable regulatory requirements.

Essential Documents also serve a number of other important purposes. Filing essential documents at the investigator/institution and sponsor sites in a timely manner can greatly assist in the successful management of a trial by the investigator, sponsor and monitor. These documents are also the ones which are usually audited by the sponsor's independent audit function and inspected by the regulatory authority(ies) as part of the process to confirm the validity of the trial conduct and the integrity of data collected.

The minimum list of essential documents which has been developed follows. The various documents are grouped in three sections according to the stage of the trial during which they will normally be generated: 1) before the clinical phase of the trial commences, 2) during the clinical conduct of the trial, and 3) after completion or termination of the trial. A description is given of the purpose of each document, and whether it should be filed in either the investigator/institution or sponsor files, or both. It is acceptable to combine some of the documents, provided the individual elements are readily identifiable.

Trial master files should be established at the beginning of the trial, both at the investigator/institution's site and at the sponsor's office. A final close-out of a trial can only be done when the monitor has reviewed both investigator/institution and sponsor files and confirmed that all necessary documents are in the appropriate files.

Any or all of the documents addressed in this guideline may be subject to, and should be available for, audit by the sponsor's auditor and inspection by the regulatory authority(ies).

ADDENDUM

The sponsor and investigator/institution should maintain a record of the location(s) of their respective essential documents including source documents. The storage system used during the trial and for archiving (irrespective of the type of media used) should provide for document identification, version history, search, and retrieval.

Essential documents for the trial should be supplemented or may be reduced where justified (in advance of trial initiation) based on the importance and relevance of the specific documents to the trial.

The sponsor should ensure that the investigator has control of and continuous access to the CRF data reported to the sponsor. The sponsor should not have exclusive control of those data.

When a copy is used to replace an original document (e.g., source documents, CRF), the copy should fulfill the requirements for certified copies.

The investigator/institution should have control of all essential documents and records generated by the investigator/institution before, during, and after the trial.

8.2 Before the Clinical Phase of the Trial Commences

During this planning stage the following documents should be generated and should be on file before the trial formally starts

	Title of Document	Purpose	Located in Files of Investigator/ Institution	Sponsor
8.2.1	**INVESTIGATOR'S BROCHURE**	To document that relevant and current scientific information about the investigational product has been provided to the investigator	X	X
8.2.2	**SIGNED PROTOCOL AND AMENDMENTS, IF ANY, AND SAMPLE CASE REPORT FORM (CRF)**	To document investigator and sponsor agreement to the protocol/ amendment(s) and CRF	X	X
8.2.3	**INFORMATION GIVEN TO TRIAL SUBJECT- INFORMED CONSENT FORM(including all applicable translations)**	To document the informed consent	X	X
	- ANY OTHER WRITTEN INFORMATION	To document that subjects will be given appropriate written information (content and wording) to support their ability to give fully informed consent	X	X
	- ADVERTISEMENT FOR SUBJECT RECRUITMENT (if used)	To document that recruitment measures are appropriate and not coercive	X	
8.2.4	**FINANCIAL ASPECTS OF THE TRIAL**	To document the financial agreement between the investigator/institution and the sponsor for the trial	X	X

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.2.5	**INSURANCE STATEMENT(where required)**	To document that compensation to subject(s) for trial-related injury will be available	X	X
8.2.6	**SIGNED AGREEMENT BETWEEN INVOLVED PARTIES, e.g.:**	To document agreements		
	- investigator/institution and sponsor		X	X
	- investigator/institution and CRO		X	X (where required)
	- sponsor and CRO			X
	- investigator/institution and authority(ies) (where required)		X	X

	Title of Document	Purpose	Located in Files of Investigator/ Institution	Sponsor
8.2.7	**DATED, DOCUMENTED APPROVAL/FAVOURABLE OPINION OF INSTITUTIONAL REVIEW BOARD (IRB) /INDEPENDENT ETHICS COMMITTEE (IEC) OF THE FOLLOWING:** - protocol and any amendments - CRF (if applicable) - informed consent form(s) - any other written information to be provided to the subject(s) - advertisement for subject recruitment	To document that the trial has been subject toIRB/IEC review and given approval/favourable opinion. To identify the version number and date of the document(s)	X	X
8.2.8	**INSTITUTIONAL REVIEW BOARD/ INDEPENDENT ETHICS COMMITTEE COMPOSITION**	To document that the IRB/IEC is constituted in agreement with GCP	X	X (where required)
8.2.9	**REGULATORY AUTHORITY(IES) AUTHORISATION/APPROVAL/NOTIFICATION OF PROTOCOL** (where required)	To document appropriate authorisation/ approval/notification by the regulatory authority(ies) has been obtained prior to initiation of the trial in compliance with the applicable regulatory requirement(s)	X (where required)	X (where required)

	Title of Document	Purpose	Located in Files of Investigator/ Institution	Sponsor
8.2.10	**CURRICULUM VITAE AND/OR OTHER RELEVANT DOCUMENTS EVIDENCING QUALIFICATIONS OF INVESTIGATOR(S) AND SUB-INVESTIGATOR(S)**	To document qualifications and eligibility to conduct trial and/or provide medical supervision of subjects	X	X
8.2.11	**NORMAL VALUE(S)/ RANGE(S) FOR MEDICAL/ LABORATORY/TECHNICAL PROCEDURE(S) AND/OR TEST(S) INCLUDED IN THE PROTOCOL**	To document normal values and/or ranges of the tests		X
8.2.12	**MEDICAL/LABORATORY/TECHNICAL PROCEDURES / TESTS** - certification or - accreditation or - established quality control and/or external quality assessment or - other validation (where required)	To document competence of facility to perform required test(s), and support reliability of results	X (where required)	X
8.2.13	**SAMPLE OF LABEL(S) ATTACHED TO INVESTIGATIONAL PRODUCT CONTAINER(S)**	To document compliance with applicable labelling regulations and appropriateness of instructions provided to the subjects		X

	Title of Document	Purpose	Located in Files of Investigator/ Institution	Sponsor
8.2.14	**INSTRUCTIONS FOR HANDLING OF INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS** (if not included in protocol or Investigator's Brochure)	To document instructions needed to ensure proper storage, packaging, dispensing and disposition of investigational products and trial-related materials	X	X
8.2.15	**SHIPPING RECORDS FOR INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS**	To document shipment dates, batch numbers and method of shipment of investigational product(s) and trial-related materials. Allows tracking of product batch, review of shipping conditions, and accountability	X	X
8.2.16	**CERTIFICATE(S) OF ANALYSIS OF INVESTIGATIONAL PRODUCT(S) SHIPPED**	To document identity, purity, and strength of investigational product(s) to be used in the trial		X
8.2.17	**DECODING PROCEDURES FOR BLINDED TRIALS**	To document how, in case of an emergency, identity of blinded investigational product can be revealed without breaking the blind for the remaining subjects' treatment	X	X (third party if applicable)
8.2.18	**MASTER RANDOMISATION LIST**	To document method for randomisation of trial population		X (third party if applicable)

	Title of Document	Purpose	Located in Files of Investigator/ Institution	Sponsor
8.2.19	**PRE-TRIAL MONITORING REPORT**	To document that the site is suitable for the trial (may be combined with 8.2.20)	X	
8.2.20	**TRIAL INITIATION MONITORING REPORT**	To document that trial procedures were reviewed with the investigator and the investigator's trial staff (may be combined with 8.2.19)	X	X

8.3 During the Clinical Conduct of the Trial

In addition to having on file the above documents, the following should be added to the files during the trial as evidence that all new relevant information is documented as it becomes available

	Title of Document	Purpose	Located in Files of Investigator/ Institution	Sponsor
8.3.1	**INVESTIGATOR'S BROCHURE UPDATES**	To document that investigator is informed in a timely manner of relevant information as it becomes available	X	X
8.3.2	**ANY REVISION TO:** - protocol/ amendment(s) and CRF - informed consent form - any other written information provided to subjects - advertisement for subject recruitment (if used)	To document revisions of these trial related documents that take effect during trial	X	X

	Title of Document	Purpose	Located in Files of Investigator/ Institution	Sponsor
8.3.3	**DATED, DOCUMENTED APPROVAL/FAVOURABLE OPINION OF INSTITUTIONAL REVIEW BOARD (IRB) /INDEPENDENT ETHICS COMMITTEE (IEC) OF THE FOLLOWING:** - protocol amendment(s) - revision(s) of: - informed consent form - any other written information to be provided to the subject - advertisement for subject recruitment (if used) - any other documents given approval/favourable opinion - continuing review of trial (where required)	To document that the amendment(s) and/or revision(s) have been subject to IRB/IEC review and were given approval/favourable opinion. To identify the version number and date of the document(s).	X	X
8.3.4	**REGULATORY AUTHORITY(IES) AUTHORISATIONS/APPROVALS/NOTIFICATIONS WHERE REQUIRED FOR:** - protocol amendment(s) and other documents	To document compliance with applicable regulatory requirements	X (where required)	X
8.3.5	**CURRICULUM VITAE FOR NEW INVESTIGATOR(S) AND/OR SUB-INVESTIGATOR(S)**	(see 8.2.10)	X	X

	Title of Document	Purpose	Located in Files of Investigator/ Institution	Sponsor
8.3.6	**UPDATES TO NORMAL VALUE(S)/ RANGE(S) FOR MEDICAL/ LABORATORY/ TECHNICAL PROCEDURE(S)/ TEST(S) INCLUDED IN THE PROTOCOL**	To document normal values and ranges that are revised during the trial (see 8.2.11)	X	X
8.3.7	**UPDATES OF MEDICAL/LABORATORY/ TECHNICAL PROCEDURES/TESTS** - certification or - accreditation or - established quality control and/or external quality assessment or - other validation (where required)	To document that tests remain adequate throughout the trial period (see 8.2.12)	X (where required)	X
8.3.8	**DOCUMENTATION OF INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS SHIPMENT**	(see 8.2.15)	X	X
8.3.9	**CERTIFICATE(S) OF ANALYSIS FOR NEW BATCHES OF INVESTIGATIONAL PRODUCTS**	(see 8.2.16)		X
8.3.10	**MONITORING VISIT REPORTS**	To document site visits by, and findings of, the monitor		X

	Title of Document	Purpose	Located in Files of Investigator/ Institution	Sponsor
8.3.11	**RELEVANT COMMUNICATIONS OTHER THAN SITE VISITS** - letters - meeting notes - notes of telephone calls	To document any agreements or significant discussions regarding trial administration, protocol violations, trial conduct, adverse event (AE) reporting	X	X
8.3.12	**SIGNED INFORMED CONSENT FORMS**	To document that consent is obtained in accordance with GCP and protocol and dated prior to participation of each subject in trial. Also to document direct access permission (see 8.2.3)	X	
8.3.13	**SOURCE DOCUMENTS**	To document the existence of the subject and substantiate integrity of trial data collected. To include original documents related to the trial, to medical treatment, and history of subject	X	
8.3.14	**SIGNED, DATED AND COMPLETED CASE REPORT FORMS (CRF)**	To document that the investigator or authorised member of the investigator's staff confirms the observations recorded	X (copy)	X (original)
8.3.15	**DOCUMENTATION OF CRF CORRECTIONS**	To document all changes/additions or corrections made to CRF after initial data were recorded	X (copy)	X (original)

	Title of Document	Purpose	Located in Files of Investigator/ Institution	Sponsor
8.3.16	**NOTIFICATION BY ORIGINATING INVESTIGATOR TO SPONSOR OF SERIOUS ADVERSE EVENTS AND RELATED REPORTS**	Notification by originating investigator to sponsor of serious adverse events and related reports in accordance with 4.11	X	X
8.3.17	**NOTIFICATION BY SPONSOR AND/ OR INVESTIGATOR, WHERE APPLICABLE, TO REGULATORY AUTHORITY(IES) AND IRB(S)/IEC(S) OF UNEXPECTED SERIOUS ADVERSE DRUG REACTIONS AND OF OTHER SAFETY INFORMATION**	Notification by sponsor and/or investigator, where applicable, to regulatory authorities and IRB(s)/ IEC(s) of unexpected serious adverse drug reactions in accordance with 5.17 and 4.11.1 and of other safety information in accordance with 5.16.2 and 4.11.2	X (where required)	X
8.3.18	**NOTIFICATION BY SPONSOR TO INVESTIGATORS OF SAFETY INFORMATION**	Notification by sponsor to investigators of safety information in accordance with 5.16.2	X	X
8.3.19	**INTERIM OR ANNUAL REPORTS TO IRB/IEC AND AUTHORITY(IES)**	Interim or annual reports provided to IRB/IEC in accordance with 4.10 and to authority(ies) in accordance with 5.17.3	X	X (where required)
8.3.20	**SUBJECT SCREENING LOG**	To document identification of subjects who entered pre-trial screening	X	X (where required)

	Title of Document	Purpose	Located in Files of Investigator/ Institution	Sponsor
8.3.21	**SUBJECT IDENTIFICATION CODE LIST**	To document that investigator/institution keeps a confidential list of names of all subjects allocated to trial numbers on enrolling in the trial. Allows investigator/ institution to reveal identity of any subject	X	
8.3.22	**SUBJECT ENROLMENT LOG**	To document chronological enrolment of subjects by trial number	X	
8.3.23	**INVESTIGATIONAL PRODUCTS ACCOUNTABILITY AT THE SITE**	To document that investigational product(s) have been used according to the protocol	X	X
8.3.24	**SIGNATURE SHEET**	To document signatures and initials of all persons authorised to make entries and/or corrections on CRFs	X	X
8.3.25	**RECORD OF RETAINED BODY FLUIDS/ TISSUE SAMPLES (IF ANY)**	To document location and identification of retained samples if assays need to be repeated	X	X

8.4 After Completion or Termination of the Trial

After completion or termination of the trial, all of the documents identified in Sections 8.2 and 8.3 should be in the file together with the following

	Title of Document	Purpose	Located in Files of Investigator/ Institution	Sponsor
8.4.1	**INVESTIGATIONAL PRODUCT(S) ACCOUNTABILITY AT SITE**	To document that the investigational product(s) have been used according to the protocol. To documents the final accounting of investigational product(s) received at the site, dispensed to subjects, returned by the subjects, and returned to sponsor	X	X
8.4.2	**DOCUMENTATION OF INVESTIGATIONAL PRODUCT DESTRUCTION**	To document destruction of unused investigational products by sponsor or at site	X (if destroyed at site)	X
8.4.3	**COMPLETED SUBJECT IDENTIFICATION CODE LIST**	To permit identification of all subjects enrolled in the trial in case follow-up is required. List should be kept in a confidential manner and for agreed upon time	X	
8.4.4	**AUDIT CERTIFICATE (if available)**	To document that audit was performed		X

	Title of Document	Purpose	Located in Files of Investigator/ Institution	Sponsor
8.4.5	**FINAL TRIAL CLOSE-OUT MONITORING REPORT**	To document that all activities required for trial close-out are completed, and copies of essential documents are held in the appropriate files		X
8.4.6	**TREATMENT ALLOCATION AND DECODING DOCUMENTATION**	Returned to sponsor to document any decoding that may have occurred		X
8.4.7	**FINAL REPORT BY INVESTIGATOR TO IRB/IEC WHERE REQUIRED, AND WHERE APPLICABLE, TO THE REGULATORY AUTHORITY(IES)**	To document completion of the trial	X	
8.4.8	**CLINICAL STUDY REPORT**	To document results and interpretation of trial	X (if applicable)	X

APPENDIX G

Title 21—Food and Drugs

Chapter 1—Food and Drug Administration, Department of Health and Human Services

SUBCHAPTER A—GENERAL

PART 11—ELECTRONIC RECORDS; ELECTRONIC SIGNATURES

Authority: 21 U.S.C. 321-393; 42 U.S.C. 262.
Source: 62 FR 13464, Mar. 20, 1997, unless otherwise noted.

(a) The regulations in this part set forth the criteria under which the agency considers electronic records, electronic signatures, and handwritten signatures executed to electronic records to be trustworthy, reliable, and generally equivalent to paper records and handwritten signatures executed on paper.

(b) This part applies to records in electronic form that are created, modified, maintained, archived, retrieved, or transmitted, under any records requirements set forth in agency regulations. This part also applies to electronic records submitted to the agency under requirements of the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act, even if such records are not specifically identified in agency regulations. However, this part does not apply to paper records that are, or have been, transmitted by electronic means.

(c) Where electronic signatures and their associated electronic records meet the requirements of this part, the agency will consider the electronic signatures to be equivalent to full handwritten signatures, initials, and other general signings as required by agency regulations, unless specifically excepted by regulation(s) effective on or after August 20, 1997.

(d) Electronic records that meet the requirements of this part may be used in lieu of paper records, in accordance with § 11.2, unless paper records are specifically required.

(e) Computer systems (including hardware and software), controls, and attendant documentation maintained under this part shall be readily available for, and subject to, FDA inspection.

(f) This part does not apply to records required to be established or maintained by §§ 1.326 through 1.368 of this chapter. Records that satisfy the requirements of part 1, subpart J of this chapter, but that also are required under other applicable statutory provisions or regulations, remain subject to this part.

(g) This part does not apply to electronic signatures obtained under § 101.11(d) of this chapter.

(h) This part does not apply to electronic signatures obtained under § 101.8(d) of this chapter.

(i) This part does not apply to records required to be established or maintained by part 117 of this chapter. Records that satisfy the requirements of part 117 of this chapter, but that also are required under other applicable statutory provisions or regulations, remain subject to this part.

(j) This part does not apply to records required to be established or maintained by part 507 of this chapter. Records that satisfy the requirements of part 507 of this chapter, but that also are required under other applicable statutory provisions or regulations, remain subject to this part.

(k) This part does not apply to records required to be established or maintained by part 112 of this chapter. Records that satisfy the requirements of part 112 of this chapter, but that also are required under other applicable statutory provisions or regulations, remain subject to this part.

(l) This part does not apply to records required to be established or maintained by subpart L of part 1 of this chapter. Records that satisfy the requirements of subpart L of part 1 of this chapter, but that also are required under other applicable statutory provisions or regulations, remain subject to this part.

(m) This part does not apply to records required to be established or maintained by subpart M of part 1 of this chapter. Records that satisfy the requirements of subpart M of part 1 of this chapter, but that also are required under other applicable statutory provisions or regulations, remain subject to this part.

(n) This part does not apply to records required to be established or maintained by subpart O of part 1 of this chapter. Records that satisfy the requirements of subpart O of part 1 of this chapter, but that also are required under other applicable statutory provisions or regulations, remain subject to this part.

(o) This part does not apply to records required to be established or maintained by part 121 of this chapter. Records that satisfy the requirements of part 121 of this chapter, but that also are required under other applicable statutory provisions or regulations, remain subject to this part.

[62 FR 13464, Mar. 20, 1997, as amended at 69 FR 71655, Dec. 9, 2004; 79 FR 71253, 71291, Dec. 1, 2014; 80 FR 71253, June 19, 2015; 80 FR 56144, 56336, Sept. 17, 2015; 80 FR 74352, 74547, 74667, Nov. 27, 2015; 81 FR 20170, Apr. 6, 2016; 81 FR 34218, May 27, 2016]

§ 11.2 Implementation.

(a) For records required to be maintained but not submitted to the agency, persons may use electronic records in lieu of paper records or electronic signatures in lieu of traditional signatures, in whole or in part, provided that the requirements of this part are met.

(b) For records submitted to the agency, persons may use electronic records in lieu of paper records or electronic signatures in lieu of traditional signatures, in whole or in part, provided that:

(1) The requirements of this part are met; and

(2) The document or parts of a document to be submitted have been identified in public docket No. 92S-0251 as being the type of submission the agency accepts in electronic form. This docket will identify specifically what types of documents or parts of documents are acceptable for submission in electronic form without paper records and the agency receiving unit(s) (e.g., specific center, office, division, branch) to which such submissions may be made. Documents to agency receiving unit(s) not specified in the public docket will not be considered as official if they are submitted in electronic

form; paper forms of such documents will be considered as official and must accompany any electronic records. Persons are expected to consult with the intended agency receiving unit for details on how (e.g., method of transmission, media, file formats, and technical protocols) and whether to proceed with the electronic submission.

§11.3 Definitions.

(a) The definitions and interpretations of terms contained in section 201 of the act apply to those terms when used in this part.

(b) The following definitions of terms also apply to this part:

(1) *Act* means the Federal Food, Drug, and Cosmetic Act (secs. 201-903 (21 U.S.C. 321-393)).

(2) *Agency* means the Food and Drug Administration.

(3) *Biometrics* means a method of verifying an individual's identity based on measurement of the individual's physical feature(s) or repeatable action(s) where those features and/or actions are both unique to that individual and measurable.

(4) *Closed system* means an environment in which system access is controlled by persons who are responsible for the content of electronic records that are on the system.

(5) *Digital signature* means an electronic signature based upon cryptographic methods of originator authentication, computed by using a set of rules and a set of parameters such that the identity of the signer and the integrity of the data can be verified.

(6) *Electronic record* means any combination of text, graphics, data, audio, pictorial, or other information representation in digital form that is created, modified, maintained, archived, retrieved, or distributed by a computer system.

(7) *Electronic signature* means a computer data compilation of any symbol or series of symbols executed, adopted, or authorized by an individual to be the legally binding equivalent of the individual's handwritten signature.

(8) *Handwritten signature* means the scripted name or legal mark of an individual handwritten by that individual and executed or adopted with the present intention to authenticate a writing in a permanent form. The act of signing with a writing or marking instrument such as a pen or stylus is preserved. The scripted name or legal mark, while conventionally applied to paper, may also be applied to other devices that capture the name or mark.

(9) *Open system* means an environment in which system access is not controlled by persons who are responsible for the content of electronic records that are on the system.

Subpart B—Electronic Records

§11.10 Controls for closed systems.

Persons who use closed systems to create, modify, maintain, or transmit electronic records shall employ procedures and controls designed to ensure the authenticity, integrity, and, when appropriate, the confidentiality of electronic records, and to ensure that the signer cannot readily repudiate the signed record as not genuine. Such procedures and controls shall include the following:

(a) Validation of systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records.

(b) The ability to generate accurate and complete copies of records in both human readable and electronic form suitable for inspection, review, and copying by the agency. Persons should contact the agency if there are any questions regarding the ability of the agency to perform such review and copying of the electronic records.

(c) Protection of records to enable their accurate and ready retrieval throughout the records retention period.

(d) Limiting system access to authorized individuals.

(e) Use of secure, computer-generated, time-stamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records. Record changes shall not obscure previously recorded information. Such audit trail documentation shall be retained for a period at least as long as that required for the subject electronic records and shall be available for agency review and copying.

(f) Use of operational system checks to enforce permitted sequencing of steps and events, as appropriate.

(g) Use of authority checks to ensure that only authorized individuals can use the system, electronically sign a record, access the operation or computer system input or output device, alter a record, or perform the operation at hand.

(h) Use of device (e.g., terminal) checks to determine, as appropriate, the validity of the source of data input or operational instruction.

(i) Determination that persons who develop, maintain, or use electronic record/electronic signature systems have the education, training, and experience to perform their assigned tasks.

(j) The establishment of, and adherence to, written policies that hold individuals accountable and responsible for actions initiated under their electronic signatures, in order to deter record and signature falsification.

(k) Use of appropriate controls over systems documentation including:

(1) Adequate controls over the distribution of, access to, and use of documentation for system operation and maintenance.

(2) Revision and change control procedures to maintain an audit trail that documents time-sequenced development and modification of systems documentation.

§11.30 Controls for open systems.

Persons who use open systems to create, modify, maintain, or transmit electronic records shall employ procedures and controls designed to ensure the authenticity, integrity, and, as appropriate, the confidentiality of electronic records from the point of their creation to the point of their receipt. Such procedures and controls shall include those identified in §11.10, as appropriate, and additional measures such as document encryption and use of appropriate digital signature standards to ensure, as necessary under the circumstances, record authenticity, integrity, and confidentiality.

§11.50 Signature manifestations.

(a) Signed electronic records shall contain information associated with the signing that clearly indicates all of the following:

(1) The printed name of the signer;

(2) The date and time when the signature was executed; and

(3) The meaning (such as review, approval, responsibility, or authorship) associated with the signature.

(b) The items identified in paragraphs (a)(1), (a)(2), and (a)(3) of this section shall be subject to the same controls as for electronic records and shall be included as part of any human readable form of the electronic record (such as electronic display or printout).

§ 11.70 Signature/record linking.

Electronic signatures and handwritten signatures executed to electronic records shall be linked to their respective electronic records to ensure that the signatures cannot be excised, copied, or otherwise transferred to falsify an electronic record by ordinary means.

Subpart C—Electronic Signatures

§ 11.100 General requirements.

(a) Each electronic signature shall be unique to one individual and shall not be reused by, or reassigned to, anyone else.

(b) Before an organization establishes, assigns, certifies, or otherwise sanctions an individual's electronic signature, or any element of such electronic signature, the organization shall verify the identity of the individual.

(c) Persons using electronic signatures shall, prior to or at the time of such use, certify to the agency that the electronic signatures in their system, used on or after August 20, 1997, are intended to be the legally binding equivalent of traditional handwritten signatures.

(1) The certification shall be submitted in paper form and signed with a traditional handwritten signature, to the Office of Regional Operations (HFC-100), 5600 Fishers Lane, Rockville, MD 20857.

(2) Persons using electronic signatures shall, upon agency request, provide additional certification or testimony that a specific electronic signature is the legally binding equivalent of the signer's handwritten signature.

§ 11.200 Electronic signature components and controls.

(a) Electronic signatures that are not based upon biometrics shall:

(1) Employ at least two distinct identification components such as an identification code and password.

(i) When an individual executes a series of signings during a single, continuous period of controlled system access, the first signing shall be executed using all electronic signature components; subsequent signings shall be executed using at least one electronic signature component that is only executable by, and designed to be used only by, the individual.

(ii) When an individual executes one or more signings not performed during a single, continuous period of controlled system access, each signing shall be executed using all of the electronic signature components.

(2) Be used only by their genuine owners; and

(3) Be administered and executed to ensure that attempted use of an individual's electronic signature by anyone other than its genuine owner requires collaboration of two or more individuals.

(b) Electronic signatures based upon biometrics shall be designed to ensure that they cannot be used by anyone other than their genuine owners.

§ 11.300 Controls for identification codes/passwords.

Persons who use electronic signatures based upon use of identification codes in combination with passwords shall employ controls to ensure their security and integrity. Such controls shall include:

(a) Maintaining the uniqueness of each combined identification code and password, such that no two individuals have the same combination of identification code and password.

(b) Ensuring that identification code and password issuances are periodically checked, recalled, or revised (e.g., to cover such events as password aging).

(c) Following loss management procedures to electronically deauthorize lost, stolen, missing, or otherwise potentially compromised tokens, cards, and other devices that bear or generate identification code or password information, and to issue temporary or permanent replacements using suitable, rigorous controls.

(d) Use of transaction safeguards to prevent unauthorized use of passwords and/or identification codes, and to detect and report in an immediate and urgent manner any attempts at their unauthorized use to the system security unit, and, as appropriate, to organizational management.

(e) Initial and periodic testing of devices, such as tokens or cards, that bear or generate identification code or password information to ensure that they function properly and have not been altered in an unauthorized manner.

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PART 50—PROTECTION OF HUMAN SUBJECTS

Authority: 21 U.S.C 321, 343, 346, 346a, 348, 350a, 350b, 352, 353, 355, 360, 360c-360f, 360h-360j, 371, 379e, 381; 42 U.S.C. 216, 241, 262, 263b-263n.
Source: 45 FR 36390, May 30, 1980, unless otherwise noted.

Subpart A—General Provisions

§ 50.1 Scope.

(a) This part applies to all clinical investigations regulated by the Food and Drug Administration under sections 505(i) and 520(g) of the Federal Food, Drug, and Cosmetic Act, as well as clinical investigations that support applications for research or marketing permits for products regulated by the Food and Drug Administration, including foods, including dietary supplements, that bear a nutrient content claim or a health claim, infant formulas, food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products. Additional specific obligations and commitments of, and standards of conduct for, persons who sponsor or monitor clinical investigations involving particular test articles may also be found in other parts (e.g., parts 312 and 812). Compliance with these parts is intended to protect the rights and safety of subjects involved in investigations filed with the Food and Drug Administration pursuant to sections 403, 406, 409, 412, 413, 502, 503, 505, 510, 513-516, 518-520, 721, and 801 of the Federal Food, Drug, and Cosmetic Act and sections 351 and 354-360F of the Public Health Service Act.

(b) References in this part to regulatory sections of the Code of Federal Regulations are to chapter I of title 21, unless otherwise noted.

[45 FR 36390, May 30, 1980; 46 FR 8979, Jan. 27, 1981, as amended at 63 FR 26697, May 13, 1998; 64 FR 399, Jan. 5, 1999; 66 FR 20597, Apr. 24, 2001]

§ 50.3 Definitions.

As used in this part:

(a) *Act* means the Federal Food, Drug, and Cosmetic Act, as amended (secs. 201-902, 52 Stat. 1040 et seq. as amended (21 U.S.C. 321-392)).

(b) *Application for research or marketing permit* includes:

(1) A color additive petition, described in part 71.

(2) A food additive petition, described in parts 171 and 571.

(3) Data and information about a substance submitted as part of the procedures for establishing that the substance is generally recognized as safe for use that results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food, described in §§ 170.30 and 570.30.

(4) Data and information about a food additive submitted as part of the procedures for food additives permitted to be used on an interim basis pending additional study, described in § 180.1.

(5) Data and information about a substance submitted as part of the procedures for establishing a tolerance for unavoidable contaminants in food and food-packaging materials, described in section 406 of the act.

(6) An investigational new drug application, described in part 312 of this chapter.

(7) A new drug application, described in part 314.

(8) Data and information about the bioavailability or bioequivalence of drugs for human use submitted as part of the procedures for issuing, amending, or repealing a bioequivalence requirement, described in part 320.

(9) Data and information about an over-the-counter drug for human use submitted as part of the procedures for classifying these drugs as generally recognized as safe and effective and not misbranded, described in part 330.

(10) Data and information about a prescription drug for human use submitted as part of the procedures for classifying these drugs as generally recognized as safe and effective and not misbranded, described in this chapter.

(11) [Reserved]

(12) An application for a biologics license, described in part 601 of this chapter.

(13) Data and information about a biological product submitted as part of the procedures for determining that licensed biological products are safe and effective and not misbranded, described in part 601.

(14) Data and information about an in vitro diagnostic product submitted as part of the procedures for establishing, amending, or repealing a standard for these products, described in part 809.

(15) *An Application for an Investigational Device Exemption*, described in part 812.

(16) Data and information about a medical device submitted as part of the procedures for classifying these devices, described in section 513.

(17) Data and information about a medical device submitted as part of the procedures for establishing, amending, or repealing a standard for these devices, described in section 514.

(18) An application for premarket approval of a medical device, described in section 515.

(19) A product development protocol for a medical device, described in section 515.

(20) Data and information about an electronic product submitted as part of the procedures for establishing, amending, or repealing a standard for these products, described in section 358 of the Public Health Service Act.

(21) Data and information about an electronic product submitted as part of the procedures for obtaining a variance from any electronic product performance standard, as described in § 1010.4.

(22) Data and information about an electronic product submitted as part of the procedures for granting, amending, or extending an exemption from a radiation safety performance standard, as described in § 1010.5.

(23) Data and information about a clinical study of an infant formula when submitted as part of an infant formula notification under section 412(c) of the Federal Food, Drug, and Cosmetic Act.

(24) Data and information submitted in a petition for a nutrient content claim, described in § 101.69 of this chapter, or for a health claim, described in § 101.70 of this chapter.

(25) Data and information from investigations involving children submitted in a new dietary ingredient notification, described in § 190.6 of this chapter.

(c) *Clinical investigation* means any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that are subject to the provisions of part 58 of this chapter, regarding nonclinical laboratory studies.

(d) *Investigator* means an individual who actually conducts a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject, or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team.

(e) *Sponsor* means a person who initiates a clinical investigation, but who does not actually conduct the investigation, i.e., the test article is administered or dispensed to or used involving, a subject under the immediate direction of another individual. A person other than an individual (e.g., corporation or agency) that uses one or more of its own employees to conduct a clinical investigation it has initiated is considered to be a sponsor (not a sponsor-investigator), and the employees are considered to be investigators.

(f) *Sponsor-investigator* means an individual who both initiates and actually conducts, alone or with others, a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject. The term does not include any person other than an individual, e.g., corporation or agency.

(g) *Human subject* means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient.

(h) *Institution* means any public or private entity or agency (including Federal, State, and other agencies). The word facility as used in section 520(g) of the act is deemed to be synonymous with the term *institution* for purposes of this part.

(i) *Institutional review board* (IRB) means any board, committee, or other group formally designated by an institution to review biomedical research involving humans as subjects, to approve the initiation of and conduct periodic review of such research. The term has the same meaning as the phrase *institutional review committee* as used in section 520(g) of the act.

(j) *Test article* means any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 and 354-360F of the Public Health Service Act (42 U.S.C. 262 and 263b-263n).

(k) *Minimal risk* means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

(l) *Legally authorized representative* means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's particpation in the procedure(s) involved in the research.

(m) *Family member* means any one of the following legally competent persons: Spouse; parents; children (including adopted children); brothers, sisters, and spouses of brothers and sisters; and any

individual related by blood or affinity whose close association with the subject is the equivalent of a family relationship.

(n) *Assent* means a child's affirmative agreement to participate in a clinical investigation. Mere failure to object should not, absent affirmative agreement, be construed as assent.

(o) *Children* means persons who have not attained the legal age for consent to treatments or procedures involved in clinical investigations, under the applicable law of the jurisdiction in which the clinical investigation will be conducted.

(p) *Parent* means a child's biological or adoptive parent.

(q) *Ward* means a child who is placed in the legal custody of the State or other agency, institution, or entity, consistent with applicable Federal, State, or local law.

(r) *Permission* means the agreement of parent(s) or guardian to the participation of their child or ward in a clinical investigation.

(s) *Guardian* means an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care.

[45 FR 36390, May 30, 1980, as amended at 46 FR 8950, Jan. 27, 1981; 54 FR 9038, Mar. 3, 1989; 56 FR 28028, June 18, 1991; 61 FR 51528, Oct. 2, 1996; 62 FR 39440, July 23, 1997; 64 FR 399, Jan. 5, 1999; 64 FR 56448, Oct. 20, 1999; 66 FR 20597, Apr. 24, 2001; 78 FR 12950, Feb. 26, 2013]

Subpart B—Informed Consent of Human Subjects

Source: 46 FR 8951, Jan. 27, 1981, unless otherwise noted.

Except as provided in §§ 50.23 and 50.24, no investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

[46 FR 8951, Jan. 27, 1981, as amended at 64 FR 10942, Mar. 8, 1999]

§ 50.23 Exception from general requirements.

(a) The obtaining of informed consent shall be deemed feasible unless, before use of the test article (except as provided in paragraph (b) of this section), both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following:

(1) The human subject is confronted by a life-threatening situation necessitating the use of the test article.

(2) Informed consent cannot be obtained from the subject because of an inability to communicate with, or obtain legally effective consent from, the subject.

(3) Time is not sufficient to obtain consent from the subject's legal representative.

(4) There is available no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject.

(b) If immediate use of the test article is, in the investigator's opinion, required to preserve the life of the subject, and time is not sufficient to obtain the independent determination required in paragraph (a) of this section in advance of using the test article, the determinations of the clinical investigator shall be made and, within 5 working days after the use of the article, be reviewed and evaluated in writing by a physician who is not participating in the clinical investigation.

(c) The documentation required in paragraph (a) or (b) of this section shall be submitted to the IRB within 5 working days after the use of the test article.

(d)(1) Under 10 U.S.C. 1107(f) the President may waive the prior consent requirement for the administration of an investigational new drug to a member of the armed forces in connection with the member's participation in a particular military operation. The statute specifies that only the President may waive informed consent in this connection and the President may grant such a waiver only if the President determines in writing that obtaining consent: Is not feasible; is contrary to the best interests of the military member; or is not in the interests of national security. The statute further provides that in making a determination to waive prior informed consent on the ground that it is not feasible or the ground that it is contrary to the best interests of the military members involved, the President shall apply the standards and criteria that are set forth in the relevant FDA regulations for a waiver of the prior informed consent requirements of section 505(i)(4) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(i)(4)). Before such a determination may be made that obtaining informed consent from military personnel prior to the use of an investigational drug (including an antibiotic or biological product) in a specific protocol under an investigational new drug application (IND) sponsored by the Department of Defense (DOD) and limited to specific military personnel involved in a particular military operation is not feasible or is contrary to the best interests of the military members involved the Secretary of Defense must first request such a determination from the President, and certify and document to the President that the following standards and criteria contained in paragraphs (d)(1) through (d)(4) of this section have been met.

(i) The extent and strength of evidence of the safety and effectiveness of the investigational new drug in relation to the medical risk that could be encountered during the military operation supports the drug's administration under an IND.

(ii) The military operation presents a substantial risk that military personnel may be subject to a chemical, biological, nuclear, or other exposure likely to produce death or serious or life-threatening injury or illness.

(iii) There is no available satisfactory alternative therapeutic or preventive treatment in relation to the intended use of the investigational new drug.

(iv) Conditioning use of the investigational new drug on the voluntary participation of each member could significantly risk the safety and health of any individual member who would decline its use, the safety of other military personnel, and the accomplishment of the military mission.

(v) A duly constituted institutional review board (IRB) established and operated in accordance with the requirements of paragraphs (d)(2) and (d)(3) of this section, responsible for review of the study, has reviewed and approved the investigational new drug protocol and the administration of the investigational new drug without informed consent. DOD's request is to include the documentation required by § 56.115(a)(2) of this chapter.

(vi) DOD has explained:

(A) The context in which the investigational drug will be administered, e.g., the setting or whether it will be self-administered or it will be administered by a health professional;

(B) The nature of the disease or condition for which the preventive or therapeutic treatment is intended; and

(C) To the extent there are existing data or information available, information on conditions that could alter the effects of the investigational drug.

(vii) DOD's recordkeeping system is capable of tracking and will be used to track the proposed treatment from supplier to the individual recipient.

(viii) Each member involved in the military operation will be given, prior to the administration of the investigational new drug, a specific written information sheet (including information required by 10 U.S.C. 1107(d)) concerning the investigational new drug, the risks and benefits of its use, potential side effects, and other pertinent information about the appropriate use of the product.

(ix) Medical records of members involved in the military operation will accurately document the receipt by members of the notification required by paragraph (d)(1)(viii) of this section.

(x) Medical records of members involved in the military operation will accurately document the receipt by members of any investigational new drugs in accordance with FDA regulations including part 312 of this chapter.

(xi) DOD will provide adequate followup to assess whether there are beneficial or adverse health consequences that result from the use of the investigational product.

(xii) DOD is pursuing drug development, including a time line, and marketing approval with due diligence.

(xiii) FDA has concluded that the investigational new drug protocol may proceed subject to a decision by the President on the informed consent waiver request.

(xiv) DOD will provide training to the appropriate medical personnel and potential recipients on the specific investigational new drug to be administered prior to its use.

(xv) DOD has stated and justified the time period for which the waiver is needed, not to exceed one year, unless separately renewed under these standards and criteria.

(xvi) DOD shall have a continuing obligation to report to the FDA and to the President any changed circumstances relating to these standards and criteria (including the time period referred to in paragraph (d)(1)(xv) of this section) or that otherwise might affect the determination to use an investigational new drug without informed consent.

(xvii) DOD is to provide public notice as soon as practicable and consistent with classification requirements through notice in the Federal Register describing each waiver of informed consent determination, a summary of the most updated scientific information on the products used, and other pertinent information.

(xviii) Use of the investigational drug without informed consent otherwise conforms with applicable law.

(2) The duly constituted institutional review board, described in paragraph (d)(1)(v) of this section, must include at least 3 nonaffiliated members who shall not be employees or officers of the Federal Government (other than for purposes of membership on the IRB) and shall be required to obtain any necessary security clearances. This IRB shall review the proposed IND protocol at a convened meeting at which a majority of the members are present including at least one member whose primary concerns are in nonscientific areas and, if feasible, including a majority of the nonaffiliated members. The information required by § 56.115(a)(2) of this chapter is to be provided to the Secretary of Defense for further review.

(3) The duly constituted institutional review board, described in paragraph (d)(1)(v) of this section, must review and approve:

(i) The required information sheet;

(ii) The adequacy of the plan to disseminate information, including distribution of the information sheet to potential recipients, on the investigational product (e.g., in forms other than written);

(iii) The adequacy of the information and plans for its dissemination to health care providers, including potential side effects, contraindications, potential interactions, and other pertinent considerations; and

(iv) An informed consent form as required by part 50 of this chapter, in those circumstances in which DOD determines that informed consent may be obtained from some or all personnel involved.

(4) DOD is to submit to FDA summaries of institutional review board meetings at which the proposed protocol has been reviewed.

(5) Nothing in these criteria or standards is intended to preempt or limit FDA's and DOD's authority or obligations under applicable statutes and regulations.

(e)(1) Obtaining informed consent for investigational in vitro diagnostic devices used to identify chemical, biological, radiological, or nuclear agents will be deemed feasible unless, before use of the test article, both the investigator (e.g., clinical laboratory director or other responsible individual) and a physician who is not otherwise participating in the clinical investigation make the determinations and later certify in writing all of the following:

(i) The human subject is confronted by a life-threatening situation necessitating the use of the investigational in vitro diagnostic device to identify a chemical, biological, radiological, or nuclear agent that would suggest a terrorism event or other public health emergency.

(ii) Informed consent cannot be obtained from the subject because:

(A) There was no reasonable way for the person directing that the specimen be collected to know, at the time the specimen was collected, that there would be a need to use the investigational in vitro diagnostic device on that subject's specimen; and

(B) Time is not sufficient to obtain consent from the subject without risking the life of the subject.

(iii) Time is not sufficient to obtain consent from the subject's legally authorized representative.

(iv) There is no cleared or approved available alternative method of diagnosis, to identify the chemical, biological, radiological, or nuclear agent that provides an equal or greater likelihood of saving the life of the subject.

(2) If use of the investigational device is, in the opinion of the investigator (e.g., clinical laboratory director or other responsible person), required to preserve the life of the subject, and time is not sufficient to obtain the independent determination required in paragraph (e)(1) of this section in advance of using the investigational device, the determinations of the investigator shall be made and, within 5 working days after the use of the device, be reviewed and evaluated in writing by a physician who is not participating in the clinical investigation.

(3) The investigator must submit the written certification of the determinations made by the investigator and an independent physician required in paragraph (e)(1) or (e)(2) of this section to the IRB and FDA within 5 working days after the use of the device.

(4) An investigator must disclose the investigational status of the in vitro diagnostic device and what is known about the performance characteristics of the device in the report to the subject's health care provider and in any report to public health authorities. The investigator must provide the IRB with the information required in § 50.25 (except for the information described in § 50.25(a)(8)) and the procedures that will be used to provide this information to each subject or the subject's legally authorized representative at the time the test results are provided to the subject's health care provider and public health authorities.

(5) The IRB is responsible for ensuring the adequacy of the information required in section 50.25 (except for the information described in § 50.25(a)(8)) and for ensuring that procedures are in place to provide this information to each subject or the subject's legally authorized representative.

(6) No State or political subdivision of a State may establish or continue in effect any law, rule, regulation or other requirement that informed consent be obtained before an investigational in vitro diagnostic device may be used to identify chemical, biological, radiological, or nuclear agent in suspected terrorism events and other potential public health emergencies that is different from, or in addition to, the requirements of this regulation.

[46 FR 8951, Jan. 27, 1981, as amended at 55 FR 52817, Dec. 21, 1990; 64 FR 399, Jan. 5, 1999; 64 FR 54188, Oct. 5, 1999; 71 FR 32833, June 7, 2006; 76 FR 36993, June 24, 2011]

§ 50.24 Exception from informed consent requirements for emergency research.

(a) The IRB responsible for the review, approval, and continuing review of the clinical investigation described in this section may approve that investigation without requiring that informed consent of all research subjects be obtained if the IRB (with the concurrence of a licensed physician who is a member of or consultant to the IRB and who is not otherwise participating in the clinical investigation) finds and documents each of the following:

(1) The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.

(2) Obtaining informed consent is not feasible because:

(i) The subjects will not be able to give their informed consent as a result of their medical condition;

(ii) The intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and

(iii) There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.

(3) Participation in the research holds out the prospect of direct benefit to the subjects because:

(i) Subjects are facing a life-threatening situation that necessitates intervention;

(ii) Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and

(iii) Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.

(4) The clinical investigation could not practicably be carried out without the waiver.

(5) The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review.

(6) The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with § 50.25. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the clinical investigation consistent with paragraph (a)(7)(v) of this section.

(7) Additional protections of the rights and welfare of the subjects will be provided, including, at least:

(i) Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn;

(ii) Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits;

(iii) Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results;

(iv) Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation; and

(v) If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

(b) The IRB is responsible for ensuring that procedures are in place to inform, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, of the subject's inclusion in the clinical investigation, the details of the investigation and other information contained in the informed consent document. The IRB shall also ensure that there is a procedure to inform the subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. If a legally authorized representative or family member is told about the clinical investigation and the subject's condition improves, the subject is also to be informed as soon as feasible. If a subject is entered into a clinical investigation with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the clinical investigation is to be provided to the subject's legally authorized representative or family member, if feasible.

(c) The IRB determinations required by paragraph (a) of this section and the documentation required by paragraph (e) of this section are to be retained by the IRB for at least 3 years after completion of the clinical investigation, and the records shall be accessible for inspection and copying by FDA in accordance with § 56.115(b) of this chapter.

(d) Protocols involving an exception to the informed consent requirement under this section must be performed under a separate investigational new drug application (IND) or investigational device exemption (IDE) that clearly identifies such protocols as protocols that may include subjects who are unable to consent. The submission of those protocols in a separate IND/IDE is required even if an IND for the same drug product or an IDE for the same device already exists. Applications for investigations under this section may not be submitted as amendments under §§ 312.30 or 812.35 of this chapter.

(e) If an IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception provided under paragraph (a) of this section or because of other relevant ethical concerns, the IRB must document its findings and provide these findings promptly in writing to the clinical investigator and to the sponsor of the clinical investigation. The

sponsor of the clinical investigation must promptly disclose this information to FDA and to the sponsor's clinical investigators who are participating or are asked to participate in this or a substantially equivalent clinical investigation of the sponsor, and to other IRB's that have been, or are, asked to review this or a substantially equivalent investigation by that sponsor.

[61 FR 51528, Oct. 2, 1996]

§ 50.25 Elements of informed consent.

(a) Basic elements of informed consent. In seeking informed consent, the following information shall be provided to each subject:

(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.

(2) A description of any reasonably foreseeable risks or discomforts to the subject.

(3) A description of any benefits to the subject or to others which may reasonably be expected from the research.

(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.

(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and Drug Administration may inspect the records.

(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.

(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.

(8) A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

(b) *Additional elements of informed consent*. When appropriate, one or more of the following elements of information shall also be provided to each subject:

(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable.

(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.

(3) Any additional costs to the subject that may result from participation in the research.

(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.

(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.

(6) The approximate number of subjects involved in the study.

(c) When seeking informed consent for applicable clinical trials, as defined in 42 U.S.C. 282(j)(1)(A), the following statement shall be provided to each clinical trial subject in informed consent documents and processes. This will notify the clinical trial subject that clinical trial information has been or will be submitted for inclusion in the clinical trial registry databank under paragraph (j) of section 402 of the Public Health Service Act. The statement is: "A description of this clinical trial will be avail-

able on *http://www.ClinicalTrials.gov*, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time."

(d) The informed consent requirements in these regulations are not intended to preempt any applicable Federal, State, or local laws which require additional information to be disclosed for informed consent to be legally effective.

(e) Nothing in these regulations is intended to limit the authority of a physician to provide emergency medical care to the extent the physician is permitted to do so under applicable Federal, State, or local law.

[46 FR 8951, Jan. 27, 1981, as amended at 76 FR 270, Jan. 4, 2011]

§ 50.27 Documentation of informed consent.

(a) Except as provided in § 56.109(c), informed consent shall be documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time of consent. A copy shall be given to the person signing the form.

(b) Except as provided in § 56.109(c), the consent form may be either of the following:

(1) A written consent document that embodies the elements of informed consent required by § 50.25. This form may be read to the subject or the subject's legally authorized representative, but, in any event, the investigator shall give either the subject or the representative adequate opportunity to read it before it is signed.

(2) A *short form* written consent document stating that the elements of informed consent required by § 50.25 have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining the consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative in addition to a copy of the short form.

[46 FR 8951, Jan. 27, 1981, as amended at 61 FR 57280, Nov. 5, 1996]

Subpart C [Reserved]

Subpart D—Additional Safeguards for Children in Clinical Investigations

Source: 66 FR 20598, Apr. 24, 2001, unless otherwise noted.

In addition to other responsibilities assigned to IRBs under this part and part 56 of this chapter, each IRB must review clinical investigations involving children as subjects covered by this subpart D and approve only those clinical investigations that satisfy the criteria described in § 50.51, § 50.52, or § 50.53 and the conditions of all other applicable sections of this subpart D.

§ 50.51 Clinical investigations not involving greater than minimal risk.

Any clinical investigation within the scope described in §§ 50.1 and 56.101 of this chapter in which no greater than minimal risk to children is presented may involve children as subjects only if the IRB finds that:

(a) No greater than minimal risk to children is presented; and

(b) Adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians as set forth in § 50.55.

[78 FR 12951, Feb. 26, 2013]

§ 50.52 Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects.

Any clinical investigation within the scope described in §§ 50.1 and 56.101 of this chapter in which more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, may involve children as subjects only if the IRB finds that:

(a) The risk is justified by the anticipated benefit to the subjects;

(b) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and

(c) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians as set forth in § 50.55.

[66 FR 20598, Apr. 24, 2001, as amended at 78 FR 12951, Feb. 26, 2013]

§ 50.53 Clinical investigations involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subjects' disorder or condition.

Any clinical investigation within the scope described in §§ 50.1 and 56.101 of this chapter in which more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is not likely to contribute to the well-being of the subject, may involve children as subjects only if the IRB finds that:

(a) The risk represents a minor increase over minimal risk;

(b) The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;

(c) The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition that is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and

(d) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians as set forth in § 50.55.

[66 FR 20598, Apr. 24, 2001, as amended at 78 FR 12951, Feb. 26, 2013]

§ 50.54 Clinical investigations not otherwise approvable that present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

If an IRB does not believe that a clinical investigation within the scope described in §§ 50.1 and 56.101 of this chapter and involving children as subjects meets the requirements of § 50.51, § 50.52, or § 50.53, the clinical investigation may proceed only if:

(a) The IRB finds that the clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and

(b) The Commissioner of Food and Drugs, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, determines either:

(1) That the clinical investigation in fact satisfies the conditions of § 50.51, § 50.52, or § 50.53, as applicable, or

(2) That the following conditions are met:

(i) The clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;

(ii) The clinical investigation will be conducted in accordance with sound ethical principles; and

(iii) Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in § 50.55.

[66 FR 20598, Apr. 24, 2001, as amended at 78 FR 12951, Feb. 26, 2013]

§ 50.55 Requirements for permission by parents or guardians and for assent by children.

(a) In addition to the determinations required under other applicable sections of this subpart D, the IRB must determine that adequate provisions are made for soliciting the assent of the children when in the judgment of the IRB the children are capable of providing assent.

(b) In determining whether children are capable of providing assent, the IRB must take into account the ages, maturity, and psychological state of the children involved. This judgment may be made for all children to be involved in clinical investigations under a particular protocol, or for each child, as the IRB deems appropriate.

(c) The assent of the children is not a necessary condition for proceeding with the clinical investigation if the IRB determines:

(1) That the capability of some or all of the children is so limited that they cannot reasonably be consulted, or

(2) That the intervention or procedure involved in the clinical investigation holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the clinical investigation.

(d) Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement if it finds and documents that:

(1) The clinical investigation involves no more than minimal risk to the subjects;

(2) The waiver will not adversely affect the rights and welfare of the subjects;

(3) The clinical investigation could not practicably be carried out without the waiver; and

(4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

(e) In addition to the determinations required under other applicable sections of this subpart D, the IRB must determine, in accordance with and to the extent that consent is required under part 50, that the permission of each child's parents or guardian is granted.

(1) Where parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient for clinical investigations to be conducted under § 50.51 or § 50.52.

(2) Where clinical investigations are covered by § 50.53 or § 50.54 and permission is to be obtained from parents, both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

(f) Permission by parents or guardians must be documented in accordance with and to the extent required by § 50.27.

(g) When the IRB determines that assent is required, it must also determine whether and how assent must be documented.

[66 FR 20598, Apr. 24, 2001, as amended at 78 FR 12951, Feb. 26, 2013]

§ 50.56 Wards.

(a) Children who are wards of the State or any other agency, institution, or entity can be included in clinical investigations approved under § 50.53 or § 50.54 only if such clinical investigations are:

(1) Related to their status as wards; or

(2) Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

(b) If the clinical investigation is approved under paragraph (a) of this section, the IRB must require appointment of an advocate for each child who is a ward.

(1) The advocate will serve in addition to any other individual acting on behalf of the child as guardian or in loco parentis.

(2) One individual may serve as advocate for more than one child.

(3) The advocate must be an individual who has the background and experience to act in, and agrees to act in, the best interest of the child for the duration of the child's participation in the clinical investigation.

(4) The advocate must not be associated in any way (except in the role as advocate or member of the IRB) with the clinical investigation, the investigator(s), or the guardian organization.

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PART 54—FINANCIAL DISCLOSURE BY CLINICAL INVESTIGATORS

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 360, 360c-360j, 371, 372, 373, 374, 375, 376, 379; 42 U.S.C. 262.
Source: 63 FR 5250, Feb. 2, 1998, unless otherwise noted.

(a) The Food and Drug Administration (FDA) evaluates clinical studies submitted in marketing applications, required by law, for new human drugs and biological products and marketing applications and reclassification petitions for medical devices.

(b) The agency reviews data generated in these clinical studies to determine whether the applications are approvable under the statutory requirements. FDA may consider clinical studies inadequate and the data inadequate if, among other things, appropriate steps have not been taken in the design, conduct, reporting, and analysis of the studies to minimize bias. One potential source of bias in clinical studies is a financial interest of the clinical investigator in the outcome of the study because of the way payment is arranged (e.g., a royalty) or because the investigator has a proprietary interest in the product (e.g., a patent) or because the investigator has an equity interest in the sponsor of the covered study. This section and conforming regulations require an applicant whose submission relies in part on clinical data to disclose certain financial arrangements between sponsor(s) of the covered studies and the clinical investigators and certain interests of the clinical investigators in the product under study or in the sponsor of the covered studies. FDA will use this information, in conjunction with information about the design and purpose of the study, as well as information obtained through on-site inspections, in the agency's assessment of the reliability of the data.

§ 54.2 Definitions.

For the purposes of this part:

(a) *Compensation affected by the outcome of clinical studies* means compensation that could be higher for a favorable outcome than for an unfavorable outcome, such as compensation that is explicitly greater for a favorable result or compensation to the investigator in the form of an equity interest in the sponsor of a covered study or in the form of compensation tied to sales of the product, such as a royalty interest.

(b) *Significant equity interest in the sponsor of a covered study* means any ownership interest, stock options, or other financial interest whose value cannot be readily determined through reference to public prices (generally, interests in a nonpublicly traded corporation), or any equity interest in a publicly traded corporation that exceeds $50,000 during the time the clinical investigator is carrying out the study and for 1 year following completion of the study.

(c) *Proprietary interest in the tested product* means property or other financial interest in the product including, but not limited to, a patent, trademark, copyright or licensing agreement.

(d) *Clinical investigator* means only a listed or identified investigator or subinvestigator who is directly involved in the treatment or evaluation of research subjects. The term also includes the spouse and each dependent child of the investigator.

(e) *Covered clinical study* means any study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or any study in which a single investigator makes a significant contribution to the demonstration of safety. This would, in general, not include phase I tolerance studies or pharmacokinetic studies, most clinical pharmacology studies (unless they are critical to an efficacy determination), large open safety studies conducted at multiple sites, treatment protocols, and parallel track protocols. An applicant may consult with FDA as to which clinical studies constitute "covered clinical studies" for purposes of complying with financial disclosure requirements.

(f) *Significant payments* of other sorts means payments made by the sponsor of a covered study to the investigator or the institution to support activities of the investigator that have a monetary value of more than $25,000, exclusive of the costs of conducting the clinical study or other clinical studies, (e.g., a grant to fund ongoing research, compensation in the form of equipment or retainers for ongoing consultation or honoraria) during the time the clinical investigator is carrying out the study and for 1 year following the completion of the study.

(g) *Applicant* means the party who submits a marketing application to FDA for approval of a drug, device, or biologic product. The applicant is responsible for submitting the appropriate certification and disclosure statements required in this part.

(h) *Sponsor of the covered clinical study* means the party supporting a particular study at the time it was carried out.

[63 FR 5250, Feb. 2, 1998, as amended at 63 FR 72181, Dec. 31, 1998]

§ 54.3 Scope.

The requirements in this part apply to any applicant who submits a marketing application for a human drug, biological product, or device and who submits covered clinical studies. The applicant is responsible for making the appropriate certification or disclosure statement where the applicant either contracted with one or more clinical investigators to conduct the studies or submitted studies conducted by others not under contract to the applicant.

§ 54.4 Certification and disclosure requirements.

For purposes of this part, an applicant must submit a list of all clinical investigators who conducted covered clinical studies to determine whether the applicant's product meets FDA's marketing requirements, identifying those clinical investigators who are full-time or part-time employees of

the sponsor of each covered study. The applicant must also completely and accurately disclose or certify information concerning the financial interests of a clinical investigator who is not a full-time or part-time employee of the sponsor for each covered clinical study. Clinical investigators subject to investigational new drug or investigational device exemption regulations must provide the sponsor of the study with sufficient accurate information needed to allow subsequent disclosure or certification. The applicant is required to submit for each clinical investigator who participates in a covered study, either a certification that none of the financial arrangements described in § 54.2 exist, or disclose the nature of those arrangements to the agency. Where the applicant acts with due diligence to obtain the information required in this section but is unable to do so, the applicant shall certify that despite the applicant's due diligence in attempting to obtain the information, the applicant was unable to obtain the information and shall include the reason.

(a) The applicant (of an application submitted under sections 505, 506, 510(k), 513, or 515 of the Federal Food, Drug, and Cosmetic Act, or section 351 of the Public Health Service Act) that relies in whole or in part on clinical studies shall submit, for each clinical investigator who participated in a covered clinical study, either a certification described in paragraph (a)(1) of this section or a disclosure statement described in paragraph (a)(3) of this section.

(1) Certification: The applicant covered by this section shall submit for all clinical investigators (as defined in § 54.2(d)), to whom the certification applies, a completed Form FDA 3454 attesting to the absence of financial interests and arrangements described in paragraph (a)(3) of this section. The form shall be dated and signed by the chief financial officer or other responsible corporate official or representative.

(2) If the certification covers less than all covered clinical data in the application, the applicant shall include in the certification a list of the studies covered by this certification.

(3) Disclosure Statement: For any clinical investigator defined in § 54.2(d) for whom the applicant does not submit the certification described in paragraph (a)(1) of this section, the applicant shall submit a completed Form FDA 3455 disclosing completely and accurately the following:

(i) Any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of a covered clinical trial, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

(ii) Any significant payments of other sorts from the sponsor of the covered study, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

(iii) Any proprietary interest in the tested product held by any clinical investigator involved in a study;

(iv) Any significant equity interest in the sponsor of the covered study held by any clinical investigator involved in any clinical study; and

(v) Any steps taken to minimize the potential for bias resulting from any of the disclosed arrangements, interests, or payments.

(b) The clinical investigator shall provide to the sponsor of the covered study sufficient accurate financial information to allow the sponsor to submit complete and accurate certification or disclosure statements as required in paragraph (a) of this section. The investigator shall promptly update this information if any relevant changes occur in the course of the investigation or for 1 year following completion of the study.

(c) Refusal to file application. FDA may refuse to file any marketing application described in paragraph (a) of this section that does not contain the information required by this section or a certifica-

tion by the applicant that the applicant has acted with due diligence to obtain the information but was unable to do so and stating the reason.

[63 FR 5250, Feb. 2, 1998; 63 FR 35134, June 29, 1998, as amended at 64 FR 399, Jan. 5, 1999]

§ 54.5 Agency evaluation of financial interests.

(a) *Evaluation of disclosure statement*. FDA will evaluate the information disclosed under § 54.4(a)(2) about each covered clinical study in an application to determine the impact of any disclosed financial interests on the reliability of the study. FDA may consider both the size and nature of a disclosed financial interest (including the potential increase in the value of the interest if the product is approved) and steps that have been taken to minimize the potential for bias.

(b) *Effect of study design*. In assessing the potential of an investigator's financial interests to bias a study, FDA will take into account the design and purpose of the study. Study designs that utilize such approaches as multiple investigators (most of whom do not have a disclosable interest), blinding, objective endpoints, or measurement of endpoints by someone other than the investigator may adequately protect against any bias created by a disclosable financial interest.

(c) Agency actions to ensure reliability of data. If FDA determines that the financial interests of any clinical investigator raise a serious question about the integrity of the data, FDA will take any action it deems necessary to ensure the reliability of the data including:

(1) Initiating agency audits of the data derived from the clinical investigator in question;

(2) Requesting that the applicant submit further analyses of data, e.g., to evaluate the effect of the clinical investigator's data on overall study outcome;

(3) Requesting that the applicant conduct additional independent studies to confirm the results of the questioned study; and

(4) Refusing to treat the covered clinical study as providing data that can be the basis for an agency action.

§ 54.6 Recordkeeping and record retention.

(a) *Financial records of clinical investigators to be retained*. An applicant who has submitted a marketing application containing covered clinical studies shall keep on file certain information pertaining to the financial interests of clinical investigators who conducted studies on which the application relies and who are not full or part-time employees of the applicant, as follows:

(1) Complete records showing any financial interest or arrangement as described in § 54.4(a)(3)(i) paid to such clinical investigators by the sponsor of the covered study.

(2) Complete records showing significant payments of other sorts, as described in § 54.4(a)(3)(ii), made by the sponsor of the covered clinical study to the clinical investigator.

(3) Complete records showing any financial interests held by clinical investigators as set forth in § 54.4(a)(3)(iii) and (a)(3)(iv).

(b) Requirements for maintenance of clinical investigators' financial records. (1) For any application submitted for a covered product, an applicant shall retain records as described in paragraph (a) of this section for 2 years after the date of approval of the application.

(2) The person maintaining these records shall, upon request from any properly authorized officer or employee of FDA, at reasonable times, permit such officer or employee to have access to and copy and verify these records.

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PART 56—INSTITUTIONAL REVIEW BOARDS

Authority: 21 U.S.C. 321, 343, 346, 346a, 348, 350a, 350b, 351, 352, 353, 355, 360, 360c-360f, 360h, 360i, 360j, 360hh-360ss, 371, 379e, 381; 42 U.S.C. 216, 241, 262.

Source: 46 FR 8975, Jan. 27, 1981, unless otherwise noted.

Subpart A—General Provisions

§ 56.101 Scope.

(a) This part contains the general standards for the composition, operation, and responsibility of an Institutional Review Board (IRB) that reviews clinical investigations regulated by the Food and Drug Administration under sections 505(i) and 520(g) of the act, as well as clinical investigations that support applications for research or marketing permits for products regulated by the Food and Drug Administration, including foods, including dietary supplements, that bear a nutrient content claim or a health claim, infant formulas, food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products. Compliance with this part is intended to protect the rights and welfare of human subjects involved in such investigations.

(b) References in this part to regulatory sections of the Code of Federal Regulations are to chapter I of title 21, unless otherwise noted.

[46 FR 8975, Jan. 27, 1981, as amended at 64 FR 399, Jan. 5, 1999; 66 FR 20599, Apr. 24, 2001]

§ 56.102 Definitions.

As used in this part:

(a) Act means the Federal Food, Drug, and Cosmetic Act, as amended (secs. 201-902, 52 Stat. 1040 et seq., as amended (21 U.S.C. 321-392)).

(b) *Application for research or marketing permit* includes:

(1) A color additive petition, described in part 71.

(2) Data and information regarding a substance submitted as part of the procedures for establishing that a substance is generally recognized as safe for a use which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food, described in § 170.35.

(3) A food additive petition, described in part 171.

(4) Data and information regarding a food additive submitted as part of the procedures regarding food additives permitted to be used on an interim basis pending additional study, described in § 180.1.

(5) Data and information regarding a substance submitted as part of the procedures for establishing a tolerance for unavoidable contaminants in food and food-packaging materials, described in section 406 of the act.

(6) An investigational new drug application, described in part 312 of this chapter.

(7) A new drug application, described in part 314.

(8) Data and information regarding the bioavailability or bioequivalence of drugs for human use submitted as part of the procedures for issuing, amending, or repealing a bioequivalence requirement, described in part 320.

(9) Data and information regarding an over-the-counter drug for human use submitted as part of the procedures for classifying such drugs as generally recognized as safe and effective and not misbranded, described in part 330.

(10) An application for a biologics license, described in part 601 of this chapter.

(11) Data and information regarding a biological product submitted as part of the procedures for determining that licensed biological products are safe and effective and not misbranded, as described in part 601 of this chapter.

(12) An Application for an Investigational Device Exemption, described in part 812.

(13) Data and information regarding a medical device for human use submitted as part of the procedures for classifying such devices, described in part 860.

(14) Data and information regarding a medical device for human use submitted as part of the procedures for establishing, amending, or repealing a standard for such device, described in part 861.

(15) An application for premarket approval of a medical device for human use, described in section 515 of the act.

(16) A product development protocol for a medical device for human use, described in section 515 of the act.

(17) Data and information regarding an electronic product submitted as part of the procedures for establishing, amending, or repealing a standard for such products, described in section 358 of the Public Health Service Act.

(18) Data and information regarding an electronic product submitted as part of the procedures for obtaining a variance from any electronic product performance standard, as described in § 1010.4.

(19) Data and information regarding an electronic product submitted as part of the procedures for granting, amending, or extending an exemption from a radiation safety performance standard, as described in § 1010.5.

(20) Data and information regarding an electronic product submitted as part of the procedures for obtaining an exemption from notification of a radiation safety defect or failure of compliance with a radiation safety performance standard, described in subpart D of part 1003.

(21) Data and information about a clinical study of an infant formula when submitted as part of an infant formula notification under section 412(c) of the Federal Food, Drug, and Cosmetic Act.

(22) Data and information submitted in a petition for a nutrient content claim, described in § 101.69 of this chapter, and for a health claim, described in § 101.70 of this chapter.

(23) Data and information from investigations involving children submitted in a new dietary ingredient notification, described in § 190.6 of this chapter.

(c) *Clinical investigation* means any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or need not meet the requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be later submitted to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that must meet the provisions of part 58, regarding nonclinical laboratory studies. The terms *research, clinical research, clinical study, study,* and *clinical investigation* are deemed to be synonymous for purposes of this part.

(d) *Emergency use* means the use of a test article on a human subject in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval.

(e) *Human subject* means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy individual or a patient.

(f) *Institution* means any public or private entity or agency (including Federal, State, and other agencies). The term facility as used in section 520(g) of the act is deemed to be synonymous with the term *institution* for purposes of this part.

(g) *Institutional Review Board (IRB)* means any board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of, biomedical research involving human subjects. The primary purpose of such review is to assure the protection of the rights and welfare of the human subjects. The term has the same meaning as the phrase institutional review committee as used in section 520(g) of the act.

(h) *Investigator* means an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject) or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team.

(i) *Minimal risk* means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

(j) *Sponsor* means a person or other entity that initiates a clinical investigation, but that does not actually conduct the investigation, i.e., the test article is administered or dispensed to, or used involving, a subject under the immediate direction of another individual. A person other than an individual (e.g., a corporation or agency) that uses one or more of its own employees to conduct an investigation that it has initiated is considered to be a sponsor (not a sponsor-investigator), and the employees are considered to be investigators.

(k) *Sponsor-investigator* means an individual who both initiates and actually conducts, alone or with others, a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject. The term does not include any person other than an individual, e.g., it does not include a corporation or agency. The obligations of a sponsor-investigator under this part include both those of a sponsor and those of an investigator.

(l) *Test article* means any drug for human use, biological product for human use, medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 or 354-360F of the Public Health Service Act.

(m) *IRB approval* means the determination of the IRB that the clinical investigation has been reviewed and may be conducted at an institution within the constraints set forth by the IRB and by other institutional and Federal requirements.

[46 FR 8975, Jan. 27, 1981, as amended at 54 FR 9038, Mar. 3, 1989; 56 FR 28028, June 18, 1991; 64 FR 399, Jan. 5, 1999; 64 FR 56448, Oct. 20, 1999; 65 FR 52302, Aug. 29, 2000; 66 FR 20599, Apr. 24, 2001; 74 FR 2368, Jan. 15, 2009]

§ 56.103 Circumstances in which IRB review is required.

(a) Except as provided in §§ 56.104 and 56.105, any clinical investigation which must meet the requirements for prior submission (as required in parts 312, 812, and 813) to the Food and Drug Administration shall not be initiated unless that investigation has been reviewed and approved by, and remains subject to continuing review by, an IRB meeting the requirements of this part.

(b) Except as provided in §§ 56.104 and 56.105, the Food and Drug Administration may decide not to consider in support of an application for a research or marketing permit any data or information that has been derived from a clinical investigation that has not been approved by, and that was not subject to initial and continuing review by, an IRB meeting the requirements of this part. The determination that a clinical investigation may not be considered in support of an application for a research or marketing permit does not, however, relieve the applicant for such a permit of any obligation under any other applicable regulations to submit the results of the investigation to the Food and Drug Administration.

(c) Compliance with these regulations will in no way render inapplicable pertinent Federal, State, or local laws or regulations.

[46 FR 8975, Jan. 27, 1981; 46 FR 14340, Feb. 27, 1981]

§ 56.104 Exemptions from IRB requirement.

The following categories of clinical investigations are exempt from the requirements of this part for IRB review:

(a) Any investigation which commenced before July 27, 1981 and was subject to requirements for IRB review under FDA regulations before that date, provided that the investigation remains subject to review of an IRB which meets the FDA requirements in effect before July 27, 1981.

(b) Any investigation commenced before July 27, 1981 and was not otherwise subject to requirements for IRB review under Food and Drug Administration regulations before that date.

(c) Emergency use of a test article, provided that such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article at the institution is subject to IRB review.

(d) Taste and food quality evaluations and consumer acceptance studies, if wholesome foods without additives are consumed or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural, chemical, or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

[46 FR 8975, Jan. 27, 1981, as amended at 56 FR 28028, June 18, 1991]

§ 56.105 Waiver of IRB requirement.

On the application of a sponsor or sponsor-investigator, the Food and Drug Administration may waive any of the requirements contained in these regulations, including the requirements for IRB review, for specific research activities or for classes of research activities, otherwise covered by these regulations.

Subpart B—Organization and Personnel

§ 56.106 Registration.

(a) *Who must register?* Each IRB in the United States that reviews clinical investigations regulated by FDA under sections 505(i) or 520(g) of the act and each IRB in the United States that reviews clinical investigations that are intended to support applications for research or marketing permits for FDA-regulated products must register at a site maintained by the Department of Health and Human Services (HHS). (A research permit under section 505(i) of the act is usually known as an investigational new drug application (IND), while a research permit under section 520(g) of the act is usually known as an investigational device exemption (IDE).) An individual authorized to act on the IRB's behalf must submit the registration information. All other IRBs may register voluntarily.

(b) *What information must an IRB register?* Each IRB must provide the following information:

(1) The name, mailing address, and street address (if different from the mailing address) of the institution operating the IRB and the name, mailing address, phone number, facsimile number, and electronic mail address of the senior officer of that institution who is responsible for overseeing activities performed by the IRB;

(2) The IRB's name, mailing address, street address (if different from the mailing address), phone number, facsimile number, and electronic mail address; each IRB chairperson's name, phone number, and electronic mail address; and the name, mailing address, phone number, facsimile number, and electronic mail address of the contact person providing the registration information.

(3) The approximate number of active protocols involving FDA-regulated products reviewed. For purposes of this rule, an "active protocol" is any protocol for which an IRB conducted an initial review

or a continuing review at a convened meeting or under an expedited review procedure during the preceding 12 months; and

(4) A description of the types of FDA-regulated products (such as biological products, color additives, food additives, human drugs, or medical devices) involved in the protocols that the IRB reviews.

(c) *When must an IRB register?* Each IRB must submit an initial registration. The initial registration must occur before the IRB begins to review a clinical investigation described in paragraph (a) of this section. Each IRB must renew its registration every 3 years. IRB registration becomes effective after review and acceptance by HHS.

(d) *Where can an IRB register?* Each IRB may register electronically through http://ohrp.cit.nih.gov/efile. If an IRB lacks the ability to register electronically, it must send its registration information, in writing, to the Office of Good Clinical Practice, Office of Special Medical Programs, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 32, Rm. 5129, Silver Spring, MD 20993.

(e) *How does an IRB revise its registration information?* If an IRB's contact or chair person information changes, the IRB must revise its registration information by submitting any changes in that information within 90 days of the change. An IRB's decision to review new types of FDA-regulated products (such as a decision to review studies pertaining to food additives whereas the IRB previously reviewed studies pertaining to drug products), or to discontinue reviewing clinical investigations regulated by FDA is a change that must be reported within 30 days of the change. An IRB's decision to disband is a change that must be reported within 30 days of permanent cessation of the IRB's review of research. All other information changes may be reported when the IRB renews its registration. The revised information must be sent to FDA either electronically or in writing in accordance with paragraph (d) of this section.

[74 FR 2368, Jan. 15, 2009, as amended at 78 FR 16401, Mar. 15, 2013]

§ 56.107 IRB membership.

(a) Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, cultural backgrounds, and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review the specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. * * * The IRB shall therefore include persons knowledgeable in these areas. If an IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, or handicapped or mentally disabled persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with those subjects.

(b) Every nondiscriminatory effort will be made to ensure that no IRB consists entirely of men or entirely of women, including the instituton's consideration of qualified persons of both sexes, so long as no selection is made to the IRB on the basis of gender. No IRB may consist entirely of members of one profession.

(c) Each IRB shall include at least one member whose primary concerns are in the scientific area and at least one member whose primary concerns are in nonscientific areas.

(d) Each IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.

(e) No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

(f) An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of complex issues which require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB.

[46 FR 8975, Jan. 27, 1981, as amended at 56 FR 28028, June 18, 1991; 56 FR 29756, June 28, 1991; 78 FR 16401, Mar. 15, 2013]

Subpart C—IRB Functions and Operations

§ 56.108 IRB functions and operations.

In order to fulfill the requirements of these regulations, each IRB shall:

(a) Follow written procedures: (1) For conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution; (2) for determining which projects require review more often than annually and which projects need verification from sources other than the investigator that no material changes have occurred since previous IRB review; (3) for ensuring prompt reporting to the IRB of changes in research activity; and (4) for ensuring that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the human subjects.

(b) Follow written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the Food and Drug Administration of: (1) Any unanticipated problems involving risks to human subjects or others; (2) any instance of serious or continuing noncompliance with these regulations or the requirements or determinations of the IRB; or (3) any suspension or termination of IRB approval.

(c) Except when an expedited review procedure is used (see § 56.110), review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas. In order for the research to be approved, it shall receive the approval of a majority of those members present at the meeting.

[46 FR 8975, Jan. 27, 1981, as amended at 56 FR 28028, June 18, 1991; 67 FR 9585, Mar. 4, 2002]

§ 56.109 IRB review of research.

(a) An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by these regulations.

(b) An IRB shall require that information given to subjects as part of informed consent is in accordance with § 50.25. The IRB may require that information, in addition to that specifically mentioned in § 50.25, be given to the subjects when in the IRB's judgment the information would meaningfully add to the protection of the rights and welfare of subjects.

(c) An IRB shall require documentation of informed consent in accordance with § 50.27 of this chapter, except as follows:

(1) The IRB may, for some or all subjects, waive the requirement that the subject, or the subject's legally authorized representative, sign a written consent form if it finds that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context; or

(2) The IRB may, for some or all subjects, find that the requirements in § 50.24 of this chapter for an exception from informed consent for emergency research are met.

(d) In cases where the documentation requirement is waived under paragraph (c)(1) of this section, the IRB may require the investigator to provide subjects with a written statement regarding the research.

(e) An IRB shall notify investigators and the institution in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure IRB approval of the research activity. If the IRB decides to disapprove a research activity, it shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing. For investigations involving an exception to informed consent under § 50.24 of this chapter, an IRB shall promptly notify in writing the investigator and the sponsor of the research when an IRB determines that it cannot approve the research because it does not meet the criteria in the exception provided under § 50.24(a) of this chapter or because of other relevant ethical concerns. The written notification shall include a statement of the reasons for the IRB's determination.

(f) An IRB shall conduct continuing review of research covered by these regulations at intervals appropriate to the degree of risk, but not less than once per year, and shall have authority to observe or have a third party observe the consent process and the research.

(g) An IRB shall provide in writing to the sponsor of research involving an exception to informed consent under § 50.24 of this chapter a copy of information that has been publicly disclosed under § 50.24(a)(7)(ii) and (a)(7)(iii) of this chapter. The IRB shall provide this information to the sponsor promptly so that the sponsor is aware that such disclosure has occurred. Upon receipt, the sponsor shall provide copies of the information disclosed to FDA.

(h) When some or all of the subjects in a study are children, an IRB must determine that the research study is in compliance with part 50, subpart D of this chapter, at the time of its initial review of the research. When some or all of the subjects in a study that was ongoing on April 30, 2001, are children, an IRB must conduct a review of the research to determine compliance with part 50, subpart D of this chapter, either at the time of continuing review or, at the discretion of the IRB, at an earlier date.

[46 FR 8975, Jan. 27, 1981, as amended at 61 FR 51529, Oct. 2, 1996; 66 FR 20599, Apr. 24, 2001; 78 FR 12951, Feb. 26, 2013]

§ 56.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.

(a) The Food and Drug Administration has established, and published in the Federal Register, a list of categories of research that may be reviewed by the IRB through an expedited review procedure. The list will be amended, as appropriate, through periodic republication in the Federal Register.

(b) An IRB may use the expedited review procedure to review either or both of the following: (1) Some or all of the research appearing on the list and found by the reviewer(s) to involve no more than minimal risk, (2) minor changes in previously approved research during the period (of 1 year or less) for which approval is authorized. Under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the IRB chairperson from among the members of the IRB. In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may be disapproved only after review in accordance with the nonexpedited review procedure set forth in § 56.108(c).

(c) Each IRB which uses an expedited review procedure shall adopt a method for keeping all members advised of research proposals which have been approved under the procedure.

(d) The Food and Drug Administration may restrict, suspend, or terminate an institution's or IRB's use of the expedited review procedure when necessary to protect the rights or welfare of subjects.

[46 FR 8975, Jan. 27, 1981, as amended at 56 FR 28029, June 18, 1991]

§ 56.111 Criteria for IRB approval of research.

(a) In order to approve research covered by these regulations the IRB shall determine that all of the following requirements are satisfied:

(1) Risks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies that subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

(3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons.

(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with and to the extent required by part 50.

(5) Informed consent will be appropriately documented, in accordance with and to the extent required by § 50.27.

(6) Where appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

(7) Where appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

(b) When some or all of the subjects, such as children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons, are likely to be vulnerable to coercion or undue influence additional safeguards have been included in the study to protect the rights and welfare of these subjects.

(c) In order to approve research in which some or all of the subjects are children, an IRB must determine that all research is in compliance with part 50, subpart D of this chapter.

[46 FR 8975, Jan. 27, 1981, as amended at 56 FR 28029, June 18, 1991; 66 FR 20599, Apr. 24, 2001]

§ 56.112 Review by institution.

Research covered by these regulations that has been approved by an IRB may be subject to further appropriate review and approval or disapproval by officials of the institution. However, those officials may not approve the research if it has not been approved by an IRB.

§ 56.113 Suspension or termination of IRB approval of research.

An IRB shall have authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval shall include a statement of the reasons for the IRB's action and shall be reported promptly to the investigator, appropriate institutional officials, and the Food and Drug Administration.

§ 56.114 Cooperative research.

In complying with these regulations, institutions involved in multi-institutional studies may use joint review, reliance upon the review of another qualified IRB, or similar arrangements aimed at avoidance of duplication of effort.

Subpart D—Records and Reports

§ 56.115 IRB records.

(a) An institution, or where appropriate an IRB, shall prepare and maintain adequate documentation of IRB activities, including the following:

(1) Copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent documents, progress reports submitted by investigators, and reports of injuries to subjects.

(2) Minutes of IRB meetings which shall be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution.

(3) Records of continuing review activities.

(4) Copies of all correspondence between the IRB and the investigators.

(5) A list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; and any employment or other relationship between each member and the institution; for example: full-time employee, part-time employee, a member of governing panel or board, stockholder, paid or unpaid consultant.

(6) Written procedures for the IRB as required by § 56.108 (a) and (b).

(7) Statements of significant new findings provided to subjects, as required by § 50.25.

(b) The records required by this regulation shall be retained for at least 3 years after completion of the research, and the records shall be accessible for inspection and copying by authorized representatives of the Food and Drug Administration at reasonable times and in a reasonable manner.

(c) The Food and Drug Administration may refuse to consider a clinical investigation in support of an application for a research or marketing permit if the institution or the IRB that reviewed the investigation refuses to allow an inspection under this section.

[46 FR 8975, Jan. 27, 1981, as amended at 56 FR 28029, June 18, 1991; 67 FR 9585, Mar. 4, 2002]

Subpart E—Administrative Actions for Noncompliance

§ 56.120 Lesser administrative actions.

(a) If apparent noncompliance with these regulations in the operation of an IRB is observed by an FDA investigator during an inspection, the inspector will present an oral or written summary of observations to an appropriate representative of the IRB. The Food and Drug Administration may subsequently send a letter describing the noncompliance to the IRB and to the parent institution. The agency will require that the IRB or the parent institution respond to this letter within a time period specified by FDA and describe the corrective actions that will be taken by the IRB, the institution, or both to achieve compliance with these regulations.

(b) On the basis of the IRB's or the institution's response, FDA may schedule a reinspection to confirm the adequacy of corrective actions. In addition, until the IRB or the parent institution takes appropriate corrective action, the Agency may require the IRB to:

(1) Withhold approval of new studies subject to the requirements of this part that are conducted at the institution or reviewed by the IRB;

(2) Direct that no new subjects be added to ongoing studies subject to this part; or

(3) Terminate ongoing studies subject to this part when doing so would not endanger the subjects.

(c) When the apparent noncompliance creates a significant threat to the rights and welfare of human subjects, FDA may notify relevant State and Federal regulatory agencies and other parties with a direct interest in the Agency's action of the deficiencies in the operation of the IRB.

(d) The parent institution is presumed to be responsible for the operation of an IRB, and the Food and Drug Administration will ordinarily direct any administrative action under this subpart against the institution. However, depending on the evidence of responsibility for deficiencies, determined during the investigation, the Food and Drug Administration may restrict its administrative actions to the IRB or to a component of the parent institution determined to be responsible for formal designation of the IRB.

[46 FR 8975, Jan. 27, 1981, as amended at 81 FR 19035, Apr. 4, 2016]

§ 56.121 Disqualification of an IRB or an institution.

(a) Whenever the IRB or the institution has failed to take adequate steps to correct the noncompliance stated in the letter sent by the agency under § 56.120(a), and the Commissioner of Food and Drugs determines that this noncompliance may justify the disqualification of the IRB or of the parent institution, the Commissioner will institute proceedings in accordance with the requirements for a regulatory hearing set forth in part 16.

(b) The Commissioner may disqualify an IRB or the parent institution if the Commissioner determines that:

(1) The IRB has refused or repeatedly failed to comply with any of the regulations set forth in this part, and

(2) The noncompliance adversely affects the rights or welfare of the human subjects in a clinical investigation.

(c) If the Commissioner determines that disqualification is appropriate, the Commissioner will issue an order that explains the basis for the determination and that prescribes any actions to be taken with regard to ongoing clinical research conducted under the review of the IRB. The Food and Drug Administration will send notice of the disqualification to the IRB and the parent institution. Other parties with a direct interest, such as sponsors and clinical investigators, may also be sent a notice of the disqualification. In addition, the agency may elect to publish a notice of its action in the Federal Register.

(d) The Food and Drug Administration will not approve an application for a research permit for a clinical investigation that is to be under the review of a disqualified IRB or that is to be conducted at a disqualified institution, and it may refuse to consider in support of a marketing permit the data from a clinical investigation that was reviewed by a disqualified IRB as conducted at a disqualified institution, unless the IRB or the parent institution is reinstated as provided in § 56.123.

§ 56.122 Public disclosure of information regarding revocation.

A determination that the Food and Drug Administration has disqualified an institution and the administrative record regarding that determination are disclosable to the public under part 20.

§ 56.123 Reinstatement of an IRB or an institution.

An IRB or an institution may be reinstated if the Commissioner determines, upon an evaluation of a written submission from the IRB or institution that explains the corrective action that the insti-

tution or IRB plans to take, that the IRB or institution has provided adequate assurance that it will operate in compliance with the standards set forth in this part. Notification of reinstatement shall be provided to all persons notified under § 56.121(c).

§ 56.124 Actions alternative or additional to disqualification.

Disqualification of an IRB or of an institution is independent of, and neither in lieu of nor a precondition to, other proceedings or actions authorized by the act. The Food and Drug Administration may, at any time, through the Department of Justice institute any appropriate judicial proceedings (civil or criminal) and any other appropriate regulatory action, in addition to or in lieu of, and before, at the time of, or after, disqualification. The agency may also refer pertinent matters to another Federal, State, or local government agency for any action that that agency determines to be appropriate.

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SUBCHAPTER D—DRUGS FOR HUMAN USE

PART 312—INVESTIGATIONAL NEW DRUG APPLICATION

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 360bbb, 371; 42 U.S.C. 262.
Source: 52 FR 8831, Mar. 19, 1987, unless otherwise noted.
Editorial note: Nomenclature changes to part 312 appear at 69 FR 13717, Mar. 24, 2004.

Subpart A—General Provisions

§ 312.1 Scope.

(a) This part contains procedures and requirements governing the use of investigational new drugs, including procedures and requirements for the submission to, and review by, the Food and Drug Administration of investigational new drug applications (IND's). An investigational new drug for which an IND is in effect in accordance with this part is exempt from the premarketing approval requirements that are otherwise applicable and may be shipped lawfully for the purpose of conducting clinical investigations of that drug.

(b) References in this part to regulations in the Code of Federal Regulations are to chapter I of title 21, unless otherwise noted.

§ 312.2 Applicability.

(a) *Applicability*. Except as provided in this section, this part applies to all clinical investigations of products that are subject to section 505 of the Federal Food, Drug, and Cosmetic Act or to the licensing provisions of the Public Health Service Act (58 Stat. 632, as amended (42 U.S.C. 201 et seq.)).

(b) *Exemptions*. (1) The clinical investigation of a drug product that is lawfully marketed in the United States is exempt from the requirements of this part if all the following apply:

(i) The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;

(ii) If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product;

(iii) The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;

(iv) The investigation is conducted in compliance with the requirements for institutional review set forth in part 56 and with the requirements for informed consent set forth in part 50; and

(v) The investigation is conducted in compliance with the requirements of § 312.7.

(2)(i) A clinical investigation involving an in vitro diagnostic biological product listed in paragraph (b)(2)(ii) of this section is exempt from the requirements of this part if (a) it is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure and (b) it is shipped in compliance with § 312.160.

(ii) In accordance with paragraph (b)(2)(i) of this section, the following products are exempt from the requirements of this part: (a) blood grouping serum; (b) reagent red blood cells; and (c) anti-human globulin.

(3) A drug intended solely for tests in vitro or in laboratory research animals is exempt from the requirements of this part if shipped in accordance with § 312.160.

(4) FDA will not accept an application for an investigation that is exempt under the provisions of paragraph (b)(1) of this section.

(5) A clinical investigation involving use of a placebo is exempt from the requirements of this part if the investigation does not otherwise require submission of an IND.

(6) A clinical investigation involving an exception from informed consent under § 50.24 of this chapter is not exempt from the requirements of this part.

(c) *Bioavailability studies.* The applicability of this part to in vivo bioavailability studies in humans is subject to the provisions of § 320.31.

(d) *Unlabeled indication.* This part does not apply to the use in the practice of medicine for an unlabeled indication of a new drug product approved under part 314 or of a licensed biological product.

(e) *Guidance.* FDA may, on its own initiative, issue guidance on the applicability of this part to particular investigational uses of drugs. On request, FDA will advise on the applicability of this part to a planned clinical investigation.

[52 FR 8831, Mar. 19, 1987, as amended at 61 FR 51529, Oct. 2, 1996; 64 FR 401, Jan. 5, 1999]

§ 312.3 Definitions and interpretations.

(a) The definitions and interpretations of terms contained in section 201 of the Act apply to those terms when used in this part:

(b) The following definitions of terms also apply to this part:

Act means the Federal Food, Drug, and Cosmetic Act (secs. 201-902, 52 Stat. 1040 et seq., as amended (21 U.S.C. 301-392)).

Clinical investigation means any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. For the purposes of this part, an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice.

Contract research organization means a person that assumes, as an independent contractor with the sponsor, one or more of the obligations of a sponsor, e.g., design of a protocol, selection or monitoring of investigations, evaluation of reports, and preparation of materials to be submitted to the Food and Drug Administration.

FDA means the Food and Drug Administration.

IND means an investigational new drug application. For purposes of this part, "IND" is synonymous with "Notice of Claimed Investigational Exemption for a New Drug."

Independent ethics committee (IEC) means a review panel that is responsible for ensuring the protection of the rights, safety, and well-being of human subjects involved in a clinical investigation and is adequately constituted to provide assurance of that protection. An institutional review board (IRB), as defined in §56.102(g) of this chapter and subject to the requirements of part 56 of this chapter, is one type of IEC.

Investigational new drug means a new drug or biological drug that is used in a clinical investigation. The term also includes a biological product that is used in vitro for diagnostic purposes. The terms "investigational drug" and "investigational new drug" are deemed to be synonymous for purposes of this part.

Investigator means an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the drug is administered or dispensed to a subject). In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. "Subinvestigator" includes any other individual member of that team.

Marketing application means an application for a new drug submitted under section 505(b) of the act or a biologics license application for a biological product submitted under the Public Health Service Act.

Sponsor means a person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization. The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators.

Sponsor-Investigator means an individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. The term does not include any person other than an individual. The requirements applicable to a sponsor-investigator under this part include both those applicable to an investigator and a sponsor.

Subject means a human who participates in an investigation, either as a recipient of the investigational new drug or as a control. A subject may be a healthy human or a patient with a disease.

[52 FR 8831, Mar. 19, 1987, as amended at 64 FR 401, Jan. 5, 1999; 64 FR 56449, Oct. 20, 1999; 73 FR 22815, Apr. 28, 2008]

§312.6 Labeling of an investigational new drug.

(a) The immediate package of an investigational new drug intended for human use shall bear a label with the statement "Caution: New Drug—Limited by Federal (or United States) law to investigational use."

(b) The label or labeling of an investigational new drug shall not bear any statement that is false or misleading in any particular and shall not represent that the investigational new drug is safe or effective for the purposes for which it is being investigated.

(c) The appropriate FDA Center Director, according to the procedures set forth in §§201.26 or 610.68 of this chapter, may grant an exception or alternative to the provision in paragraph (a) of this section, to the extent that this provision is not explicitly required by statute, for specified lots, batches, or other units of a human drug product that is or will be included in the Strategic National Stockpile.

[52 FR 8831, Mar. 19, 1987, as amended at 72 FR 73599, Dec. 28, 2007]

§312.7 Promotion of investigational drugs.

(a) *Promotion of an investigational new drug.* A sponsor or investigator, or any person acting on behalf of a sponsor or investigator, shall not represent in a promotional context that an investigational new drug is safe or effective for the purposes for which it is under investigation or otherwise promote the drug. This provision is not intended to restrict the full exchange of scientific information concerning the drug, including dissemination of scientific findings in scientific or lay media. Rather, its intent is to restrict promotional claims of safety or effectiveness of the drug for a use for which it is under investigation and to preclude commercialization of the drug before it is approved for commercial distribution.

(b) *Commercial distribution of an investigational new drug.* A sponsor or investigator shall not commercially distribute or test market an investigational new drug.

(c) *Prolonging an investigation.* A sponsor shall not unduly prolong an investigation after finding that the results of the investigation appear to establish sufficient data to support a marketing application.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 19476, May 22, 1987; 67 FR 9585, Mar. 4, 2002; 74 FR 40899, Aug. 13, 2009]

§312.8 Charging for investigational drugs under an IND.

(a) *General criteria for charging.* (1) A sponsor must meet the applicable requirements in paragraph (b) of this section for charging in a clinical trial or paragraph (c) of this section for charging for expanded access to an investigational drug for treatment use under subpart I of this part, except that sponsors need not fulfill the requirements in this section to charge for an approved drug obtained from another entity not affiliated with the sponsor for use as part of the clinical trial evaluation (e.g., in a clinical trial of a new use of the approved drug, for use of the approved drug as an active control).

(2) A sponsor must justify the amount to be charged in accordance with paragraph (d) of this section.

(3) A sponsor must obtain prior written authorization from FDA to charge for an investigational drug.

(4) FDA will withdraw authorization to charge if it determines that charging is interfering with the development of a drug for marketing approval or that the criteria for the authorization are no longer being met.

(b) *Charging in a clinical trial*—(1) *Charging for a sponsor's drug.* A sponsor who wishes to charge for its investigational drug, including investigational use of its approved drug, must:

(i) Provide evidence that the drug has a potential clinical benefit that, if demonstrated in the clinical investigations, would provide a significant advantage over available products in the diagnosis, treatment, mitigation, or prevention of a disease or condition;

(ii) Demonstrate that the data to be obtained from the clinical trial would be essential to establishing that the drug is effective or safe for the purpose of obtaining initial approval of a drug, or would support a significant change in the labeling of an approved drug (e.g., new indication, inclusion of comparative safety information); and

(iii) Demonstrate that the clinical trial could not be conducted without charging because the cost of the drug is extraordinary to the sponsor. The cost may be extraordinary due to manufacturing complexity, scarcity of a natural resource, the large quantity of drug needed (e.g., due to the size or duration of the trial), or some combination of these or other extraordinary circumstances (e.g., resources available to a sponsor).

(2) *Duration of charging in a clinical trial.* Unless FDA specifies a shorter period, charging may continue for the length of the clinical trial.

(c) *Charging for expanded access to investigational drug for treatment use.* (1) A sponsor who wishes to charge for expanded access to an investigational drug for treatment use under subpart I of this part must provide reasonable assurance that charging will not interfere with developing the drug for marketing approval.

(2) For expanded access under § 312.320 (treatment IND or treatment protocol), such assurance must include:

(i) Evidence of sufficient enrollment in any ongoing clinical trial(s) needed for marketing approval to reasonably assure FDA that the trial(s) will be successfully completed as planned;

(ii) Evidence of adequate progress in the development of the drug for marketing approval; and

(iii) Information submitted under the general investigational plan (§ 312.23(a)(3)(iv)) specifying the drug development milestones the sponsor plans to meet in the next year.

(3) The authorization to charge is limited to the number of patients authorized to receive the drug under the treatment use, if there is a limitation.

(4) Unless FDA specifies a shorter period, charging for expanded access to an investigational drug for treatment use under subpart I of this part may continue for 1 year from the time of FDA authorization. A sponsor may request that FDA reauthorize charging for additional periods.

(d) *Costs recoverable when charging for an investigational drug.* (1) A sponsor may recover only the direct costs of making its investigational drug available.

(i) Direct costs are costs incurred by a sponsor that can be specifically and exclusively attributed to providing the drug for the investigational use for which FDA has authorized cost recovery. Direct costs include costs per unit to manufacture the drug (e.g., raw materials, labor, and nonreusable supplies and equipment used to manufacture the quantity of drug needed for the use for which charging is authorized) or costs to acquire the drug from another manufacturing source, and direct costs to ship and handle (e.g., store) the drug.

(ii) Indirect costs include costs incurred primarily to produce the drug for commercial sale (e.g., costs for facilities and equipment used to manufacture the supply of investigational drug, but that are primarily intended to produce large quantities of drug for eventual commercial sale) and research and development, administrative, labor, or other costs that would be incurred even if the clinical trial or treatment use for which charging is authorized did not occur.

(2) For expanded access to an investigational drug for treatment use under §§ 312.315 (intermediate-size patient populations) and 312.320 (treatment IND or treatment protocol), in addition to the direct costs described in paragraph (d)(1)(i) of this section, a sponsor may recover the costs of monitoring the expanded access IND or protocol, complying with IND reporting requirements, and other administrative costs directly associated with the expanded access IND.

(3) To support its calculation for cost recovery, a sponsor must provide supporting documentation to show that the calculation is consistent with the requirements of paragraphs (d)(1) and, if applicable, (d)(2) of this section. The documentation must be accompanied by a statement that an independent certified public accountant has reviewed and approved the calculations.

[74 FR 40899, Aug. 13, 2009]

§ 312.10 Waivers.

(a) A sponsor may request FDA to waive applicable requirement under this part. A waiver request may be submitted either in an IND or in an information amendment to an IND. In an emergency, a request may be made by telephone or other rapid communication means. A waiver request is required to contain at least one of the following:

(1) An explanation why the sponsor's compliance with the requirement is unnecessary or cannot be achieved;

(2) A description of an alternative submission or course of action that satisfies the purpose of the requirement; or

(3) Other information justifying a waiver.

(b) FDA may grant a waiver if it finds that the sponsor's noncompliance would not pose a significant and unreasonable risk to human subjects of the investigation and that one of the following is met:

(1) The sponsor's compliance with the requirement is unnecessary for the agency to evaluate the application, or compliance cannot be achieved;

(2) The sponsor's proposed alternative satisfies the requirement; or

(3) The applicant's submission otherwise justifies a waiver.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 67 FR 9585, Mar. 4, 2002]

Subpart B—Investigational New Drug Application (IND)

§ 312.20 Requirement for an IND.

(a) A sponsor shall submit an IND to FDA if the sponsor intends to conduct a clinical investigation with an investigational new drug that is subject to § 312.2(a).

(b) A sponsor shall not begin a clinical investigation subject to § 312.2(a) until the investigation is subject to an IND which is in effect in accordance with § 312.40.

(c) A sponsor shall submit a separate IND for any clinical investigation involving an exception from informed consent under § 50.24 of this chapter. Such a clinical investigation is not permitted to proceed without the prior written authorization from FDA. FDA shall provide a written determination 30 days after FDA receives the IND or earlier.

[52 FR 8831, Mar. 19, 1987, as amended at 61 FR 51529, Oct. 2, 1996; 62 FR 32479, June 16, 1997]

§ 312.21 Phases of an investigation.

An IND may be submitted for one or more phases of an investigation. The clinical investigation of a previously untested drug is generally divided into three phases. Although in general the phases are conducted sequentially, they may overlap. These three phases of an investigation are a follows:

(a) *Phase 1.* (1) Phase 1 includes the initial introduction of an investigational new drug into humans. Phase 1 studies are typically closely monitored and may be conducted in patients or normal volunteer subjects. These studies are designed to determine the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. During Phase 1, sufficient information about the drug's pharmacokinetics and pharmacological effects should be obtained to permit the design of well-controlled, scientifically valid, Phase 2 studies. The total number of subjects and patients included in Phase 1 studies varies with the drug, but is generally in the range of 20 to 80.

(2) Phase 1 studies also include studies of drug metabolism, structure-activity relationships, and mechanism of action in humans, as well as studies in which investigational drugs are used as research tools to explore biological phenomena or disease processes.

(b) *Phase 2.* Phase 2 includes the controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks associated with the drug. Phase 2 studies are typically well controlled, closely monitored, and conducted in a relatively small number of patients, usually involving no more than several hundred subjects.

(c) *Phase 3.* Phase 3 studies are expanded controlled and uncontrolled trials. They are performed after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intend-

ed to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling. Phase 3 studies usually include from several hundred to several thousand subjects.

§ 312.22 General principles of the IND submission.

(a) FDA's primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects, and, in Phase 2 and 3, to help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug's effectiveness and safety. Therefore, although FDA's review of Phase 1 submissions will focus on assessing the safety of Phase 1 investigations, FDA's review of Phases 2 and 3 submissions will also include an assessment of the scientific quality of the clinical investigations and the likelihood that the investigations will yield data capable of meeting statutory standards for marketing approval.

(b) The amount of information on a particular drug that must be submitted in an IND to assure the accomplishment of the objectives described in paragraph (a) of this section depends upon such factors as the novelty of the drug, the extent to which it has been studied previously, the known or suspected risks, and the developmental phase of the drug.

(c) The central focus of the initial IND submission should be on the general investigational plan and the protocols for specific human studies. Subsequent amendments to the IND that contain new or revised protocols should build logically on previous submissions and should be supported by additional information, including the results of animal toxicology studies or other human studies as appropriate. Annual reports to the IND should serve as the focus for reporting the status of studies being conducted under the IND and should update the general investigational plan for the coming year.

(d) The IND format set forth in § 312.23 should be followed routinely by sponsors in the interest of fostering an efficient review of applications. Sponsors are expected to exercise considerable discretion, however, regarding the content of information submitted in each section, depending upon the kind of drug being studied and the nature of the available information. Section 312.23 outlines the information needed for a commercially sponsored IND for a new molecular entity. A sponsor-investigator who uses, as a research tool, an investigational new drug that is already subject to a manufacturer's IND or marketing application should follow the same general format, but ordinarily may, if authorized by the manufacturer, refer to the manufacturer's IND or marketing application in providing the technical information supporting the proposed clinical investigation. A sponsor-investigator who uses an investigational drug not subject to a manufacturer's IND or marketing application is ordinarily required to submit all technical information supporting the IND, unless such information may be referenced from the scientific literature.

§ 312.23 IND content and format.

(a) A sponsor who intends to conduct a clinical investigation subject to this part shall submit an "Investigational New Drug Application" (IND) including, in the following order:

(1) *Cover sheet (Form FDA-1571).* A cover sheet for the application containing the following:

(i) The name, address, and telephone number of the sponsor, the date of the application, and the name of the investigational new drug.

(ii) Identification of the phase or phases of the clinical investigation to be conducted.

(iii) A commitment not to begin clinical investigations until an IND covering the investigations is in effect.

(iv) A commitment that an Institutional Review Board (IRB) that complies with the requirements set forth in part 56 will be responsible for the initial and continuing review and approval of each

of the studies in the proposed clinical investigation and that the investigator will report to the IRB proposed changes in the research activity in accordance with the requirements of part 56.

(v) A commitment to conduct the investigation in accordance with all other applicable regulatory requirements.

(vi) The name and title of the person responsible for monitoring the conduct and progress of the clinical investigations.

(vii) The name(s) and title(s) of the person(s) responsible under § 312.32 for review and evaluation of information relevant to the safety of the drug.

(viii) If a sponsor has transferred any obligations for the conduct of any clinical study to a contract research organization, a statement containing the name and address of the contract research organization, identification of the clinical study, and a listing of the obligations transferred. If all obligations governing the conduct of the study have been transferred, a general statement of this transfer—in lieu of a listing of the specific obligations transferred—may be submitted.

(ix) The signature of the sponsor or the sponsor's authorized representative. If the person signing the application does not reside or have a place of business within the United States, the IND is required to contain the name and address of, and be countersigned by, an attorney, agent, or other authorized official who resides or maintains a place of business within the United States.

(2) *A table of contents.*

(3) *Introductory statement and general investigational plan.* (i) A brief introductory statement giving the name of the drug and all active ingredients, the drug's pharmacological class, the structural formula of the drug (if known), the formulation of the dosage form(s) to be used, the route of administration, and the broad objectives and planned duration of the proposed clinical investigation(s).

(ii) A brief summary of previous human experience with the drug, with reference to other IND's if pertinent, and to investigational or marketing experience in other countries that may be relevant to the safety of the proposed clinical investigation(s).

(iii) If the drug has been withdrawn from investigation or marketing in any country for any reason related to safety or effectiveness, identification of the country(ies) where the drug was withdrawn and the reasons for the withdrawal.

(iv) A brief description of the overall plan for investigating the drug product for the following year. The plan should include the following: (a) The rationale for the drug or the research study; (b) the indication(s) to be studied; (c) the general approach to be followed in evaluating the drug; (d) the kinds of clinical trials to be conducted in the first year following the submission (if plans are not developed for the entire year, the sponsor should so indicate); (e) the estimated number of patients to be given the drug in those studies; and (f) any risks of particular severity or seriousness anticipated on the basis of the toxicological data in animals or prior studies in humans with the drug or related drugs.

(4) [Reserved]

(5) *Investigator's brochure.* If required under § 312.55, a copy of the investigator's brochure, containing the following information:

(i) A brief description of the drug substance and the formulation, including the structural formula, if known.

(ii) A summary of the pharmacological and toxicological effects of the drug in animals and, to the extent known, in humans.

(iii) A summary of the pharmacokinetics and biological disposition of the drug in animals and, if known, in humans.

(iv) A summary of information relating to safety and effectiveness in humans obtained from prior clinical studies. (Reprints of published articles on such studies may be appended when useful.)

(v) A description of possible risks and side effects to be anticipated on the basis of prior experience with the drug under investigation or with related drugs, and of precautions or special monitoring to be done as part of the investigational use of the drug.

(6) *Protocols.* (i) A protocol for each planned study. (Protocols for studies not submitted initially in the IND should be submitted in accordance with §312.30(a).) In general, protocols for Phase 1 studies may be less detailed and more flexible than protocols for Phase 2 and 3 studies. Phase 1 protocols should be directed primarily at providing an outline of the investigation—an estimate of the number of patients to be involved, a description of safety exclusions, and a description of the dosing plan including duration, dose, or method to be used in determining dose—and should specify in detail only those elements of the study that are critical to safety, such as necessary monitoring of vital signs and blood chemistries. Modifications of the experimental design of Phase 1 studies that do not affect critical safety assessments are required to be reported to FDA only in the annual report.

(ii) In Phases 2 and 3, detailed protocols describing all aspects of the study should be submitted. A protocol for a Phase 2 or 3 investigation should be designed in such a way that, if the sponsor anticipates that some deviation from the study design may become necessary as the investigation progresses, alternatives or contingencies to provide for such deviation are built into the protocols at the outset. For example, a protocol for a controlled short-term study might include a plan for an early crossover of nonresponders to an alternative therapy.

(iii) A protocol is required to contain the following, with the specific elements and detail of the protocol reflecting the above distinctions depending on the phase of study:

(a) A statement of the objectives and purpose of the study.

(b) The name and address and a statement of the qualifications (curriculum vitae or other statement of qualifications) of each investigator, and the name of each subinvestigator (e.g., research fellow, resident) working under the supervision of the investigator; the name and address of the research facilities to be used; and the name and address of each reviewing Institutional Review Board.

(c) The criteria for patient selection and for exclusion of patients and an estimate of the number of patients to be studied.

(d) A description of the design of the study, including the kind of control group to be used, if any, and a description of methods to be used to minimize bias on the part of subjects, investigators, and analysts.

(e) The method for determining the dose(s) to be administered, the planned maximum dosage, and the duration of individual patient exposure to the drug.

(f) A description of the observations and measurements to be made to fulfill the objectives of the study.

(g) A description of clinical procedures, laboratory tests, or other measures to be taken to monitor the effects of the drug in human subjects and to minimize risk.

(7) *Chemistry, manufacturing, and control information.* (i) As appropriate for the particular investigations covered by the IND, a section describing the composition, manufacture, and control of the drug substance and the drug product. Although in each phase of the investigation sufficient information is required to be submitted to assure the proper identification, quality, purity, and strength of the investigational drug, the amount of information needed to make that assurance will vary with the phase of the investigation, the proposed duration of the investigation, the dosage form, and the amount of information otherwise available. FDA recognizes that modifications to the method of preparation of the new drug substance and dosage form and changes in the dosage form itself are likely as the investigation progresses. Therefore, the emphasis in an initial Phase 1 submission

should generally be placed on the identification and control of the raw materials and the new drug substance. Final specifications for the drug substance and drug product are not expected until the end of the investigational process.

(ii) It should be emphasized that the amount of information to be submitted depends upon the scope of the proposed clinical investigation. For example, although stability data are required in all phases of the IND to demonstrate that the new drug substance and drug product are within acceptable chemical and physical limits for the planned duration of the proposed clinical investigation, if very short-term tests are proposed, the supporting stability data can be correspondingly limited.

(iii) As drug development proceeds and as the scale or production is changed from the pilot-scale production appropriate for the limited initial clinical investigations to the larger-scale production needed for expanded clinical trials, the sponsor should submit information amendments to supplement the initial information submitted on the chemistry, manufacturing, and control processes with information appropriate to the expanded scope of the investigation.

(iv) Reflecting the distinctions described in this paragraph (a)(7), and based on the phase(s) to be studied, the submission is required to contain the following:

(a) *Drug substance.* A description of the drug substance, including its physical, chemical, or biological characteristics; the name and address of its manufacturer; the general method of preparation of the drug substance; the acceptable limits and analytical methods used to assure the identity, strength, quality, and purity of the drug substance; and information sufficient to support stability of the drug substance during the toxicological studies and the planned clinical studies. Reference to the current edition of the United States Pharmacopeia—National Formulary may satisfy relevant requirements in this paragraph.

(b) *Drug product.* A list of all components, which may include reasonable alternatives for inactive compounds, used in the manufacture of the investigational drug product, including both those components intended to appear in the drug product and those which may not appear but which are used in the manufacturing process, and, where applicable, the quantitative composition of the investigational drug product, including any reasonable variations that may be expected during the investigational stage; the name and address of the drug product manufacturer; a brief general description of the manufacturing and packaging procedure as appropriate for the product; the acceptable limits and analytical methods used to assure the identity, strength, quality, and purity of the drug product; and information sufficient to assure the product's stability during the planned clinical studies. Reference to the current edition of the United States Pharmacopeia—National Formulary may satisfy certain requirements in this paragraph.

(c) A brief general description of the composition, manufacture, and control of any placebo used in a controlled clinical trial.

(d) *Labeling*. A copy of all labels and labeling to be provided to each investigator.

(e) *Environmental analysis requirements.* A claim for categorical exclusion under § 25.30 or 25.31 or an environmental assessment under § 25.40.

(8) *Pharmacology and toxicology information.* Adequate information about pharmacological and toxicological studies of the drug involving laboratory animals or in vitro, on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations. The kind, duration, and scope of animal and other tests required varies with the duration and nature of the proposed clinical investigations. Guidance documents are available from FDA that describe ways in which these requirements may be met. Such information is required to include the identification and qualifications of the individuals who evaluated the results of such studies and concluded that it is reasonably safe to begin the proposed investigations and a statement of where the investigations were conducted and where the records are available for inspection. As drug development

proceeds, the sponsor is required to submit informational amendments, as appropriate, with additional information pertinent to safety.

(i) *Pharmacology and drug disposition.* A section describing the pharmacological effects and mechanism(s) of action of the drug in animals, and information on the absorption, distribution, metabolism, and excretion of the drug, if known.

(ii) *Toxicology*. (a) An integrated summary of the toxicological effects of the drug in animals and in vitro. Depending on the nature of the drug and the phase of the investigation, the description is to include the results of acute, subacute, and chronic toxicity tests; tests of the drug's effects on reproduction and the developing fetus; any special toxicity test related to the drug's particular mode of administration or conditions of use (e.g., inhalation, dermal, or ocular toxicology); and any in vitro studies intended to evaluate drug toxicity.

(b) For each toxicology study that is intended primarily to support the safety of the proposed clinical investigation, a full tabulation of data suitable for detailed review.

(iii) For each nonclinical laboratory study subject to the good laboratory practice regulations under part 58, a statement that the study was conducted in compliance with the good laboratory practice regulations in part 58, or, if the study was not conducted in compliance with those regulations, a brief statement of the reason for the noncompliance.

(9) *Previous human experience with the investigational drug.* A summary of previous human experience known to the applicant, if any, with the investigational drug. The information is required to include the following:

(i) If the investigational drug has been investigated or marketed previously, either in the United States or other countries, detailed information about such experience that is relevant to the safety of the proposed investigation or to the investigation's rationale. If the drug has been the subject of controlled trials, detailed information on such trials that is relevant to an assessment of the drug's effectiveness for the proposed investigational use(s) should also be provided. Any published material that is relevant to the safety of the proposed investigation or to an assessment of the drug's effectiveness for its proposed investigational use should be provided in full. Published material that is less directly relevant may be supplied by a bibliography.

(ii) If the drug is a combination of drugs previously investigated or marketed, the information required under paragraph (a)(9)(i) of this section should be provided for each active drug component. However, if any component in such combination is subject to an approved marketing application or is otherwise lawfully marketed in the United States, the sponsor is not required to submit published material concerning that active drug component unless such material relates directly to the proposed investigational use (including publications relevant to component-component interaction).

(iii) If the drug has been marketed outside the United States, a list of the countries in which the drug has been marketed and a list of the countries in which the drug has been withdrawn from marketing for reasons potentially related to safety or effectiveness.

(10) *Additional information.* In certain applications, as described below, information on special topics may be needed. Such information shall be submitted in this section as follows:

(i) *Drug dependence and abuse potential.* If the drug is a psychotropic substance or otherwise has abuse potential, a section describing relevant clinical studies and experience and studies in test animals.

(ii) *Radioactive drugs.* If the drug is a radioactive drug, sufficient data from animal or human studies to allow a reasonable calculation of radiation-absorbed dose to the whole body and critical organs upon administration to a human subject. Phase 1 studies of radioactive drugs must include studies which will obtain sufficient data for dosimetry calculations.

(iii) *Pediatric studies.* Plans for assessing pediatric safety and effectiveness.

(iv) *Other information.* A brief statement of any other information that would aid evaluation of the proposed clinical investigations with respect to their safety or their design and potential as controlled clinical trials to support marketing of the drug.

(11) Relevant information. If requested by FDA, any other relevant information needed for review of the application.

(b) *Information previously submitted*. The sponsor ordinarily is not required to resubmit information previously submitted, but may incorporate the information by reference. A reference to information submitted previously must identify the file by name, reference number, volume, and page number where the information can be found. A reference to information submitted to the agency by a person other than the sponsor is required to contain a written statement that authorizes the reference and that is signed by the person who submitted the information.

(c) *Material in a foreign language.* The sponsor shall submit an accurate and complete English translation of each part of the IND that is not in English. The sponsor shall also submit a copy of each original literature publication for which an English translation is submitted.

(d) *Number of copies*. The sponsor shall submit an original and two copies of all submissions to the IND file, including the original submission and all amendments and reports.

(e) *Numbering of IND submissions.* Each submission relating to an IND is required to be numbered serially using a single, three-digit serial number. The initial IND is required to be numbered 000; each subsequent submission (e.g., amendment, report, or correspondence) is required to be numbered chronologically in sequence.

(f) *Identification of exception from informed consent*. If the investigation involves an exception from informed consent under § 50.24 of this chapter, the sponsor shall prominently identify on the cover sheet that the investigation is subject to the requirements in § 50.24 of this chapter.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 53 FR 1918, Jan. 25, 1988; 61 FR
[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 53 FR 1918, Jan. 25, 1988; 61 FR
51529, Oct. 2, 1996; 62 FR 40599, July 29, 1997; 63 FR 66669, Dec. 2, 1998; 65 FR 56479, Sept. 19, 2000; 67 FR 9585, Mar. 4, 2002]

§ 312.30 Protocol amendments.

Once an IND is in effect, a sponsor shall amend it as needed to ensure that the clinical investigations are conducted according to protocols included in the application. This section sets forth the provisions under which new protocols may be submitted and changes in previously submitted protocols may be made. Whenever a sponsor intends to conduct a clinical investigation with an exception from informed consent for emergency research as set forth in § 50.24 of this chapter, the sponsor shall submit a separate IND for such investigation.

(a) *New protocol.* Whenever a sponsor intends to conduct a study that is not covered by a protocol already contained in the IND, the sponsor shall submit to FDA a protocol amendment containing the protocol for the study. Such study may begin provided two conditions are met: (1) The sponsor has submitted the protocol to FDA for its review; and (2) the protocol has been approved by the Institutional Review Board (IRB) with responsibility for review and approval of the study in accordance with the requirements of part 56. The sponsor may comply with these two conditions in either order.

(b) *Changes in a protocol.* (1) A sponsor shall submit a protocol amendment describing any change in a Phase 1 protocol that significantly affects the safety of subjects or any change in a Phase 2 or 3 protocol that significantly affects the safety of subjects, the scope of the investigation, or the scientific quality of the study. Examples of changes requiring an amendment under this paragraph include:

(i) Any increase in drug dosage or duration of exposure of individual subjects to the drug beyond that in the current protocol, or any significant increase in the number of subjects under study.

(ii) Any significant change in the design of a protocol (such as the addition or dropping of a control group).

(iii) The addition of a new test or procedure that is intended to improve monitoring for, or reduce the risk of, a side effect or adverse event; or the dropping of a test intended to monitor safety.

(2)(i) A protocol change under paragraph (b)(1) of this section may be made provided two conditions are met:

(a) The sponsor has submitted the change to FDA for its review; and

(b) The change has been approved by the IRB with responsibility for review and approval of the study. The sponsor may comply with these two conditions in either order.

(ii) Notwithstanding paragraph (b)(2)(i) of this section, a protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately provided FDA is subsequently notified by protocol amendment and the reviewing IRB is notified in accordance with §56.104(c).

(c) *New investigator.* A sponsor shall submit a protocol amendment when a new investigator is added to carry out a previously submitted protocol, except that a protocol amendment is not required when a licensed practitioner is added in the case of a treatment protocol under §312.315 or §312.320. Once the investigator is added to the study, the investigational drug may be shipped to the investigator and the investigator may begin participating in the study. The sponsor shall notify FDA of the new investigator within 30 days of the investigator being added.

(d) *Content and format.* A protocol amendment is required to be prominently identified as such (i.e., "Protocol Amendment: New Protocol", "Protocol Amendment: Change in Protocol", or "Protocol Amendment: New Investigator"), and to contain the following:

(1)(i) In the case of a new protocol, a copy of the new protocol and a brief description of the most clinically significant differences between it and previous protocols.

(ii) In the case of a change in protocol, a brief description of the change and reference (date and number) to the submission that contained the protocol.

(iii) In the case of a new investigator, the investigator's name, the qualifications to conduct the investigation, reference to the previously submitted protocol, and all additional information about the investigator's study as is required under §312.23(a)(6)(iii)(b).

(2) Reference, if necessary, to specific technical information in the IND or in a concurrently submitted information amendment to the IND that the sponsor relies on to support any clinically significant change in the new or amended protocol. If the reference is made to supporting information already in the IND, the sponsor shall identify by name, reference number, volume, and page number the location of the information.

(3) If the sponsor desires FDA to comment on the submission, a request for such comment and the specific questions FDA's response should address.

(e) *When submitted.* A sponsor shall submit a protocol amendment for a new protocol or a change in protocol before its implementation. Protocol amendments to add a new investigator or to provide additional information about investigators may be grouped and submitted at 30-day intervals. When several submissions of new protocols or protocol changes are anticipated during a short period, the sponsor is encouraged, to the extent feasible, to include these all in a single submission.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 53 FR 1918, Jan. 25, 1988; 61 FR 51530, Oct. 2, 1996; 67 FR 9585, Mar. 4, 2002; 74 FR 40942, Aug. 13, 2009]

§312.31 Information amendments.

(a) *Requirement for information amendment.* A sponsor shall report in an information amendment essential information on the IND that is not within the scope of a protocol amendment, IND safety reports, or annual report. Examples of information requiring an information amendment include:

(1) New toxicology, chemistry, or other technical information; or

(2) A report regarding the discontinuance of a clinical investigation.

(b) *Content and format of an information amendment.* An information amendment is required to bear prominent identification of its contents (e.g., "Information Amendment: Chemistry, Manufacturing, and Control", "Information Amendment: Pharmacology-Toxicology", "Information Amendment: Clinical"), and to contain the following:

(1) A statement of the nature and purpose of the amendment.

(2) An organized submission of the data in a format appropriate for scientific review.

(3) If the sponsor desires FDA to comment on an information amendment, a request for such comment.

(c) *When submitted*. Information amendments to the IND should be submitted as necessary but, to the extent feasible, not more than every 30 days.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 53 FR 1918, Jan. 25, 1988; 67 FR 9585, Mar. 4, 2002]

§312.32 IND safety reporting.

(a) *Definitions*. The following definitions of terms apply to this section:

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Life-threatening adverse event or life-threatening suspected adverse reaction. An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Serious adverse event or *serious suspected adverse reaction*. An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Unexpected adverse event or unexpected suspected adverse reaction. An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or

is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

(b) Review of safety information. The sponsor must promptly review all information relevant to the safety of the drug obtained or otherwise received by the sponsor from foreign or domestic sources, including information derived from any clinical or epidemiological investigations, animal or in vitro studies, reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities and reports of foreign commercial marketing experience for drugs that are not marketed in the United States.

(c)(1) IND safety reports. The sponsor must notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting under paragraph (c)(1)(i), (c)(1)(ii), (c)(1)(iii), or (c)(1)(iv) of this section. In each IND safety report, the sponsor must identify all IND safety reports previously submitted to FDA concerning a similar suspected adverse reaction, and must analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information.

(i) Serious and unexpected suspected adverse reaction. The sponsor must report any suspected adverse reaction that is both serious and unexpected. The sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:

(A) A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome);

(B) One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture);

(C) An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

(ii) Findings from other studies. The sponsor must report any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies (other than those reported under paragraph (c)(1)(i) of this section), whether or not conducted under an IND, and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug. Ordinarily, such a finding would result in a safety-related change in the protocol, informed consent, investigator brochure (excluding routine updates of these documents), or other aspects of the overall conduct of the clinical investigation.

(iii) Findings from animal or in vitro testing. The sponsor must report any findings from animal or in vitro testing, whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug, such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of significant organ toxicity at or near the expected human exposure. Ordinarily, any such findings would result in a safety-related change in the protocol, informed consent, investigator brochure (ex-

cluding routine updates of these documents), or other aspects of the overall conduct of the clinical investigation.

(iv) Increased rate of occurrence of serious suspected adverse reactions. The sponsor must report any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure.

(v) Submission of IND safety reports. The sponsor must submit each IND safety report in a narrative format or on FDA Form 3500A or in an electronic format that FDA can process, review, and archive. FDA will periodically issue guidance on how to provide the electronic submission (e.g., method of transmission, media, file formats, preparation and organization of files). The sponsor may submit foreign suspected adverse reactions on a Council for International Organizations of Medical Sciences (CIOMS) I Form instead of a FDA Form 3500A. Reports of overall findings or pooled analyses from published and unpublished in vitro, animal, epidemiological, or clinical studies must be submitted in a narrative format. Each notification to FDA must bear prominent identification of its contents, i.e., "IND Safety Report," and must be transmitted to the review division in the Center for Drug Evaluation and Research or in the Center for Biologics Evaluation and Research that has responsibility for review of the IND. Upon request from FDA, the sponsor must submit to FDA any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request.

(2) Unexpected fatal or life-threatening suspected adverse reaction reports. The sponsor must also notify FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

(3) Reporting format or frequency. FDA may require a sponsor to submit IND safety reports in a format or at a frequency different than that required under this paragraph. The sponsor may also propose and adopt a different reporting format or frequency if the change is agreed to in advance by the director of the FDA review division that has responsibility for review of the IND.

(4) Investigations of marketed drugs. A sponsor of a clinical study of a drug marketed or approved in the United States that is conducted under an IND is required to submit IND safety reports for suspected adverse reactions that are observed in the clinical study, at domestic or foreign study sites. The sponsor must also submit safety information from the clinical study as prescribed by the postmarketing safety reporting requirements (e.g., §§ 310.305, 314.80, and 600.80 of this chapter).

(5) Reporting study endpoints. Study endpoints (e.g., mortality or major morbidity) must be reported to FDA by the sponsor as described in the protocol and ordinarily would not be reported under paragraph (c) of this section. However, if a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the drug and the event (e.g., death from anaphylaxis), the event must be reported under § 312.32(c)(1)(i) as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (e.g., all-cause mortality).

(d) Followup. (1) The sponsor must promptly investigate all safety information it receives.

(2) Relevant followup information to an IND safety report must be submitted as soon as the information is available and must be identified as such, i.e., "Followup IND Safety Report."

(3) If the results of a sponsor's investigation show that an adverse event not initially determined to be reportable under paragraph (c) of this section is so reportable, the sponsor must report such suspected adverse reaction in an IND safety report as soon as possible, but in no case later than 15 calendar days after the determination is made.

(e) Disclaimer. A safety report or other information submitted by a sponsor under this part (and any release by FDA of that report or information) does not necessarily reflect a conclusion by the sponsor or FDA that the report or information constitutes an admission that the drug caused or contributed to an adverse event. A sponsor need not admit, and may deny, that the report or infor-

mation submitted by the sponsor constitutes an admission that the drug caused or contributed to an adverse event.

[75 FR 59961, Sept. 29, 2010]

§312.33 Annual reports.

A sponsor shall within 60 days of the anniversary date that the IND went into effect, submit a brief report of the progress of the investigation that includes:

(a) *Individual study information*. A brief summary of the status of each study in progress and each study completed during the previous year. The summary is required to include the following information for each study:

(1) The title of the study (with any appropriate study identifiers such as protocol number), its purpose, a brief statement identifying the patient population, and a statement as to whether the study is completed.

(2) The total number of subjects initially planned for inclusion in the study; the number entered into the study to date, tabulated by age group, gender, and race; the number whose participation in the study was completed as planned; and the number who dropped out of the study for any reason.

(3) If the study has been completed, or if interim results are known, a brief description of any available study results.

(b) *Summary information*. Information obtained during the previous year's clinical and nonclinical investigations, including:

(1) A narrative or tabular summary showing the most frequent and most serious adverse experiences by body system.

(2) A summary of all IND safety reports submitted during the past year.

(3) A list of subjects who died during participation in the investigation, with the cause of death for each subject.

(4) A list of subjects who dropped out during the course of the investigation in association with any adverse experience, whether or not thought to be drug related.

(5) A brief description of what, if anything, was obtained that is pertinent to an understanding of the drug's actions, including, for example, information about dose response, information from controlled trials, and information about bioavailability.

(6) A list of the preclinical studies (including animal studies) completed or in progress during the past year and a summary of the major preclinical findings.

(7) A summary of any significant manufacturing or microbiological changes made during the past year.

(c) A description of the general investigational plan for the coming year to replace that submitted 1 year earlier. The general investigational plan shall contain the information required under §312.23(a)(3)(iv).

(d) If the investigator brochure has been revised, a description of the revision and a copy of the new brochure.

(e) A description of any significant Phase 1 protocol modifications made during the previous year and not previously reported to the IND in a protocol amendment.

(f) A brief summary of significant foreign marketing developments with the drug during the past year, such as approval of marketing in any country or withdrawal or suspension from marketing in any country.

(g) If desired by the sponsor, a log of any outstanding business with respect to the IND for which the sponsor requests or expects a reply, comment, or meeting.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 63 FR 6862, Feb. 11, 1998; 67 FR 9585, Mar. 4, 2002]

§ 312.38 Withdrawal of an IND.

(a) At any time a sponsor may withdraw an effective IND without prejudice.

(b) If an IND is withdrawn, FDA shall be so notified, all clinical investigations conducted under the IND shall be ended, all current investigators notified, and all stocks of the drug returned to the sponsor or otherwise disposed of at the request of the sponsor in accordance with § 312.59.

(c) If an IND is withdrawn because of a safety reason, the sponsor shall promptly so inform FDA, all participating investigators, and all reviewing Institutional Review Boards, together with the reasons for such withdrawal.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 67 FR 9586, Mar. 4, 2002]

Subpart C—Administrative Actions

§ 312.40 General requirements for use of an investigational new drug in a clinical investigation.

(a) An investigational new drug may be used in a clinical investigation if the following conditions are met:

(1) The sponsor of the investigation submits an IND for the drug to FDA; the IND is in effect under paragraph (b) of this section; and the sponsor complies with all applicable requirements in this part and parts 50 and 56 with respect to the conduct of the clinical investigations; and

(2) Each participating investigator conducts his or her investigation in compliance with the requirements of this part and parts 50 and 56.

(b) An IND goes into effect:

(1) Thirty days after FDA receives the IND, unless FDA notifies the sponsor that the investigations described in the IND are subject to a clinical hold under § 312.42; or

(2) On earlier notification by FDA that the clinical investigations in the IND may begin. FDA will notify the sponsor in writing of the date it receives the IND.

(c) A sponsor may ship an investigational new drug to investigators named in the IND:

(1) Thirty days after FDA receives the IND; or

(2) On earlier FDA authorization to ship the drug.

(d) An investigator may not administer an investigational new drug to human subjects until the IND goes into effect under paragraph (b) of this section.

§ 312.41 Comment and advice on an IND.

(a) FDA may at any time during the course of the investigation communicate with the sponsor orally or in writing about deficiencies in the IND or about FDA's need for more data or information.

(b) On the sponsor's request, FDA will provide advice on specific matters relating to an IND. Examples of such advice may include advice on the adequacy of technical data to support an investigational plan, on the design of a clinical trial, and on whether proposed investigations are likely to produce the data and information that is needed to meet requirements for a marketing application.

(c) Unless the communication is accompanied by a clinical hold order under § 312.42, FDA communications with a sponsor under this section are solely advisory and do not require any modification in the planned or ongoing clinical investigations or response to the agency.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 67 FR 9586, Mar. 4, 2002]

§ 312.42 Clinical holds and requests for modification.

(a) *General.* A clinical hold is an order issued by FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation. The clinical hold order may apply to one or more of the investigations covered by an IND. When a proposed study is placed on clinical hold, subjects may not be given the investigational drug. When an ongoing study is placed on clinical hold, no new subjects may be recruited to the study and placed on the investigational drug; patients already in the study should be taken off therapy involving the investigational drug unless specifically permitted by FDA in the interest of patient safety.

(b) *Grounds for imposition of clinical hold*—(1) *Clinical hold of a Phase 1 study under an IND.* FDA may place a proposed or ongoing Phase 1 investigation on clinical hold if it finds that:

(i) Human subjects are or would be exposed to an unreasonable and significant risk of illness or injury;

(ii) The clinical investigators named in the IND are not qualified by reason of their scientific training and experience to conduct the investigation described in the IND;

(iii) The investigator brochure is misleading, erroneous, or materially incomplete; or

(iv) The IND does not contain sufficient information required under § 312.23 to assess the risks to subjects of the proposed studies.

(v) The IND is for the study of an investigational drug intended to treat a life-threatening disease or condition that affects both genders, and men or women with reproductive potential who have the disease or condition being studied are excluded from eligibility because of a risk or potential risk from use of the investigational drug of reproductive toxicity (*i.e.*, affecting reproductive organs) or developmental toxicity (*i.e.*, affecting potential offspring). The phrase "women with reproductive potential" does not include pregnant women. For purposes of this paragraph, "life-threatening illnesses or diseases" are defined as "diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted." The clinical hold would not apply under this paragraph to clinical studies conducted:

(A) Under special circumstances, such as studies pertinent only to one gender (e.g., studies evaluating the excretion of a drug in semen or the effects on menstrual function);

(B) Only in men or women, as long as a study that does not exclude members of the other gender with reproductive potential is being conducted concurrently, has been conducted, or will take place within a reasonable time agreed upon by the agency; or

(C) Only in subjects who do not suffer from the disease or condition for which the drug is being studied.

(2) *Clinical hold of a Phase 2 or 3 study under an IND.* FDA may place a proposed or ongoing Phase 2 or 3 investigation on clinical hold if it finds that:

(i) Any of the conditions in paragraphs (b)(1)(i) through (b)(1)(v) of this section apply; or

(ii) The plan or protocol for the investigation is clearly deficient in design to meet its stated objectives.

(3) *Clinical hold of an expanded access IND or expanded access protocol.* FDA may place an expanded access IND or expanded access protocol on clinical hold under the following conditions:

(i) *Final use.* FDA may place a proposed expanded access IND or treatment use protocol on clinical hold if it is determined that:

(A) The pertinent criteria in subpart I of this part for permitting the expanded access use to begin are not satisfied; or

(B) The expanded access IND or expanded access protocol does not comply with the requirements for expanded access submissions in subpart I of this part.

(ii) *Ongoing use*. FDA may place an ongoing expanded access IND or expanded access protocol on clinical hold if it is determined that the pertinent criteria in subpart I of this part for permitting the expanded access are no longer satisfied.

(4) *Clinical hold of any study that is not designed to be adequate and well-controlled.* FDA may place a proposed or ongoing investigation that is not designed to be adequate and well-controlled on clinical hold if it finds that:

(i) Any of the conditions in paragraph (b)(1) or (b)(2) of this section apply; or

(ii) There is reasonable evidence the investigation that is not designed to be adequate and well-controlled is impeding enrollment in, or otherwise interfering with the conduct or completion of, a study that is designed to be an adequate and well-controlled investigation of the same or another investigational drug; or

(iii) Insufficient quantities of the investigational drug exist to adequately conduct both the investigation that is not designed to be adequate and well-controlled and the investigations that are designed to be adequate and well-controlled; or

(iv) The drug has been studied in one or more adequate and well-controlled investigations that strongly suggest lack of effectiveness; or

(v) Another drug under investigation or approved for the same indication and available to the same patient population has demonstrated a better potential benefit/risk balance; or

(vi) The drug has received marketing approval for the same indication in the same patient population; or

(vii) The sponsor of the study that is designed to be an adequate and well-controlled investigation is not actively pursuing marketing approval of the investigational drug with due diligence; or

(viii) The Commissioner determines that it would not be in the public interest for the study to be conducted or continued. FDA ordinarily intends that clinical holds under paragraphs (b)(4)(ii), (b)(4)(iii) and (b)(4)(v) of this section would only apply to additional enrollment in nonconcurrently controlled trials rather than eliminating continued access to individuals already receiving the investigational drug.

(5) *Clinical hold of any investigation involving an exception from informed consent under § 50.24 of this chapter.* FDA may place a proposed or ongoing investigation involving an exception from informed consent under § 50.24 of this chapter on clinical hold if it is determined that:

(i) Any of the conditions in paragraphs (b)(1) or (b)(2) of this section apply; or

(ii) The pertinent criteria in § 50.24 of this chapter for such an investigation to begin or continue are not submitted or not satisfied.

(6) Clinical hold of any investigation involving an exception from informed consent under § 50.23(d) of this chapter. FDA may place a proposed or ongoing investigation involving an exception from informed consent under § 50.23(d) of this chapter on clinical hold if it is determined that:

(i) Any of the conditions in paragraphs (b)(1) or (b)(2) of this section apply; or

(ii) A determination by the President to waive the prior consent requirement for the administration of an investigational new drug has not been made.

(c) Discussion of deficiency. Whenever FDA concludes that a deficiency exists in a clinical investigation that may be grounds for the imposition of clinical hold FDA will, unless patients are exposed to immediate and serious risk, attempt to discuss and satisfactorily resolve the matter with the sponsor before issuing the clinical hold order.

(d) *Imposition of clinical hold*. The clinical hold order may be made by telephone or other means of rapid communication or in writing. The clinical hold order will identify the studies under the IND to which the hold applies, and will briefly explain the basis for the action. The clinical hold order will be made by or on behalf of the Division Director with responsibility for review of the IND. As soon as possible, and no more than 30 days after imposition of the clinical hold, the Division Director will provide the sponsor a written explanation of the basis for the hold.

(e) *Resumption of clinical investigations.* An investigation may only resume after FDA (usually the Division Director, or the Director's designee, with responsibility for review of the IND) has notified the sponsor that the investigation may proceed. Resumption of the affected investigation(s) will be authorized when the sponsor corrects the deficiency(ies) previously cited or otherwise satisfies the agency that the investigation(s) can proceed. FDA may notify a sponsor of its determination regarding the clinical hold by telephone or other means of rapid communication. If a sponsor of an IND that has been placed on clinical hold requests in writing that the clinical hold be removed and submits a complete response to the issue(s) identified in the clinical hold order, FDA shall respond in writing to the sponsor within 30-calendar days of receipt of the request and the complete response. FDA's response will either remove or maintain the clinical hold, and will state the reasons for such determination. Notwithstanding the 30-calendar day response time, a sponsor may not proceed with a clinical trial on which a clinical hold has been imposed until the sponsor has been notified by FDA that the hold has been lifted.

(f) *Appeal*. If the sponsor disagrees with the reasons cited for the clinical hold, the sponsor may request reconsideration of the decision in accordance with § 312.48.

(g) *Conversion of IND on clinical hold to inactive status.* If all investigations covered by an IND remain on clinical hold for 1 year or more, the IND may be placed on inactive status by FDA under § 312.45.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 19477, May 22, 1987; 57 FR 13249, Apr. 15, 1992; 61 FR 51530, Oct. 2, 1996; 63 FR 68678, Dec. 14, 1998; 64 FR 54189, Oct. 5, 1999; 65 FR 34971, June 1, 2000; 74 FR 40942, Aug. 13, 2009]

§ 312.44 Termination.

(a) *General*. This section describes the procedures under which FDA may terminate an IND. If an IND is terminated, the sponsor shall end all clinical investigations conducted under the IND and recall or otherwise provide for the disposition of all unused supplies of the drug. A termination action may be based on deficiencies in the IND or in the conduct of an investigation under an IND. Except as provided in paragraph (d) of this section, a termination shall be preceded by a proposal to terminate by FDA and an opportunity for the sponsor to respond. FDA will, in general, only initiate an action under this section after first attempting to resolve differences informally or, when appropriate, through the clinical hold procedures described in § 312.42.

(b) *Grounds for termination*—(1) *Phase 1*. FDA may propose to terminate an IND during Phase 1 if it finds that:

(i) Human subjects would be exposed to an unreasonable and significant risk of illness or injury.

(ii) The IND does not contain sufficient information required under § 312.23 to assess the safety to subjects of the clinical investigations.

(iii) The methods, facilities, and controls used for the manufacturing, processing, and packing of the investigational drug are inadequate to establish and maintain appropriate standards of identity, strength, quality, and purity as needed for subject safety.

(iv) The clinical investigations are being conducted in a manner substantially different than that described in the protocols submitted in the IND.

(v) The drug is being promoted or distributed for commercial purposes not justified by the requirements of the investigation or permitted by § 312.7.

(vi) The IND, or any amendment or report to the IND, contains an untrue statement of a material fact or omits material information required by this part.

(vii) The sponsor fails promptly to investigate and inform the Food and Drug Administration and all investigators of serious and unexpected adverse experiences in accordance with § 312.32 or fails to make any other report required under this part.

(viii) The sponsor fails to submit an accurate annual report of the investigations in accordance with § 312.33.

(ix) The sponsor fails to comply with any other applicable requirement of this part, part 50, or part 56.

(x) The IND has remained on inactive status for 5 years or more.

(xi) The sponsor fails to delay a proposed investigation under the IND or to suspend an ongoing investigation that has been placed on clinical hold under § 312.42(b)(4).

(2) *Phase 2 or 3.* FDA may propose to terminate an IND during Phase 2 or Phase 3 if FDA finds that:

(i) Any of the conditions in paragraphs (b)(1)(i) through (b)(1)(xi) of this section apply; or

(ii) The investigational plan or protocol(s) is not reasonable as a bona fide scientific plan to determine whether or not the drug is safe and effective for use; or

(iii) There is convincing evidence that the drug is not effective for the purpose for which it is being investigated.

(3) FDA may propose to terminate a treatment IND if it finds that:

(i) Any of the conditions in paragraphs (b)(1)(i) through (x) of this section apply; or

(ii) Any of the conditions in § 312.42(b)(3) apply.

(c) *Opportunity for sponsor response.* (1) If FDA proposes to terminate an IND, FDA will notify the sponsor in writing, and invite correction or explanation within a period of 30 days.

(2) On such notification, the sponsor may provide a written explanation or correction or may request a conference with FDA to provide the requested explanation or correction. If the sponsor does not respond to the notification within the allocated time, the IND shall be terminated.

(3) If the sponsor responds but FDA does not accept the explanation or correction submitted, FDA shall inform the sponsor in writing of the reason for the nonacceptance and provide the sponsor with an opportunity for a regulatory hearing before FDA under part 16 on the question of whether the IND should be terminated. The sponsor's request for a regulatory hearing must be made within 10 days of the sponsor's receipt of FDA's notification of nonacceptance.

(d) *Immediate termination of IND.* Notwithstanding paragraphs (a) through (c) of this section, if at any time FDA concludes that continuation of the investigation presents an immediate and substantial danger to the health of individuals, the agency shall immediately, by written notice to the sponsor from the Director of the Center for Drug Evaluation and Research or the Director of the Center for Biologics Evaluation and Research, terminate the IND. An IND so terminated is subject to reinstatement by the Director on the basis of additional submissions that eliminate such danger. If an IND is terminated under this paragraph, the agency will afford the sponsor an opportunity for a regulatory hearing under part 16 on the question of whether the IND should be reinstated.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 55 FR 11579, Mar. 29, 1990; 57 FR 13249, Apr. 15, 1992; 67 FR 9586, Mar. 4, 2002]

§ 312.45 Inactive status.

(a) If no subjects are entered into clinical studies for a period of 2 years or more under an IND, or if all investigations under an IND remain on clinical hold for 1 year or more, the IND may be placed by FDA on inactive status. This action may be taken by FDA either on request of the sponsor or on

FDA's own initiative. If FDA seeks to act on its own initiative under this section, it shall first notify the sponsor in writing of the proposed inactive status. Upon receipt of such notification, the sponsor shall have 30 days to respond as to why the IND should continue to remain active.

(b) If an IND is placed on inactive status, all investigators shall be so notified and all stocks of the drug shall be returned or otherwise disposed of in accordance with § 312.59.

(c) A sponsor is not required to submit annual reports to an IND on inactive status. An inactive IND is, however, still in effect for purposes of the public disclosure of data and information under § 312.130.

(d) A sponsor who intends to resume clinical investigation under an IND placed on inactive status shall submit a protocol amendment under § 312.30 containing the proposed general investigational plan for the coming year and appropriate protocols. If the protocol amendment relies on information previously submitted, the plan shall reference such information. Additional information supporting the proposed investigation, if any, shall be submitted in an information amendment. Notwithstanding the provisions of § 312.30, clinical investigations under an IND on inactive status may only resume (1) 30 days after FDA receives the protocol amendment, unless FDA notifies the sponsor that the investigations described in the amendment are subject to a clinical hold under § 312.42, or (2) on earlier notification by FDA that the clinical investigations described in the protocol amendment may begin.

(e) An IND that remains on inactive status for 5 years or more may be terminated under § 312.44.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 67 FR 9586, Mar. 4, 2002]

§ 312.47 Meetings.

(a) *General*. Meetings between a sponsor and the agency are frequently useful in resolving questions and issues raised during the course of a clinical investigation. FDA encourages such meetings to the extent that they aid in the evaluation of the drug and in the solution of scientific problems concerning the drug, to the extent that FDA's resources permit. The general principle underlying the conduct of such meetings is that there should be free, full, and open communication about any scientific or medical question that may arise during the clinical investigation. These meetings shall be conducted and documented in accordance with part 10.

(b) *"End-of-Phase 2" meetings and meetings held before submission of a marketing application.* At specific times during the drug investigation process, meetings between FDA and a sponsor can be especially helpful in minimizing wasteful expenditures of time and money and thus in speeding the drug development and evaluation process. In particular, FDA has found that meetings at the end of Phase 2 of an investigation (end-of-Phase 2 meetings) are of considerable assistance in planning later studies and that meetings held near completion of Phase 3 and before submission of a marketing application ("pre-NDA" meetings) are helpful in developing methods of presentation and submission of data in the marketing application that facilitate review and allow timely FDA response.

(1) *End-of-Phase 2 meetings*—(i) *Purpose*. The purpose of an end-of-phase 2 meeting is to determine the safety of proceeding to Phase 3, to evaluate the Phase 3 plan and protocols and the adequacy of current studies and plans to assess pediatric safety and effectiveness, and to identify any additional information necessary to support a marketing application for the uses under investigation.

(ii) *Eligibility for meeting.* While the end-of-Phase 2 meeting is designed primarily for IND's involving new molecular entities or major new uses of marketed drugs, a sponsor of any IND may request and obtain an end-of-Phase 2 meeting.

(iii) *Timing*. To be most useful to the sponsor, end-of-Phase 2 meetings should be held before major commitments of effort and resources to specific Phase 3 tests are made. The scheduling of an

end-of-Phase 2 meeting is not, however, intended to delay the transition of an investigation from Phase 2 to Phase 3.

(iv) *Advance information.* At least 1 month in advance of an end-of-Phase 2 meeting, the sponsor should submit background information on the sponsor's plan for Phase 3, including summaries of the Phase 1 and 2 investigations, the specific protocols for Phase 3 clinical studies, plans for any additional nonclinical studies, plans for pediatric studies, including a time line for protocol finalization, enrollment, completion, and data analysis, or information to support any planned request for waiver or deferral of pediatric studies, and, if available, tentative labeling for the drug. The recommended contents of such a submission are described more fully in FDA Staff Manual Guide 4850.7 that is publicly available under FDA's public information regulations in part 20.

(v) *Conduct of meeting*. Arrangements for an end-of-Phase 2 meeting are to be made with the division in FDA's Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research which is responsible for review of the IND. The meeting will be scheduled by FDA at a time convenient to both FDA and the sponsor. Both the sponsor and FDA may bring consultants to the meeting. The meeting should be directed primarily at establishing agreement between FDA and the sponsor of the overall plan for Phase 3 and the objectives and design of particular studies. The adequacy of the technical information to support Phase 3 studies and/or a marketing application may also be discussed. FDA will also provide its best judgment, at that time, of the pediatric studies that will be required for the drug product and whether their submission will be deferred until after approval. Agreements reached at the meeting on these matters will be recorded in minutes of the conference that will be taken by FDA in accordance with § 10.65 and provided to the sponsor. The minutes along with any other written material provided to the sponsor will serve as a permanent record of any agreements reached. Barring a significant scientific development that requires otherwise, studies conducted in accordance with the agreement shall be presumed to be sufficient in objective and design for the purpose of obtaining marketing approval for the drug.

(2) *"Pre-NDA" and "pre-BLA" meetings.* FDA has found that delays associated with the initial review of a marketing application may be reduced by exchanges of information about a proposed marketing application. The primary purpose of this kind of exchange is to uncover any major unresolved problems, to identify those studies that the sponsor is relying on as adequate and well-controlled to establish the drug's effectiveness, to identify the status of ongoing or needed studies adequate to assess pediatric safety and effectiveness, to acquaint FDA reviewers with the general information to be submitted in the marketing application (including technical information), to discuss appropriate methods for statistical analysis of the data, and to discuss the best approach to the presentation and formatting of data in the marketing application. Arrangements for such a meeting are to be initiated by the sponsor with the division responsible for review of the IND. To permit FDA to provide the sponsor with the most useful advice on preparing a marketing application, the sponsor should submit to FDA's reviewing division at least 1 month in advance of the meeting the following information:

(i) A brief summary of the clinical studies to be submitted in the application.

(ii) A proposed format for organizing the submission, including methods for presenting the data.

(iii) Information on the status of needed or ongoing pediatric studies.

(iv) Any other information for discussion at the meeting.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 55 FR 11580, Mar. 29, 1990; 63 FR 66669, Dec. 2, 1998; 67 FR 9586, Mar. 4, 2002]

§ 312.48 Dispute resolution.

(a) *General*. The Food and Drug Administration is committed to resolving differences between sponsors and FDA reviewing divisions with respect to requirements for IND's as quickly and amicably as possible through the cooperative exchange of information and views.

(b) *Administrative and procedural issues.* When administrative or procedural disputes arise, the sponsor should first attempt to resolve the matter with the division in FDA's Center for Drug Evaluation and Research or Center for Biologics Evaluation and Research which is responsible for review of the IND, beginning with the consumer safety officer assigned to the application. If the dispute is not resolved, the sponsor may raise the matter with the person designated as ombudsman, whose function shall be to investigate what has happened and to facilitate a timely and equitable resolution. Appropriate issues to raise with the ombudsman include resolving difficulties in scheduling meetings and obtaining timely replies to inquiries. Further details on this procedure are contained in FDA Staff Manual Guide 4820.7 that is publicly available under FDA's public information regulations in part 20.

(c) *Scientific and medical disputes.* (1) When scientific or medical disputes arise during the drug investigation process, sponsors should discuss the matter directly with the responsible reviewing officials. If necessary, sponsors may request a meeting with the appropriate reviewing officials and management representatives in order to seek a resolution. Requests for such meetings shall be directed to the director of the division in FDA's Center for Drug Evaluation and Research or Center for Biologics Evaluation and Research which is responsible for review of the IND. FDA will make every attempt to grant requests for meetings that involve important issues and that can be scheduled at mutually convenient times.

(2) The "end-of-Phase 2" and "pre-NDA" meetings described in § 312.47(b) will also provide a timely forum for discussing and resolving scientific and medical issues on which the sponsor disagrees with the agency.

(3) In requesting a meeting designed to resolve a scientific or medical dispute, applicants may suggest that FDA seek the advice of outside experts, in which case FDA may, in its discretion, invite to the meeting one or more of its advisory committee members or other consultants, as designated by the agency. Applicants may rely on, and may bring to any meeting, their own consultants. For major scientific and medical policy issues not resolved by informal meetings, FDA may refer the matter to one of its standing advisory committees for its consideration and recommendations.

[52 FR 8831, Mar. 19, 1987, as amended at 55 FR 11580, Mar. 29, 1990]

Subpart D—Responsibilities of Sponsors and Investigators

§ 312.50 General responsibilities of sponsors.

Sponsors are responsible for selecting qualified investigators, providing them with the information they need to conduct an investigation properly, ensuring proper monitoring of the investigation(s), ensuring that the investigation(s) is conducted in accordance with the general investigational plan and protocols contained in the IND, maintaining an effective IND with respect to the investigations, and ensuring that FDA and all participating investigators are promptly informed of significant new adverse effects or risks with respect to the drug. Additional specific responsibilities of sponsors are described elsewhere in this part.

§ 312.52 Transfer of obligations to a contract research organization.

(a) A sponsor may transfer responsibility for any or all of the obligations set forth in this part to a contract research organization. Any such transfer shall be described in writing. If not all obligations are transferred, the writing is required to describe each of the obligations being assumed by the contract research organization. If all obligations are transferred, a general statement that all obligations

have been transferred is acceptable. Any obligation not covered by the written description shall be deemed not to have been transferred.

(b) A contract research organization that assumes any obligation of a sponsor shall comply with the specific regulations in this chapter applicable to this obligation and shall be subject to the same regulatory action as a sponsor for failure to comply with any obligation assumed under these regulations. Thus, all references to "sponsor" in this part apply to a contract research organization to the extent that it assumes one or more obligations of the sponsor.

§ 312.53 Selecting investigators and monitors.

(a) *Selecting investigators.* A sponsor shall select only investigators qualified by training and experience as appropriate experts to investigate the drug.

(b) *Control of drug.* A sponsor shall ship investigational new drugs only to investigators participating in the investigation.

(c) *Obtaining information from the investigator.* Before permitting an investigator to begin participation in an investigation, the sponsor shall obtain the following:

(1) A signed investigator statement (Form FDA-1572) containing:

(i) The name and address of the investigator;

(ii) The name and code number, if any, of the protocol(s) in the IND identifying the study(ies) to be conducted by the investigator;

(iii) The name and address of any medical school, hospital, or other research facility where the clinical investigation(s) will be conducted;

(iv) The name and address of any clinical laboratory facilities to be used in the study;

(v) The name and address of the IRB that is responsible for review and approval of the study(ies);

(vi) A commitment by the investigator that he or she:

(a) Will conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, the rights, or welfare of subjects;

(b) Will comply with all requirements regarding the obligations of clinical investigators and all other pertinent requirements in this part;

(c) Will personally conduct or supervise the described investigation(s);

(d) Will inform any potential subjects that the drugs are being used for investigational purposes and will ensure that the requirements relating to obtaining informed consent (21 CFR part 50) and institutional review board review and approval (21 CFR part 56) are met;

(e) Will report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with § 312.64;

(f) Has read and understands the information in the investigator's brochure, including the potential risks and side effects of the drug; and

(g) Will ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

(vii) A commitment by the investigator that, for an investigation subject to an institutional review requirement under part 56, an IRB that complies with the requirements of that part will be responsible for the initial and continuing review and approval of the clinical investigation and that the investigator will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others, and will not make any changes in the research

without IRB approval, except where necessary to eliminate apparent immediate hazards to the human subjects.

(viii) A list of the names of the subinvestigators (e.g., research fellows, residents) who will be assisting the investigator in the conduct of the investigation(s).

(2) *Curriculum vitae*. A curriculum vitae or other statement of qualifications of the investigator showing the education, training, and experience that qualifies the investigator as an expert in the clinical investigation of the drug for the use under investigation.

(3) *Clinical protocol.* (i) For Phase 1 investigations, a general outline of the planned investigation including the estimated duration of the study and the maximum number of subjects that will be involved.

(ii) For Phase 2 or 3 investigations, an outline of the study protocol including an approximation of the number of subjects to be treated with the drug and the number to be employed as controls, if any; the clinical uses to be investigated; characteristics of subjects by age, sex, and condition; the kind of clinical observations and laboratory tests to be conducted; the estimated duration of the study; and copies or a description of case report forms to be used.

(4) *Financial disclosure information.* Sufficient accurate financial information to allow the sponsor to submit complete and accurate certification or disclosure statements required under part 54 of this chapter. The sponsor shall obtain a commitment from the clinical investigator to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

(d) *Selecting monitors.* A sponsor shall select a monitor qualified by training and experience to monitor the progress of the investigation.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 61 FR 57280, Nov. 5, 1996; 63 FR 5252, Feb. 2, 1998; 67 FR 9586, Mar. 4, 2002]

§ 312.54 Emergency research under § 50.24 of this chapter.

(a) The sponsor shall monitor the progress of all investigations involving an exception from informed consent under § 50.24 of this chapter. When the sponsor receives from the IRB information concerning the public disclosures required by § 50.24(a)(7)(ii) and (a)(7)(iii) of this chapter, the sponsor promptly shall submit to the IND file and to Docket Number 95S-0158 in the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, copies of the information that was disclosed, identified by the IND number.

(b) The sponsor also shall monitor such investigations to identify when an IRB determines that it cannot approve the research because it does not meet the criteria in the exception in § 50.24(a) of this chapter or because of other relevant ethical concerns. The sponsor promptly shall provide this information in writing to FDA, investigators who are asked to participate in this or a substantially equivalent clinical investigation, and other IRB's that are asked to review this or a substantially equivalent investigation.

[61 FR 51530, Oct. 2, 1996, as amended at 68 FR 24879, May 9, 2003]

§ 312.55 Informing investigators.

(a) Before the investigation begins, a sponsor (other than a sponsor-investigator) shall give each participating clinical investigator an investigator brochure containing the information described in § 312.23(a)(5).

(b) The sponsor shall, as the overall investigation proceeds, keep each participating investigator informed of new observations discovered by or reported to the sponsor on the drug, particularly with respect to adverse effects and safe use. Such information may be distributed to investigators by means of periodically revised investigator brochures, reprints or published studies, reports or letters

to clinical investigators, or other appropriate means. Important safety information is required to be relayed to investigators in accordance with § 312.32.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 67 FR 9586, Mar. 4, 2002]

§ 312.56 Review of ongoing investigations.

(a) The sponsor shall monitor the progress of all clinical investigations being conducted under its IND.

(b) A sponsor who discovers that an investigator is not complying with the signed agreement (Form FDA-1572), the general investigational plan, or the requirements of this part or other applicable parts shall promptly either secure compliance or discontinue shipments of the investigational new drug to the investigator and end the investigator's participation in the investigation. If the investigator's participation in the investigation is ended, the sponsor shall require that the investigator dispose of or return the investigational drug in accordance with the requirements of § 312.59 and shall notify FDA.

(c) The sponsor shall review and evaluate the evidence relating to the safety and effectiveness of the drug as it is obtained from the investigator. The sponsors shall make such reports to FDA regarding information relevant to the safety of the drug as are required under § 312.32. The sponsor shall make annual reports on the progress of the investigation in accordance with § 312.33.

(d) A sponsor who determines that its investigational drug presents an unreasonable and significant risk to subjects shall discontinue those investigations that present the risk, notify FDA, all institutional review boards, and all investigators who have at any time participated in the investigation of the discontinuance, assure the disposition of all stocks of the drug outstanding as required by § 312.59, and furnish FDA with a full report of the sponsor's actions. The sponsor shall discontinue the investigation as soon as possible, and in no event later than 5 working days after making the determination that the investigation should be discontinued. Upon request, FDA will confer with a sponsor on the need to discontinue an investigation.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 67 FR 9586, Mar. 4, 2002]

§ 312.57 Recordkeeping and record retention.

(a) A sponsor shall maintain adequate records showing the receipt, shipment, or other disposition of the investigational drug. These records are required to include, as appropriate, the name of the investigator to whom the drug is shipped, and the date, quantity, and batch or code mark of each such shipment.

(b) A sponsor shall maintain complete and accurate records showing any financial interest in § 54.4(a)(3)(i), (a)(3)(ii), (a)(3)(iii), and (a)(3)(iv) of this chapter paid to clinical investigators by the sponsor of the covered study. A sponsor shall also maintain complete and accurate records concerning all other financial interests of investigators subject to part 54 of this chapter.

(c) A sponsor shall retain the records and reports required by this part for 2 years after a marketing application is approved for the drug; or, if an application is not approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and FDA has been so notified.

(d) A sponsor shall retain reserve samples of any test article and reference standard identified in, and used in any of the bioequivalence or bioavailability studies described in, § 320.38 or § 320.63 of this chapter, and release the reserve samples to FDA upon request, in accordance with, and for the period specified in § 320.38.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 58 FR 25926, Apr. 28, 1993; 63 FR 5252, Feb. 2, 1998; 67 FR 9586, Mar. 4, 2002]

§ 312.58 Inspection of sponsor's records and reports.

(a) *FDA inspection.* A sponsor shall upon request from any properly authorized officer or employee of the Food and Drug Administration, at reasonable times, permit such officer or employee to have access to and copy and verify any records and reports relating to a clinical investigation conducted under this part. Upon written request by FDA, the sponsor shall submit the records or reports (or copies of them) to FDA. The sponsor shall discontinue shipments of the drug to any investigator who has failed to maintain or make available records or reports of the investigation as required by this part.

(b) *Controlled substances.* If an investigational new drug is a substance listed in any schedule of the Controlled Substances Act (21 U.S.C. 801; 21 CFR part 1308), records concerning shipment, delivery, receipt, and disposition of the drug, which are required to be kept under this part or other applicable parts of this chapter shall, upon the request of a properly authorized employee of the Drug Enforcement Administration of the U.S. Department of Justice, be made available by the investigator or sponsor to whom the request is made, for inspection and copying. In addition, the sponsor shall assure that adequate precautions are taken, including storage of the investigational drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance into illegal channels of distribution.

§ 312.59 Disposition of unused supply of investigational drug.

The sponsor shall assure the return of all unused supplies of the investigational drug from each individual investigator whose participation in the investigation is discontinued or terminated. The sponsor may authorize alternative disposition of unused supplies of the investigational drug provided this alternative disposition does not expose humans to risks from the drug. The sponsor shall maintain written records of any disposition of the drug in accordance with § 312.57.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 67 FR 9586, Mar. 4, 2002]

§ 312.60 General responsibilities of investigators.

An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation. An investigator shall, in accordance with the provisions of part 50 of this chapter, obtain the informed consent of each human subject to whom the drug is administered, except as provided in §§ 50.23 or 50.24 of this chapter. Additional specific responsibilities of clinical investigators are set forth in this part and in parts 50 and 56 of this chapter.

[52 FR 8831, Mar. 19, 1987, as amended at 61 FR 51530, Oct. 2, 1996]

§ 312.61 Control of the investigational drug.

An investigator shall administer the drug only to subjects under the investigator's personal supervision or under the supervision of a subinvestigator responsible to the investigator. The investigator shall not supply the investigational drug to any person not authorized under this part to receive it.

§ 312.62 Investigator recordkeeping and record retention.

(a) *Disposition of drug.* An investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects. If the investigation is terminated, suspended, discontinued, or completed, the investigator shall return the unused supplies of the drug to the sponsor, or otherwise provide for disposition of the unused supplies of the drug under § 312.59.

(b) *Case histories.* An investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each indi-

vidual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

(c) *Record retention.* An investigator shall retain records required to be maintained under this part for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 61 FR 57280, Nov. 5, 1996; 67 FR 9586, Mar. 4, 2002]

§ 312.64 Investigator reports.

(a) *Progress reports.* The investigator shall furnish all reports to the sponsor of the drug who is responsible for collecting and evaluating the results obtained. The sponsor is required under § 312.33 to submit annual reports to FDA on the progress of the clinical investigations.

(b) *Safety reports.* An investigator must immediately report to the sponsor any serious adverse event, whether or not considered drug related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the drug caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor. The investigator must record nonserious adverse events and report them to the sponsor according to the timetable for reporting specified in the protocol.

(c) *Final report.* An investigator shall provide the sponsor with an adequate report shortly after completion of the investigator's participation in the investigation.

(d) *Financial disclosure reports.* The clinical investigator shall provide the sponsor with sufficient accurate financial information to allow an applicant to submit complete and accurate certification or disclosure statements as required under part 54 of this chapter. The clinical investigator shall promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 63 FR 5252, Feb. 2, 1998; 67 FR 9586, Mar. 4, 2002; 75 FR 59963, Sept. 29, 2010]

§ 312.66 Assurance of IRB review.

An investigator shall assure that an IRB that complies with the requirements set forth in part 56 will be responsible for the initial and continuing review and approval of the proposed clinical study. The investigator shall also assure that he or she will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risk to human subjects or others, and that he or she will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 67 FR 9586, Mar. 4, 2002]

§ 312.68 Inspection of investigator's records and reports.

An investigator shall upon request from any properly authorized officer or employee of FDA, at reasonable times, permit such officer or employee to have access to, and copy and verify any records or reports made by the investigator pursuant to § 312.62. The investigator is not required to divulge subject names unless the records of particular individuals require a more detailed study of the cases,

or unless there is reason to believe that the records do not represent actual case studies, or do not represent actual results obtained.

§ 312.69 Handling of controlled substances.

If the investigational drug is subject to the Controlled Substances Act, the investigator shall take adequate precautions, including storage of the investigational drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance into illegal channels of distribution.

§ 312.70 Disqualification of a clinical investigator.

(a) If FDA has information indicating that an investigator (including a sponsor-investigator) has repeatedly or deliberately failed to comply with the requirements of this part, part 50 or part 56 of this chapter, or has repeatedly or deliberately submitted to FDA or to the sponsor false information in any required report, the Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research will furnish the investigator written notice of the matter complained of and offer the investigator an opportunity to explain the matter in writing, or, at the option of the investigator, in an informal conference. If an explanation is offered and accepted by the applicable Center, the Center will discontinue the disqualification proceeding. If an explanation is offered but not accepted by the applicable Center, the investigator will be given an opportunity for a regulatory hearing under part 16 of this chapter on the question of whether the investigator is eligible to receive test articles under this part and eligible to conduct any clinical investigation that supports an application for a research or marketing permit for products regulated by FDA.

(b) After evaluating all available information, including any explanation presented by the investigator, if the Commissioner determines that the investigator has repeatedly or deliberately failed to comply with the requirements of this part, part 50 or part 56 of this chapter, or has repeatedly or deliberately submitted to FDA or to the sponsor false information in any required report, the Commissioner will notify the investigator, the sponsor of any investigation in which the investigator has been named as a participant, and the reviewing institutional review boards (IRBs) that the investigator is not eligible to receive test articles under this part. The notification to the investigator, sponsor, and IRBs will provide a statement of the basis for such determination. The notification also will explain that an investigator determined to be ineligible to receive test articles under this part will be ineligible to conduct any clinical investigation that supports an application for a research or marketing permit for products regulated by FDA, including drugs, biologics, devices, new animal drugs, foods, including dietary supplements, that bear a nutrient content claim or a health claim, infant formulas, food and color additives, and tobacco products.

(c) Each application or submission to FDA under the provisions of this chapter containing data reported by an investigator who has been determined to be ineligible to receive FDA-regulated test articles is subject to examination to determine whether the investigator has submitted unreliable data that are essential to the continuation of an investigation or essential to the approval of a marketing application, or essential to the continued marketing of an FDA-regulated product.

(d) If the Commissioner determines, after the unreliable data submitted by the investigator are eliminated from consideration, that the data remaining are inadequate to support a conclusion that it is reasonably safe to continue the investigation, the Commissioner will notify the sponsor, who shall have an opportunity for a regulatory hearing under part 16 of this chapter. If a danger to the public health exists, however, the Commissioner shall terminate the IND immediately and notify the sponsor and the reviewing IRBs of the termination. In such case, the sponsor shall have an opportunity for a regulatory hearing before FDA under part 16 on the question of whether the IND should be reinstated. The determination that an investigation may not be considered in support of a research or marketing application or a notification or petition submission does not, however, relieve

the sponsor of any obligation under any other applicable regulation to submit to FDA the results of the investigation.

(e) If the Commissioner determines, after the unreliable data submitted by the investigator are eliminated from consideration, that the continued approval of the product for which the data were submitted cannot be justified, the Commissioner will proceed to withdraw approval of the product in accordance with the applicable provisions of the relevant statutes.

(f) An investigator who has been determined to be ineligible under paragraph (b) of this section may be reinstated as eligible when the Commissioner determines that the investigator has presented adequate assurances that the investigator will employ all test articles, and will conduct any clinical investigation that supports an application for a research or marketing permit for products regulated by FDA, solely in compliance with the applicable provisions of this chapter.

[77 FR 25359, Apr. 30, 2012]

Subpart E—Drugs Intended to Treat Life-threatening and Severely-debilitating Illnesses

Authority: 21 U.S.C. 351, 352, 353, 355, 371; 42 U.S.C. 262.

Source: 53 FR 41523, Oct. 21, 1988, unless otherwise noted.

The purpose of this section is to establish procedures designed to expedite the development, evaluation, and marketing of new therapies intended to treat persons with life-threatening and severely-debilitating illnesses, especially where no satisfactory alternative therapy exists. As stated §314.105(c) of this chapter, while the statutory standards of safety and effectiveness apply to all drugs, the many kinds of drugs that are subject to them, and the wide range of uses for those drugs, demand flexibility in applying the standards. The Food and Drug Administration (FDA) has determined that it is appropriate to exercise the broadest flexibility in applying the statutory standards, while preserving appropriate guarantees for safety and effectiveness. These procedures reflect the recognition that physicians and patients are generally willing to accept greater risks or side effects from products that treat life-threatening and severely-debilitating illnesses, than they would accept from products that treat less serious illnesses. These procedures also reflect the recognition that the benefits of the drug need to be evaluated in light of the severity of the disease being treated. The procedure outlined in this section should be interpreted consistent with that purpose.

§312.81 Scope.

This section applies to new drug and biological products that are being studied for their safety and effectiveness in treating life-threatening or severely-debilitating diseases.

(a) For purposes of this section, the term "life-threatening" means:

(1) Diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted; and

(2) Diseases or conditions with potentially fatal outcomes, where the end point of clinical trial analysis is survival.

(b) For purposes of this section, the term "severely debilitating" means diseases or conditions that cause major irreversible morbidity.

(c) Sponsors are encouraged to consult with FDA on the applicability of these procedures to specific products.

[53 FR 41523, Oct. 21, 1988, as amended at 64 FR 401, Jan. 5, 1999]

§ 312.82 Early consultation.

For products intended to treat life-threatening or severely-debilitating illnesses, sponsors may request to meet with FDA-reviewing officials early in the drug development process to review and reach agreement on the design of necessary preclinical and clinical studies. Where appropriate, FDA will invite to such meetings one or more outside expert scientific consultants or advisory committee members. To the extent FDA resources permit, agency reviewing officials will honor requests for such meetings

(a) *Pre-investigational new drug (IND) meetings.* Prior to the submission of the initial IND, the sponsor may request a meeting with FDA-reviewing officials. The primary purpose of this meeting is to review and reach agreement on the design of animal studies needed to initiate human testing. The meeting may also provide an opportunity for discussing the scope and design of phase 1 testing, plans for studying the drug product in pediatric populations, and the best approach for presentation and formatting of data in the IND.

(b) *End-of-phase 1 meetings.* When data from phase 1 clinical testing are available, the sponsor may again request a meeting with FDA-reviewing officials. The primary purpose of this meeting is to review and reach agreement on the design of phase 2 controlled clinical trials, with the goal that such testing will be adequate to provide sufficient data on the drug's safety and effectiveness to support a decision on its approvability for marketing, and to discuss the need for, as well as the design and timing of, studies of the drug in pediatric patients. For drugs for life-threatening diseases, FDA will provide its best judgment, at that time, whether pediatric studies will be required and whether their submission will be deferred until after approval. The procedures outlined in § 312.47(b)(1) with respect to end-of-phase 2 conferences, including documentation of agreements reached, would also be used for end-of-phase 1 meetings.

[53 FR 41523, Oct. 21, 1988, as amended at 63 FR 66669, Dec. 2, 1998]

§ 312.83 Treatment protocols.

If the preliminary analysis of phase 2 test results appears promising, FDA may ask the sponsor to submit a treatment protocol to be reviewed under the procedures and criteria listed in §§ 312.305 and 312.320. Such a treatment protocol, if requested and granted, would normally remain in effect while the complete data necessary for a marketing application are being assembled by the sponsor and reviewed by FDA (unless grounds exist for clinical hold of ongoing protocols, as provided in § 312.42(b)(3)(ii)).

[53 FR 41523, Oct. 21, 1988, as amended at 76 FR 13880, Mar. 15, 2011]

§ 312.84 Risk-benefit analysis in review of marketing applications for drugs to treat life-threatening and severely-debilitating illnesses.

(a) FDA's application of the statutory standards for marketing approval shall recognize the need for a medical risk-benefit judgment in making the final decision on approvability. As part of this evaluation, consistent with the statement of purpose in § 312.80, FDA will consider whether the benefits of the drug outweigh the known and potential risks of the drug and the need to answer remaining questions about risks and benefits of the drug, taking into consideration the severity of the disease and the absence of satisfactory alternative therapy.

(b) In making decisions on whether to grant marketing approval for products that have been the subject of an end-of-phase 1 meeting under § 312.82, FDA will usually seek the advice of outside expert scientific consultants or advisory committees. Upon the filing of such a marketing application under § 314.101 or part 601 of this chapter, FDA will notify the members of the relevant standing advisory committee of the application's filing and its availability for review.

(c) If FDA concludes that the data presented are not sufficient for marketing approval, FDA will issue a complete response letter under § 314.110 of this chapter or the biological product licensing

procedures. Such letter, in describing the deficiencies in the application, will address why the results of the research design agreed to under § 312.82, or in subsequent meetings, have not provided sufficient evidence for marketing approval. Such letter will also describe any recommendations made by the advisory committee regarding the application.

(d) Marketing applications submitted under the procedures contained in this section will be subject to the requirements and procedures contained in part 314 or part 600 of this chapter, as well as those in this subpart.

[53 FR 41523, Oct. 21, 1988, as amended at 73 FR 39607, July 10, 2008]

§ 312.85 Phase 4 studies.

Concurrent with marketing approval, FDA may seek agreement from the sponsor to conduct certain postmarketing (phase 4) studies to delineate additional information about the drug's risks, benefits, and optimal use. These studies could include, but would not be limited to, studying different doses or schedules of administration than were used in phase 2 studies, use of the drug in other patient populations or other stages of the disease, or use of the drug over a longer period of time.

§ 312.86 Focused FDA regulatory research.

At the discretion of the agency, FDA may undertake focused regulatory research on critical rate-limiting aspects of the preclinical, chemical/manufacturing, and clinical phases of drug development and evaluation. When initiated, FDA will undertake such research efforts as a means for meeting a public health need in facilitating the development of therapies to treat life-threatening or severely debilitating illnesses.

§ 312.87 Active monitoring of conduct and evaluation of clinical trials.

For drugs covered under this section, the Commissioner and other agency officials will monitor the progress of the conduct and evaluation of clinical trials and be involved in facilitating their appropriate progress.

§ 312.88 Safeguards for patient safety.

All of the safeguards incorporated within parts 50, 56, 312, 314, and 600 of this chapter designed to ensure the safety of clinical testing and the safety of products following marketing approval apply to drugs covered by this section. This includes the requirements for informed consent (part 50 of this chapter) and institutional review boards (part 56 of this chapter). These safeguards further include the review of animal studies prior to initial human testing (§ 312.23), and the monitoring of adverse drug experiences through the requirements of IND safety reports (§ 312.32), safety update reports during agency review of a marketing application (§ 314.50 of this chapter), and postmarketing adverse reaction reporting (§ 314.80 of this chapter).

Subpart F—Miscellaneous

§ 312.110 Import and export requirements.

(a) *Imports*. An investigational new drug offered for import into the United States complies with the requirements of this part if it is subject to an IND that is in effect for it under § 312.40 and: (1) The consignee in the United States is the sponsor of the IND; (2) the consignee is a qualified investigator named in the IND; or (3) the consignee is the domestic agent of a foreign sponsor, is responsible for the control and distribution of the investigational drug, and the IND identifies the consignee and describes what, if any, actions the consignee will take with respect to the investigational drug.

(b) *Exports*. An investigational new drug may be exported from the United States for use in a clinical investigation under any of the following conditions:

(1) An IND is in effect for the drug under § 312.40, the drug complies with the laws of the country to which it is being exported, and each person who receives the drug is an investigator in a study submitted to and allowed to proceed under the IND; or

(2) The drug has valid marketing authorization in Australia, Canada, Israel, Japan, New Zealand, Switzerland, South Africa, or in any country in the European Union or the European Economic Area, and complies with the laws of the country to which it is being exported, section 802(b)(1)(A), (f), and (g) of the act, and § 1.101 of this chapter; or

(3) The drug is being exported to Australia, Canada, Israel, Japan, New Zealand, Switzerland, South Africa, or to any country in the European Union or the European Economic Area, and complies with the laws of the country to which it is being exported, the applicable provisions of section 802(c), (f), and (g) of the act, and § 1.101 of this chapter. Drugs exported under this paragraph that are not the subject of an IND are exempt from the label requirement in § 312.6(a); or

(4) Except as provided in paragraph (b)(5) of this section, the person exporting the drug sends a written certification to the Office of International Programs (HFG-1), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, at the time the drug is first exported and maintains records documenting compliance with this paragraph. The certification shall describe the drug that is to be exported (i.e., trade name (if any), generic name, and dosage form), identify the country or countries to which the drug is to be exported, and affirm that:

(i) The drug is intended for export;

(ii) The drug is intended for investigational use in a foreign country;

(iii) The drug meets the foreign purchaser's or consignee's specifications;

(iv) The drug is not in conflict with the importing country's laws;

(v) The outer shipping package is labeled to show that the package is intended for export from the United States;

(vi) The drug is not sold or offered for sale in the United States;

(vii) The clinical investigation will be conducted in accordance with § 312.120;

(viii) The drug is manufactured, processed, packaged, and held in substantial conformity with current good manufacturing practices;

(ix) The drug is not adulterated within the meaning of section 501(a)(1), (a)(2)(A), (a)(3), (c), or (d) of the act;

(x) The drug does not present an imminent hazard to public health, either in the United States, if the drug were to be reimported, or in the foreign country; and

(xi) The drug is labeled in accordance with the foreign country's laws.

(5) In the event of a national emergency in a foreign country, where the national emergency necessitates exportation of an investigational new drug, the requirements in paragraph (b)(4) of this section apply as follows:

(i) *Situations where the investigational new drug is to be stockpiled in anticipation of a national emergency.* There may be instances where exportation of an investigational new drug is needed so that the drug may be stockpiled and made available for use by the importing country if and when a national emergency arises. In such cases:

(A) A person may export an investigational new drug under paragraph (b)(4) of this section without making an affirmation with respect to any one or more of paragraphs (b)(4)(i), (b)(4)(iv), (b)(4)(vi), (b)(4)(vii), (b)(4)(viii), and/or (b)(4)(ix) of this section, provided that he or she:

(1) Provides a written statement explaining why compliance with each such paragraph is not feasible or is contrary to the best interests of the individuals who may receive the investigational new drug;

(2) Provides a written statement from an authorized official of the importing country's government. The statement must attest that the official agrees with the exporter's statement made under paragraph (b)(5)(i)(A)(1) of this section; explain that the drug is to be stockpiled solely for use of the importing country in a national emergency; and describe the potential national emergency that warrants exportation of the investigational new drug under this provision; and

(3) Provides a written statement showing that the Secretary of Health and Human Services (the Secretary), or his or her designee, agrees with the findings of the authorized official of the importing country's government. Persons who wish to obtain a written statement from the Secretary should direct their requests to Secretary's Operations Center, Office of Emergency Operations and Security Programs, Office of Public Health Emergency Preparedness, Office of the Secretary, Department of Health and Human Services, 200 Independence Ave. SW., Washington, DC 20201. Requests may be also be sent by FAX: 202-619-7870 or by e-mail: HHS.SOC@hhs.gov.

(B) Exportation may not proceed until FDA has authorized exportation of the investigational new drug. FDA may deny authorization if the statements provided under paragraphs (b)(5)(i)(A)(1) or (b)(5)(i)(A)(2) of this section are inadequate or if exportation is contrary to public health.

(ii) *Situations where the investigational new drug is to be used for a sudden and immediate national emergency.* There may be instances where exportation of an investigational new drug is needed so that the drug may be used in a sudden and immediate national emergency that has developed or is developing. In such cases:

(A) A person may export an investigational new drug under paragraph (b)(4) of this section without making an affirmation with respect to any one or more of paragraphs (b)(4)(i), (b)(4)(iv), (b)(4)(v), (b)(4)(vi), (b)(4)(vii), (b)(4)(viii), (b)(4)(ix), and/or (b)(4)(xi), provided that he or she:

(1) Provides a written statement explaining why compliance with each such paragraph is not feasible or is contrary to the best interests of the individuals who are expected to receive the investigational new drug and

(2) Provides sufficient information from an authorized official of the importing country's government to enable the Secretary, or his or her designee, to decide whether a national emergency has developed or is developing in the importing country, whether the investigational new drug will be used solely for that national emergency, and whether prompt exportation of the investigational new drug is necessary. Persons who wish to obtain a determination from the Secretary should direct their requests to Secretary's Operations Center, Office of Emergency Operations and Security Programs, Office of Public Health Emergency Preparedness, Office of the Secretary, Department of Health and Human Services, 200 Independence Ave. SW., Washington, DC 20201. Requests may be also be sent by FAX: 202-619-7870 or by e-mail: HHS.SOC@hhs.gov.

(B) Exportation may proceed without prior FDA authorization.

(c) *Limitations*. Exportation under paragraph (b) of this section may not occur if:

(1) For drugs exported under paragraph (b)(1) of this section, the IND pertaining to the clinical investigation is no longer in effect;

(2) For drugs exported under paragraph (b)(2) of this section, the requirements in section 802(b)(1), (f), or (g) of the act are no longer met;

(3) For drugs exported under paragraph (b)(3) of this section, the requirements in section 802(c), (f), or (g) of the act are no longer met;

(4) For drugs exported under paragraph (b)(4) of this section, the conditions underlying the certification or the statements submitted under paragraph (b)(5) of this section are no longer met; or

(5) For any investigational new drugs under this section, the drug no longer complies with the laws of the importing country.

(d) *Insulin and antibiotics.* New insulin and antibiotic drug products may be exported for investigational use in accordance with section 801(e)(1) of the act without complying with this section.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 64 FR 401, Jan. 5, 1999; 67 FR 9586, Mar. 4, 2002; 70 FR 70729, Nov. 23, 2005]

§ 312.120 Foreign clinical studies not conducted under an IND.

(a) *Acceptance of studies.* (1) FDA will accept as support for an IND or application for marketing approval (an application under section 505 of the act or section 351 of the Public Health Service Act (the PHS Act) (42 U.S.C. 262)) a well-designed and well-conducted foreign clinical study not conducted under an IND, if the following conditions are met:

(i) The study was conducted in accordance with good clinical practice (GCP). For the purposes of this section, GCP is defined as a standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials in a way that provides assurance that the data and reported results are credible and accurate and that the rights, safety, and well-being of trial subjects are protected. GCP includes review and approval (or provision of a favorable opinion) by an independent ethics committee (IEC) before initiating a study, continuing review of an ongoing study by an IEC, and obtaining and documenting the freely given informed consent of the subject (or a subject's legally authorized representative, if the subject is unable to provide informed consent) before initiating a study. GCP does not require informed consent in life-threatening situations when the IEC reviewing the study finds, before initiation of the study, that informed consent is not feasible and either that the conditions present are consistent with those described in § 50.23 or § 50.24(a) of this chapter, or that the measures described in the study protocol or elsewhere will protect the rights, safety, and well-being of subjects; and

(ii) FDA is able to validate the data from the study through an onsite inspection if the agency deems it necessary.

(2) Although FDA will not accept as support for an IND or application for marketing approval a study that does not meet the conditions of paragraph (a)(1) of this section, FDA will examine data from such a study.

(3) Marketing approval of a new drug based solely on foreign clinical data is governed by § 314.106 of this chapter.

(b) *Supporting information.* A sponsor or applicant who submits data from a foreign clinical study not conducted under an IND as support for an IND or application for marketing approval must submit to FDA, in addition to information required elsewhere in parts 312, 314, or 601 of this chapter, a description of the actions the sponsor or applicant took to ensure that the research conformed to GCP as described in paragraph (a)(1)(i) of this section. The description is not required to duplicate information already submitted in the IND or application for marketing approval. Instead, the description must provide either the following information or a cross-reference to another section of the submission where the information is located:

(1) The investigator's qualifications;

(2) A description of the research facilities;

(3) A detailed summary of the protocol and results of the study and, should FDA request, case records maintained by the investigator or additional background data such as hospital or other institutional records;

(4) A description of the drug substance and drug product used in the study, including a description of the components, formulation, specifications, and, if available, bioavailability of the specific drug product used in the clinical study;

(5) If the study is intended to support the effectiveness of a drug product, information showing that the study is adequate and well controlled under §314.126 of this chapter;

(6) The name and address of the IEC that reviewed the study and a statement that the IEC meets the definition in §312.3 of this chapter. The sponsor or applicant must maintain records supporting such statement, including records of the names and qualifications of IEC members, and make these records available for agency review upon request;

(7) A summary of the IEC's decision to approve or modify and approve the study, or to provide a favorable opinion;

(8) A description of how informed consent was obtained;

(9) A description of what incentives, if any, were provided to subjects to participate in the study;

(10) A description of how the sponsor(s) monitored the study and ensured that the study was carried out consistently with the study protocol; and

(11) A description of how investigators were trained to comply with GCP (as described in paragraph (a)(1)(i) of this section) and to conduct the study in accordance with the study protocol, and a statement on whether written commitments by investigators to comply with GCP and the protocol were obtained. Any signed written commitments by investigators must be maintained by the sponsor or applicant and made available for agency review upon request.

(c) Waivers. (1) A sponsor or applicant may ask FDA to waive any applicable requirements under paragraphs (a)(1) and (b) of this section. A waiver request may be submitted in an IND or in an information amendment to an IND, or in an application or in an amendment or supplement to an application submitted under part 314 or 601 of this chapter. A waiver request is required to contain at least one of the following:

(i) An explanation why the sponsor's or applicant's compliance with the requirement is unnecessary or cannot be achieved;

(ii) A description of an alternative submission or course of action that satisfies the purpose of the requirement; or

(iii) Other information justifying a waiver.

(2) FDA may grant a waiver if it finds that doing so would be in the interest of the public health.

(d) *Records*. A sponsor or applicant must retain the records required by this section for a foreign clinical study not conducted under an IND as follows:

(1) If the study is submitted in support of an application for marketing approval, for 2 years after an agency decision on that application;

(2) If the study is submitted in support of an IND but not an application for marketing approval, for 2 years after the submission of the IND.

[73 FR 22815, Apr. 28, 2008]

§312.130 Availability for public disclosure of data and information in an IND.

(a) The existence of an investigational new drug application will not be disclosed by FDA unless it has previously been publicly disclosed or acknowledged.

(b) The availability for public disclosure of all data and information in an investigational new drug application for a new drug will be handled in accordance with the provisions established in §314.430 for the confidentiality of data and information in applications submitted in part 314. The

availability for public disclosure of all data and information in an investigational new drug application for a biological product will be governed by the provisions of §§ 601.50 and 601.51.

(c) Notwithstanding the provisions of § 314.430, FDA shall disclose upon request to an individual to whom an investigational new drug has been given a copy of any IND safety report relating to the use in the individual.

(d) The availability of information required to be publicly disclosed for investigations involving an exception from informed consent under § 50.24 of this chapter will be handled as follows: Persons wishing to request the publicly disclosable information in the IND that was required to be filed in Docket Number 95S-0158 in the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, shall submit a request under the Freedom of Information Act.

[52 FR 8831, Mar. 19, 1987. Redesignated at 53 FR 41523, Oct. 21, 1988, as amended at 61 FR 51530, Oct. 2, 1996; 64 FR 401, Jan. 5, 1999; 68 FR 24879, May 9, 2003]

§ 312.140 Address for correspondence.

(a) A sponsor must send an initial IND submission to the Center for Drug Evaluation and Research (CDER) or to the Center for Biologics Evaluation and Research (CBER), depending on the Center responsible for regulating the product as follows:

(1) *For drug products regulated by CDER*. Send the IND submission to the Central Document Room, Center for Drug Evaluation and Research, Food and Drug Administration, 5901-B Ammendale Rd., Beltsville, MD 20705-1266; except send an IND submission for an in vivo bioavailability or bioequivalence study in humans to support an abbreviated new drug application to the Office of Generic Drugs (HFD-600), Center for Drug Evaluation and Research, Food and Drug Administration, Metro Park North VII, 7620 Standish Pl., Rockville, MD 20855.

(2) *For biological products regulated by CDER*. Send the IND submission to the Central Document Room, Center for Drug Evaluation and Research, Food and Drug Administration, 5901-B Ammendale Rd., Beltsville, MD 20705-1266.

(3) *For biological products regulated by CBER*. Send the IND submission to the Food and Drug Administration, Center for Biologics Evaluation and Research, Document Control Center, 10903 New Hampshire Ave., Bldg. 71, Rm. G112, Silver Spring, MD 20993-0002.

(b) On receiving the IND, the responsible Center will inform the sponsor which one of the divisions in CDER or CBER is responsible for the IND. Amendments, reports, and other correspondence relating to matters covered by the IND should be sent to the appropriate center at the address indicated in this section and marked to the attention of the responsible division. The outside wrapper of each submission shall state what is contained in the submission, for example, "IND Application", "Protocol Amendment", etc.

(c) All correspondence relating to export of an investigational drug under § 312.110(b)(2) shall be submitted to the International Affairs Staff (HFY-50), Office of Health Affairs, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

[70 FR 14981, Mar. 24, 2005, as amended at 74 FR 13113, Mar. 26, 2009; 74 FR 55771, Oct. 29, 2009; 75 FR 37295, June 29, 2010; 80 FR 18091, Apr. 3, 2015; 81 FR 17066, Mar. 28, 2016]

§ 312.145 Guidance documents.

(a) FDA has made available guidance documents under § 10.115 of this chapter to help you to comply with certain requirements of this part.

(b) The Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) maintain lists of guidance documents that apply to the centers' regulations. The lists are maintained on the Internet and are published annually in the Federal Register. A re-

quest for a copy of the CDER list should be directed to the Office of Training and Communications, Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993-0002. A request for a copy of the CBER list should be directed to the Food and Drug Administration, Center for Biologics Evaluation and Research, Office of Communication, Outreach and Development, 10903 New Hampshire Ave., Bldg. 71, Rm. 3103, Silver Spring, MD 20993-0002.

[65 FR 56479, Sept. 19, 2000, as amended at 74 FR 13113, Mar. 26, 2009; 80 FR 18091, Apr. 3, 2015]

Subpart G—Drugs for Investigational Use in Laboratory Research Animals or In Vitro Tests

§ 312.160 Drugs for investigational use in laboratory research animals or in vitro tests.

(a) *Authorization to ship.* (1)(i) A person may ship a drug intended solely for tests in vitro or in animals used only for laboratory research purposes if it is labeled as follows:

CAUTION: Contains a new drug for investigational use only in laboratory research animals, or for tests in vitro. Not for use in humans.

(ii) A person may ship a biological product for investigational in vitro diagnostic use that is listed in § 312.2(b)(2)(ii) if it is labeled as follows:

CAUTION: Contains a biological product for investigational in vitro diagnostic tests only.

(2) A person shipping a drug under paragraph (a) of this section shall use due diligence to assure that the consignee is regularly engaged in conducting such tests and that the shipment of the new drug will actually be used for tests in vitro or in animals used only for laboratory research.

(3) A person who ships a drug under paragraph (a) of this section shall maintain adequate records showing the name and post office address of the expert to whom the drug is shipped and the date, quantity, and batch or code mark of each shipment and delivery. Records of shipments under paragraph (a)(1)(i) of this section are to be maintained for a period of 2 years after the shipment. Records and reports of data and shipments under paragraph (a)(1)(ii) of this section are to be maintained in accordance with § 312.57(b). The person who ships the drug shall upon request from any properly authorized officer or employee of the Food and Drug Administration, at reasonable times, permit such officer or employee to have access to and copy and verify records required to be maintained under this section.

(b) *Termination of authorization to ship.* FDA may terminate authorization to ship a drug under this section if it finds that:

(1) The sponsor of the investigation has failed to comply with any of the conditions for shipment established under this section; or

(2) The continuance of the investigation is unsafe or otherwise contrary to the public interest or the drug is used for purposes other than bona fide scientific investigation. FDA will notify the person shipping the drug of its finding and invite immediate correction. If correction is not immediately made, the person shall have an opportunity for a regulatory hearing before FDA pursuant to part 16.

(c) *Disposition of unused drug.* The person who ships the drug under paragraph (a) of this section shall assure the return of all unused supplies of the drug from individual investigators whenever the investigation discontinues or the investigation is terminated. The person who ships the drug may authorize in writing alternative disposition of unused supplies of the drug provided this alternative disposition does not expose humans to risks from the drug, either directly or indirectly (e.g., through food-producing animals). The shipper shall maintain records of any alternative disposition.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987. Redesignated at 53 FR 41523, Oct. 21, 1988; 67 FR 9586, Mar. 4, 2002]

Source: 74 FR 40942, Aug. 13, 2009, unless otherwise noted.

(a) *Scope*. This subpart contains the requirements for the use of investigational new drugs and approved drugs where availability is limited by a risk evaluation and mitigation strategy (REMS) when the primary purpose is to diagnose, monitor, or treat a patient's disease or condition. The aim of this subpart is to facilitate the availability of such drugs to patients with serious diseases or conditions when there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the patient's disease or condition.

(b) *Definitions*. The following definitions of terms apply to this subpart:

Immediately life-threatening disease or condition means a stage of disease in which there is reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment.

Serious disease or condition means a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible, provided it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one.

§ 312.305 Requirements for all expanded access uses.

The criteria, submission requirements, safeguards, and beginning treatment information set out in this section apply to all expanded access uses described in this subpart. Additional criteria, submission requirements, and safeguards that apply to specific types of expanded access are described in §§ 312.310 through 312.320.

(a) *Criteria*. FDA must determine that:

(1) The patient or patients to be treated have a serious or immediately life-threatening disease or condition, and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition;

(2) The potential patient benefit justifies the potential risks of the treatment use and those potential risks are not unreasonable in the context of the disease or condition to be treated; and

(3) Providing the investigational drug for the requested use will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the expanded access use or otherwise compromise the potential development of the expanded access use.

(b) *Submission*. (1) An expanded access submission is required for each type of expanded access described in this subpart. The submission may be a new IND or a protocol amendment to an existing IND. Information required for a submission may be supplied by referring to pertinent information contained in an existing IND if the sponsor of the existing IND grants a right of reference to the IND.

(2) The expanded access submission must include:

(i) A cover sheet (Form FDA 1571) meeting the requirements of § 312.23(a);

(ii) The rationale for the intended use of the drug, including a list of available therapeutic options that would ordinarily be tried before resorting to the investigational drug or an explanation of why the use of the investigational drug is preferable to the use of available therapeutic options;

(iii) The criteria for patient selection or, for an individual patient, a description of the patient's disease or condition, including recent medical history and previous treatments of the disease or condition;

(iv) The method of administration of the drug, dose, and duration of therapy;

(v) A description of the facility where the drug will be manufactured;

(vi) Chemistry, manufacturing, and controls information adequate to ensure the proper identification, quality, purity, and strength of the investigational drug;

(vii) Pharmacology and toxicology information adequate to conclude that the drug is reasonably safe at the dose and duration proposed for expanded access use (ordinarily, information that would be adequate to permit clinical testing of the drug in a population of the size expected to be treated); and

(viii) A description of clinical procedures, laboratory tests, or other monitoring necessary to evaluate the effects of the drug and minimize its risks.

(3) The expanded access submission and its mailing cover must be plainly marked "EXPANDED ACCESS SUBMISSION." If the expanded access submission is for a treatment IND or treatment protocol, the applicable box on Form FDA 1571 must be checked.

(c) *Safeguards*. The responsibilities of sponsors and investigators set forth in subpart D of this part are applicable to expanded access use under this subpart as described in this paragraph.

(1) A licensed physician under whose immediate direction an investigational drug is administered or dispensed for an expanded access use under this subpart is considered an investigator, for purposes of this part, and must comply with the responsibilities for investigators set forth in subpart D of this part to the extent they are applicable to the expanded access use.

(2) An individual or entity that submits an expanded access IND or protocol under this subpart is considered a sponsor, for purposes of this part, and must comply with the responsibilities for sponsors set forth in subpart D of this part to the extent they are applicable to the expanded access use.

(3) A licensed physician under whose immediate direction an investigational drug is administered or dispensed, and who submits an IND for expanded access use under this subpart is considered a sponsor-investigator, for purposes of this part, and must comply with the responsibilities for sponsors and investigators set forth in subpart D of this part to the extent they are applicable to the expanded access use.

(4) *Investigators*. In all cases of expanded access, investigators are responsible for reporting adverse drug events to the sponsor, ensuring that the informed consent requirements of part 50 of this chapter are met, ensuring that IRB review of the expanded access use is obtained in a manner consistent with the requirements of part 56 of this chapter, and maintaining accurate case histories and drug disposition records and retaining records in a manner consistent with the requirements of § 312.62. Depending on the type of expanded access, other investigator responsibilities under subpart D may also apply.

(5) *Sponsors*. In all cases of expanded access, sponsors are responsible for submitting IND safety reports and annual reports (when the IND or protocol continues for 1 year or longer) to FDA as required by §§ 312.32 and 312.33, ensuring that licensed physicians are qualified to administer the investigational drug for the expanded access use, providing licensed physicians with the information needed to minimize the risk and maximize the potential benefits of the investigational drug (the investigator's brochure must be provided if one exists for the drug), maintaining an effective IND for the expanded access use, and maintaining adequate drug disposition records and retaining records in a manner consistent with the requirements of § 312.57. Depending on the type of expanded access, other sponsor responsibilities under subpart D may also apply.

(d) *Beginning treatment*—(1) *INDs*. An expanded access IND goes into effect 30 days after FDA receives the IND or on earlier notification by FDA that the expanded access use may begin.

(2) *Protocols*. With the following exceptions, expanded access use under a protocol submitted under an existing IND may begin as described in §312.30(a).

(i) Expanded access use under the emergency procedures described in §312.310(d) may begin when the use is authorized by the FDA reviewing official.

(ii) Expanded access use under §312.320 may begin 30 days after FDA receives the protocol or upon earlier notification by FDA that use may begin.

(3) *Clinical holds*. FDA may place any expanded access IND or protocol on clinical hold as described in §312.42.

§312.310 Individual patients, including for emergency use.

Under this section, FDA may permit an investigational drug to be used for the treatment of an individual patient by a licensed physician.

(a) *Criteria*. The criteria in §312.305(a) must be met; and the following determinations must be made:

(1) The physician must determine that the probable risk to the person from the investigational drug is not greater than the probable risk from the disease or condition; and

(2) FDA must determine that the patient cannot obtain the drug under another IND or protocol.

(b) *Submission*. The expanded access submission must include information adequate to demonstrate that the criteria in §312.305(a) and paragraph (a) of this section have been met. The expanded access submission must meet the requirements of §312.305(b).

(1) If the drug is the subject of an existing IND, the expanded access submission may be made by the sponsor or by a licensed physician.

(2) A sponsor may satisfy the submission requirements by amending its existing IND to include a protocol for individual patient expanded access.

(3) A licensed physician may satisfy the submission requirements by obtaining from the sponsor permission for FDA to refer to any information in the IND that would be needed to support the expanded access request (right of reference) and by providing any other required information not contained in the IND (usually only the information specific to the individual patient).

(c) *Safeguards*. (1) Treatment is generally limited to a single course of therapy for a specified duration unless FDA expressly authorizes multiple courses or chronic therapy.

(2) At the conclusion of treatment, the licensed physician or sponsor must provide FDA with a written summary of the results of the expanded access use, including adverse effects.

(3) FDA may require sponsors to monitor an individual patient expanded access use if the use is for an extended duration.

(4) When a significant number of similar individual patient expanded access requests have been submitted, FDA may ask the sponsor to submit an IND or protocol for the use under §312.315 or §312.320.

(d) *Emergency procedures*. If there is an emergency that requires the patient to be treated before a written submission can be made, FDA may authorize the expanded access use to begin without a written submission. The FDA reviewing official may authorize the emergency use by telephone.

(1) Emergency expanded access use may be requested by telephone, facsimile, or other means of electronic communications. For investigational biological drug products regulated by the Center for Biologics Evaluation and Research, the request should be directed to the Office of Communication, Outreach and Development, Center for Biologics Evaluation and Research, 240-402-8010

or 1-800-835-4709, e-mail: *ocod@fda.hhs.gov*. For all other investigational drugs, the request for authorization should be directed to the Division of Drug Information, Center for Drug Evaluation and Research, 301-796-3400, e-mail: *druginfo@fda.hhs.gov*. After normal working hours (8 a.m. to 4:30 p.m.), the request should be directed to the FDA Emergency Call Center, 866-300-4374, e-mail: emergency.operations@fda.hhs.gov.

(2) The licensed physician or sponsor must explain how the expanded access use will meet the requirements of §§ 312.305 and 312.310 and must agree to submit an expanded access submission within 15 working days of FDA's authorization of the use.

[74 FR 40942, Aug. 13, 2009, as amended at 75 FR 32659, June 9, 2010; 80 FR 18091, Apr. 3, 2015]

§ 312.315 Intermediate-size patient populations.

Under this section, FDA may permit an investigational drug to be used for the treatment of a patient population smaller than that typical of a treatment IND or treatment protocol. FDA may ask a sponsor to consolidate expanded access under this section when the agency has received a significant number of requests for individual patient expanded access to an investigational drug for the same use.

(a) *Need for expanded access.* Expanded access under this section may be needed in the following situations:

(1) *Drug not being developed.* The drug is not being developed, for example, because the disease or condition is so rare that the sponsor is unable to recruit patients for a clinical trial.

(2) *Drug being developed.* The drug is being studied in a clinical trial, but patients requesting the drug for expanded access use are unable to participate in the trial. For example, patients may not be able to participate in the trial because they have a different disease or stage of disease than the one being studied or otherwise do not meet the enrollment criteria, because enrollment in the trial is closed, or because the trial site is not geographically accessible.

(3) *Approved or related drug.* (i) The drug is an approved drug product that is no longer marketed for safety reasons or is unavailable through marketing due to failure to meet the conditions of the approved application, or

(ii) The drug contains the same active moiety as an approved drug product that is unavailable through marketing due to failure to meet the conditions of the approved application or a drug shortage.

(b) *Criteria*. The criteria in § 312.305(a) must be met; and FDA must determine that:

(1) There is enough evidence that the drug is safe at the dose and duration proposed for expanded access use to justify a clinical trial of the drug in the approximate number of patients expected to receive the drug under expanded access; and

(2) There is at least preliminary clinical evidence of effectiveness of the drug, or of a plausible pharmacologic effect of the drug to make expanded access use a reasonable therapeutic option in the anticipated patient population.

(c) *Submission*. The expanded access submission must include information adequate to satisfy FDA that the criteria in § 312.305(a) and paragraph (b) of this section have been met. The expanded access submission must meet the requirements of § 312.305(b). In addition:

(1) The expanded access submission must state whether the drug is being developed or is not being developed and describe the patient population to be treated.

(2) If the drug is not being actively developed, the sponsor must explain why the drug cannot currently be developed for the expanded access use and under what circumstances the drug could be developed.

(3) If the drug is being studied in a clinical trial, the sponsor must explain why the patients to be treated cannot be enrolled in the clinical trial and under what circumstances the sponsor would conduct a clinical trial in these patients.

(d) *Safeguards*. (1) Upon review of the IND annual report, FDA will determine whether it is appropriate for the expanded access to continue under this section.

(i) If the drug is not being actively developed or if the expanded access use is not being developed (but another use is being developed), FDA will consider whether it is possible to conduct a clinical study of the expanded access use.

(ii) If the drug is being actively developed, FDA will consider whether providing the investigational drug for expanded access use is interfering with the clinical development of the drug.

(iii) As the number of patients enrolled increases, FDA may ask the sponsor to submit an IND or protocol for the use under § 312.320.

(2) The sponsor is responsible for monitoring the expanded access protocol to ensure that licensed physicians comply with the protocol and the regulations applicable to investigators.

§ 312.320 Treatment IND or treatment protocol.

Under this section, FDA may permit an investigational drug to be used for widespread treatment use.

(a) *Criteria*. The criteria in § 312.305(a) must be met, and FDA must determine that:

(1) *Trial status*. (i) The drug is being investigated in a controlled clinical trial under an IND designed to support a marketing application for the expanded access use, or

(ii) All clinical trials of the drug have been completed; and

(2) *Marketing status*. The sponsor is actively pursuing marketing approval of the drug for the expanded access use with due diligence; and

(3) *Evidence*. (i) When the expanded access use is for a serious disease or condition, there is sufficient clinical evidence of safety and effectiveness to support the expanded access use. Such evidence would ordinarily consist of data from phase 3 trials, but could consist of compelling data from completed phase 2 trials; or

(ii) When the expanded access use is for an immediately life-threatening disease or condition, the available scientific evidence, taken as a whole, provides a reasonable basis to conclude that the investigational drug may be effective for the expanded access use and would not expose patients to an unreasonable and significant risk of illness or injury. This evidence would ordinarily consist of clinical data from phase 3 or phase 2 trials, but could be based on more preliminary clinical evidence.

(b) *Submission*. The expanded access submission must include information adequate to satisfy FDA that the criteria in § 312.305(a) and paragraph (a) of this section have been met. The expanded access submission must meet the requirements of § 312.305(b).

(c) *Safeguard*. The sponsor is responsible for monitoring the treatment protocol to ensure that licensed physicians comply with the protocol and the regulations applicable to investigators.

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PART 314—APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 355a, 355f, 356, 356a, 356b, 356c, 356e, 360cc, 371, 374, 379e, 379k-1.
Source: 50 FR 7493, Feb. 22, 1985, unless otherwise noted.
Editorial note: Nomenclature changes to part 314 appear at 69 FR 13717, Mar. 24, 2004; 81 FR 69639, Oct. 6, 2016.

Subpart A—General Provisions

§ 314.1 Scope of this part.

(a) This part sets forth procedures and requirements for the submission to, and the review by, the Food and Drug Administration of applications and abbreviated applications to market a new drug under section 505 of the Federal Food, Drug, and Cosmetic Act, as well as amendments, supplements, and postmarketing reports to them.

(b) This part does not apply to drug products subject to licensing by FDA under the Public Health Service Act (58 Stat. 632 as amended (42 U.S.C. 201 et seq.)) and subchapter F of chapter I of title 21 of the Code of Federal Regulations.

(c) References in this part to regulations in the Code of Federal Regulations are to chapter I of title 21, unless otherwise noted.

[50 FR 7493, Feb. 22, 1985, as amended at 57 FR 17981, Apr. 28, 1992; 64 FR 401, Jan. 5, 1999]

§ 314.2 Purpose.

The purpose of this part is to establish an efficient and thorough drug review process in order to: (a) Facilitate the approval of drugs shown to be safe and effective; and (b) ensure the disapproval of drugs not shown to be safe and effective. These regulations are also intended to establish an effective system for FDA's surveillance of marketed drugs. These regulations shall be construed in light of these objectives.

§ 314.3 Definitions.

(a) The definitions and interpretations contained in section 201 of the Federal Food, Drug, and Cosmetic Act apply to those terms when used in this part and part 320 of this chapter.

(b) The following definitions of terms apply to this part and part 320 of this chapter:

180-day exclusivity period is the 180-day period beginning on the date of the first commercial marketing of the drug (including the commercial marketing of the reference listed drug) by any first applicant. The 180-day period ends on the day before the date on which an ANDA submitted by an applicant other than a first applicant could be approved.

505(b)(2) application is an NDA submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for a drug for which at least some of the investigations described in section 505(b)(1)(A) of the Federal Food, Drug, and Cosmetic Act and relied upon by the applicant for approval of the NDA were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.

Abbreviated application, abbreviated new drug application, or ANDA is the application described under § 314.94, including all amendments and supplements to the application.

Acknowledgment letter is a written, postmarked communication from FDA to an applicant stating that the Agency has determined that an ANDA is sufficiently complete to permit a substantive review. An acknowledgment letter indicates that the ANDA is regarded as received.

Act is the Federal Food, Drug, and Cosmetic Act (section 201 et seq. (21 U.S.C. 301 et seq.)).

Active ingredient is any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect.

Active moiety is the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.

ANDA holder is the applicant that owns an approved ANDA.

Applicant is any person who submits an NDA (including a 505(b)(2) application) or ANDA or an amendment or supplement to an NDA or ANDA under this part to obtain FDA approval of a new drug and any person who owns an approved NDA (including a 505(b)(2) application) or ANDA.

Application, new drug application, or NDA is the application described under § 314.50, including all amendments and supplements to the application. An NDA refers to "stand-alone" applications submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act and to 505(b)(2) applications.

Approval letter is a written communication to an applicant from FDA approving an NDA or an ANDA.

Assess the effects of the change is to evaluate the effects of a manufacturing change on the identity, strength, quality, purity, and potency of a drug product as these factors may relate to the safety or effectiveness of the drug product.

Authorized generic drug is a listed drug, as defined in this section, that has been approved under section 505(c) of the Federal Food, Drug, and Cosmetic Act and is marketed, sold, or distributed directly or indirectly to the retail class of trade with labeling, packaging (other than repackaging as the listed drug in blister packs, unit doses, or similar packaging for use in institutions), product code, labeler code, trade name, or trademark that differs from that of the listed drug.

Bioavailability is the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of drug action. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by scientifically valid measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of drug action.

Bioequivalence is the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study. Where there is an intentional difference in rate (e.g., in certain extended-release dosage forms), certain pharmaceutical equivalents or alternatives may be considered bioequivalent if there is no significant difference in the extent to which the active ingredient or moiety from each product becomes available at the site of drug action. This applies only if the difference in the rate at which the active ingredient or moiety becomes available at the site of drug action is intentional and is reflected in the proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug. For drug products that are not intended to be absorbed into the bloodstream, bioequivalence may be assessed by scientifically valid measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of drug action.

Bioequivalence requirement is a requirement imposed by FDA for in vitro and/or in vivo testing of specified drug products that must be satisfied as a condition of marketing.

Class 1 resubmission is the resubmission of an NDA or efficacy supplement, following receipt of a complete response letter, that contains one or more of the following: Final printed labeling, draft labeling, certain safety updates, stability updates to support provisional or final dating periods, commitments to perform postmarketing studies (including proposals for such studies), assay validation data, final release testing on the last lots used to support approval, minor reanalyses of previously submitted data, and other comparatively minor information.

Class 2 resubmission is the resubmission of an NDA or efficacy supplement, following receipt of a complete response letter, that includes any item not specified in the definition of "Class 1 resubmission," including any item that would require presentation to an advisory committee.

Commercial marketing is the introduction or delivery for introduction into interstate commerce of a drug product described in an ANDA, outside the control of the ANDA applicant, except that the term does not include transfer of the drug product for investigational use under part 312 of this chapter or transfer of the drug product to parties identified in the ANDA for reasons other than sale. Commercial marketing includes the introduction or delivery for introduction into interstate commerce of the reference listed drug by the ANDA applicant.

Complete response letter is a written communication to an applicant from FDA usually describing all of the deficiencies that the Agency has identified in an NDA or ANDA that must be satisfactorily addressed before it can be approved.

Component is any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product.

Date of approval is the date on the approval letter from FDA stating that the NDA or ANDA is approved, except that the date of approval for an NDA described in section 505(x)(1) of the Federal Food, Drug, and Cosmetic Act is determined as described in section 505(x)(2) of the Federal Food, Drug, and Cosmetic Act. "Date of approval" refers only to a final approval and not to a tentative approval.

Dosage form is the physical manifestation containing the active and inactive ingredients that delivers a dose of the drug product. This includes such factors as:

(1) The physical appearance of the drug product;

(2) The physical form of the drug product prior to dispensing to the patient;

(3) The way the product is administered; and

(4) The design features that affect frequency of dosing.

Drug product is a finished dosage form, e.g., tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients.

Drug substance is an active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body, but does not include intermediates used in the synthesis of such ingredient.

Efficacy supplement is a supplement to an approved NDA proposing to make one or more related changes from among the following changes to product labeling:

(1) Add or modify an indication or claim;

(2) Revise the dose or dose regimen;

(3) Provide for a new route of administration;

(4) Make a comparative efficacy claim naming another drug product;

(5) Significantly alter the intended patient population;

(6) Change the marketing status from prescription to over-the-counter use;

(7) Provide for, or provide evidence of effectiveness necessary for, the traditional approval of a product originally approved under subpart H of this part; or

(8) Incorporate other information based on at least one adequate and well-controlled clinical study.

FDA or Agency is the Food and Drug Administration.

First applicant is an ANDA applicant that, on the first day on which a substantially complete application containing a paragraph IV certification is submitted for approval of a drug, submits a substantially complete application that contains, and for which the applicant lawfully maintains, a paragraph IV certification for the drug.

Inactive ingredient is any component other than an active ingredient.

Listed drug is a new drug product that has been approved under section 505(c) of the Federal Food, Drug, and Cosmetic Act for safety and effectiveness or under section 505(j) of the Federal Food, Drug, and Cosmetic Act, which has not been withdrawn or suspended under section 505(e)(1) through (5) or section 505(j)(6) of the Federal Food, Drug, and Cosmetic Act, and which has not been withdrawn from sale for what FDA has determined are reasons of safety or effectiveness. Listed drug status is evidenced by the drug product's identification in the current edition of FDA's "Approved Drug Products With Therapeutic Equivalence Evaluations" (the list) as an approved drug. A drug product is deemed to be a listed drug on the date of approval for the NDA or ANDA for that drug product.

NDA holder is the applicant that owns an approved NDA.

Newly acquired information is data, analyses, or other information not previously submitted to the Agency, which may include (but is not limited to) data derived from new clinical studies, reports of adverse events, or new analyses of previously submitted data (e.g., meta-analyses) if the studies, events, or analyses reveal risks of a different type or greater severity or frequency than previously included in submissions to FDA.

Original application or original NDA is a pending NDA for which FDA has never issued a complete response letter or approval letter, or an NDA that was submitted again after FDA had refused to file it or after it was withdrawn without being approved.

Paragraph IV acknowledgment letter is a written, postmarked communication from FDA to an applicant stating that the Agency has determined that a 505(b)(2) application or ANDA containing a paragraph IV certification is sufficiently complete to permit a substantive review. A paragraph IV acknowledgment letter indicates that the 505(b)(2) application is regarded as filed or the ANDA is regarded as received.

Paragraph IV certification is a patent certification of invalidity, unenforceability, or noninfringement described in § 314.50(i)(1)(i)(A)(4) or § 314.94(a)(12)(i)(A)(4).

Patent owner is the owner of the patent for which information is submitted for an NDA.

Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.

Pharmaceutical equivalents are drug products in identical dosage forms and route(s) of administration that contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified-release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver

identical amounts of the active drug ingredient over the identical dosing period; do not necessarily contain the same inactive ingredients; and meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.

Postmark is an independently verifiable evidentiary record of the date on which a document is transmitted, in an unmodifiable format, to another party. For postmarks made by the U.S. Postal Service or a designated delivery service, the date of transmission is the date on which the document is received by the domestic mail service of the U.S. Postal Service or by a designated delivery service. For postmarks documenting an electronic event, the date of transmission is the date (in a particular time zone) that FDA sends the electronic transmission on its host system as evidenced by a verifiable record. If the sender and the intended recipient are located in different time zones, it is the sender's time zone that provides the controlling date of electronic transmission.

Reference listed drug is the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA.

Reference standard is the drug product selected by FDA that an applicant seeking approval of an ANDA must use in conducting an in vivo bioequivalence study required for approval.

Resubmission, in the context of a complete response letter, is submission by the applicant of all materials needed to fully address all deficiencies identified in the complete response letter. An NDA or ANDA for which FDA issued a complete response letter, but which was withdrawn before approval and later submitted again, is not a resubmission.

Right of reference or use is the authority to rely upon, and otherwise use, an investigation for the purpose of obtaining approval of an NDA, including the ability to make available the underlying raw data from the investigation for FDA audit, if necessary.

Same drug product formulation is the formulation of the drug product submitted for approval and any formulations that have minor differences in composition or method of manufacture from the formulation submitted for approval, but are similar enough to be relevant to the Agency's determination of bioequivalence.

Specification is the quality standard (i.e., tests, analytical procedures, and acceptance criteria) provided in an approved NDA or ANDA to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents, components, in-process materials, container closure systems, and other materials used in the production of a drug substance or drug product. For the purpose of this definition, acceptance criteria means numerical limits, ranges, or other criteria for the tests described.

Strength is the amount of drug substance contained in, delivered, or deliverable from a drug product, which includes:

(1)(i) The total quantity of drug substance in mass or units of activity in a dosage unit or container closure (e.g., weight/unit dose, weight/volume or weight/weight in a container closure, or units/volume or units/weight in a container closure); and/or, as applicable.

(ii) The concentration of the drug substance in mass or units of activity per unit volume or mass (e.g., weight/weight, weight/volume, or units/volume); or

(2) Such other criteria the Agency establishes for determining the amount of drug substance contained in, delivered, or deliverable from a drug product if the weights and measures described in paragraph (i) of this definition do not apply (e.g., certain drug-device combination products for which the amount of drug substance is emitted per use or unit time).

Substantially complete application is an ANDA that on its face is sufficiently complete to permit a substantive review. Sufficiently complete means that the ANDA contains all the information re-

quired under section 505(j)(2)(A) of the Federal Food, Drug, and Cosmetic Act and does not contain a deficiency described in § 314.101(d) and (e).

Tentative approval is notification that an NDA or ANDA otherwise meets the requirements for approval under the Federal Food, Drug, and Cosmetic Act, but cannot be approved because there is a 7-year period of orphan exclusivity for a listed drug under section 527 of the Federal Food, Drug, and Cosmetic Act and § 316.31 of this chapter, or that a 505(b)(2) application or ANDA otherwise meets the requirements for approval under the Federal Food, Drug, and Cosmetic Act, but cannot be approved until the conditions in § 314.107(b)(1)(iii), (b)(3), or (c) are met; because there is a period of exclusivity for the listed drug under § 314.108; because there is a period of pediatric exclusivity for the listed drug under section 505A of the Federal Food, Drug, and Cosmetic Act; because there is a period of exclusivity for the listed drug under section 505E of the Federal Food, Drug, and Cosmetic Act; or because a court order pursuant to 35 U.S.C. 271(e)(4)(A) orders that the NDA or ANDA may be approved no earlier than the date specified. A drug product that is granted tentative approval is not an approved drug and will not be approved until FDA issues an approval letter after any necessary additional review of the NDA or ANDA.

The list is the list of approved drug products published in FDA's current "Approved Drug Products With Therapeutic Equivalence Evaluations," available electronically on FDA's Web site at *http://www.fda.gov/cder.*

Therapeutic equivalents are approved drug products that are pharmaceutical equivalents for which bioequivalence has been demonstrated, and that can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.

[81 FR 69636, Oct. 6, 2016]

Subpart B—Applications

§ 314.50 Content and format of an NDA.

NDAs and supplements to approved NDAs are required to be submitted in the form and contain the information, as appropriate for the particular submission, required under this section. Three copies of the NDA are required: An archival copy, a review copy, and a field copy. An NDA for a new chemical entity will generally contain an application form, an index, a summary, five or six technical sections, case report tabulations of patient data, case report forms, drug samples, and labeling, including, if applicable, any Medication Guide required under part 208 of this chapter. Other NDAs will generally contain only some of those items, and information will be limited to that needed to support the particular submission. These include an NDA of the type described in section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, an amendment, and a supplement. The NDA is required to contain reports of all investigations of the drug product sponsored by the applicant, and all other information about the drug pertinent to an evaluation of the NDA that is received or otherwise obtained by the applicant from any source. FDA will maintain guidance documents on the format and content of NDAs to assist applicants in their preparation.

(a) *Application form.* The applicant must submit a completed and signed application form that contains the following:

(1) The name and address of the applicant; the date of the NDA; the NDA number if previously issued (for example, if the NDA is a resubmission or an amendment or supplement); the name of the drug product, including its established, proprietary, code, and chemical names; the dosage form and strength; the route of administration; the identification numbers of all INDs (as defined in § 312.3(b) of this chapter) that are referenced in the NDA; the identification numbers of all drug master files and other applications under this part that are referenced in the NDA; and the drug product's proposed indications for use.

(2) A statement whether the submission is an original submission, a 505(b)(2) application, a resubmission, or a supplement to an application under §314.70.

(3) A statement whether the applicant proposes to market the drug product as a prescription or an over-the-counter product.

(4) A check-list identifying what enclosures required under this section the applicant is submitting.

(5) The applicant, or the applicant's attorney, agent, or other authorized official must sign the NDA. If the person signing the NDA does not reside or have a place of business within the United States, the NDA is required to contain the name and address of, and be countersigned by, an attorney, agent, or other authorized official who resides or maintains a place of business within the United States.

(b) *Index*. The archival copy of the NDA is required to contain a comprehensive index by volume number and page number to the summary under paragraph (c) of this section, the technical sections under paragraph (d) of this section, and the supporting information under paragraph (f) of this section.

(c) *Summary*. (1) An NDA is required to contain a summary of the NDA in enough detail that the reader may gain a good general understanding of the data and information in the NDA, including an understanding of the quantitative aspects of the data. The summary is not required for supplements under §314.70. Resubmissions of an NDA should contain an updated summary, as appropriate. The summary should discuss all aspects of the NDA, and synthesize the information into a well-structured and unified document. The summary should be written at approximately the level of detail required for publication in, and meet the editorial standards generally applied by, refereed scientific and medical journals. In addition to the agency personnel reviewing the summary in the context of their review of the NDA, FDA may furnish the summary to FDA advisory committee members and agency officials whose duties require an understanding of the NDA. To the extent possible, data in the summary should be presented in tabular and graphic forms. FDA has prepared a guideline under §10.90(b) that provides information about how to prepare a summary. The summary required under this paragraph may be used by FDA or the applicant to prepare the Summary Basis of Approval document for public disclosure (under §314.430(e)(2)(ii)) when the NDA is approved.

(2) The summary is required to contain the following information:

(i) The proposed text of the labeling, including, if applicable, any Medication Guide required under part 208 of this chapter, for the drug, with annotations to the information in the summary and technical sections of the NDA that support the inclusion of each statement in the labeling, and, if the NDA is for a prescription drug, statements describing the reasons for omitting a section or subsection of the labeling format in §201.57 of this chapter.

(ii) A statement identifying the pharmacologic class of the drug and a discussion of the scientific rationale for the drug, its intended use, and the potential clinical benefits of the drug product.

(iii) A brief description of the marketing history, if any, of the drug outside the United States, including a list of the countries in which the drug has been marketed, a list of any countries in which the drug has been withdrawn from marketing for any reason related to safety or effectiveness, and a list of countries in which applications for marketing are pending. The description is required to describe both marketing by the applicant and, if known, the marketing history of other persons.

(iv) A summary of the chemistry, manufacturing, and controls section of the NDA.

(v) A summary of the nonclinical pharmacology and toxicology section of the NDA.

(vi) A summary of the human pharmacokinetics and bioavailability section of the NDA.

(vii) A summary of the microbiology section of the NDA (for anti-infective drugs only).

(viii) A summary of the clinical data section of the NDA, including the results of statistical analyses of the clinical trials.

(ix) A concluding discussion that presents the benefit and risk considerations related to the drug, including a discussion of any proposed additional studies or surveillance the applicant intends to conduct postmarketing.

(d) *Technical sections*. The NDA is required to contain the technical sections described below. Each technical section is required to contain data and information in sufficient detail to permit the agency to make a knowledgeable judgment about whether to approve the NDA or whether grounds exist under section 505(d) of the Federal Food, Drug, and Cosmetic Act to refuse to approve the NDA. The required technical sections are as follows:

(1) *Chemistry, manufacturing, and controls section.* A section describing the composition, manufacture, and specification of the drug substance and the drug product, including the following:

(i) *Drug substance.* A full description of the drug substance including its physical and chemical characteristics and stability; the name and address of its manufacturer; the method of synthesis (or isolation) and purification of the drug substance; the process controls used during manufacture and packaging; and the specifications necessary to ensure the identity, strength, quality, and purity of the drug substance and the bioavailability of the drug products made from the substance, including, for example, tests, analytical procedures, and acceptance criteria relating to stability, sterility, particle size, and crystalline form. The NDA may provide additionally for the use of alternatives to meet any of these requirements, including alternative sources, process controls, and analytical procedures. Reference to the current edition of the U.S. Pharmacopeia and the National Formulary may satisfy relevant requirements in this paragraph.

(ii)((a)) *Drug product.* A list of all components used in the manufacture of the drug product (regardless of whether they appear in the drug product) and a statement of the composition of the drug product; the specifications for each component; the name and address of each manufacturer of the drug product; a description of the manufacturing and packaging procedures and in-process controls for the drug product; the specifications necessary to ensure the identity, strength, quality, purity, potency, and bioavailability of the drug product, including, for example, tests, analytical procedures, and acceptance criteria relating to sterility, dissolution rate, container closure systems; and stability data with proposed expiration dating. The NDA may provide additionally for the use of alternatives to meet any of these requirements, including alternative components, manufacturing and packaging procedures, in-process controls, and analytical procedures. Reference to the current edition of the U.S. Pharmacopeia and the National Formulary may satisfy relevant requirements in this paragraph.

(b) Unless provided by paragraph (d)(1)(ii)(a) of this section, for each batch of the drug product used to conduct a bioavailability or bioequivalence study described in § 320.38 or § 320.63 of this chapter or used to conduct a primary stability study: The batch production record; the specification for each component and for the drug product; the names and addresses of the sources of the active and noncompendial inactive components and of the container and closure system for the drug product; the name and address of each contract facility involved in the manufacture, processing, packaging, or testing of the drug product and identification of the operation performed by each contract facility; and the results of any test performed on the components used in the manufacture of the drug product as required by § 211.84(d) of this chapter and on the drug product as required by § 211.165 of this chapter.

(c) The proposed or actual master production record, including a description of the equipment, to be used for the manufacture of a commercial lot of the drug product or a comparably detailed description of the production process for a representative batch of the drug product.

(iii) *Environmental impact*. The NDA is required to contain either a claim for categorical exclusion under § 25.30 or 25.31 of this chapter or an environmental assessment under § 25.40 of this chapter.

(iv) The applicant may, at its option, submit a complete chemistry, manufacturing, and controls section 90 to 120 days before the anticipated submission of the remainder of the NDA. FDA will review such early submissions as resources permit.

(v) The applicant must include a statement certifying that the field copy of the NDA has been provided to the applicant's home FDA district office.

(2) Nonclinical pharmacology and toxicology section. A section describing, with the aid of graphs and tables, animal and in vitro studies with drug, including the following:

(i) Studies of the pharmacological actions of the drug in relation to its proposed therapeutic indication and studies that otherwise define the pharmacologic properties of the drug or are pertinent to possible adverse effects.

(ii) Studies of the toxicological effects of the drug as they relate to the drug's intended clinical uses, including, as appropriate, studies assessing the drug's acute, subacute, and chronic toxicity; carcinogenicity; and studies of toxicities related to the drug's particular mode of administration or conditions of use.

(iii) Studies, as appropriate, of the effects of the drug on reproduction and on the developing fetus.

(iv) Any studies of the absorption, distribution, metabolism, and excretion of the drug in animals.

(v) For each nonclinical laboratory study subject to the good laboratory practice regulations under part 58 a statement that it was conducted in compliance with the good laboratory practice regulations in part 58, or, if the study was not conducted in compliance with those regulations, a brief statement of the reason for the noncompliance.

(3) *Human pharmacokinetics and bioavailability section.* A section describing the human pharmacokinetic data and human bioavailability data, or information supporting a waiver of the submission of in vivo bioavailability data under subpart B of part 320, including the following:

(i) A description of each of the bioavailability and pharmacokinetic studies of the drug in humans performed by or on behalf of the applicant that includes a description of the analytical procedures and statistical methods used in each study and a statement with respect to each study that it either was conducted in compliance with the institutional review board regulations in part 56, or was not subject to the regulations under § 56.104 or § 56.105, and that it was conducted in compliance with the informed consent regulations in part 50.

(ii) If the NDA describes in the chemistry, manufacturing, and controls section tests, analytical procedures, and acceptance criteria needed to assure the bioavailability of the drug product or drug substance, or both, a statement in this section of the rationale for establishing the tests, analytical procedures, and acceptance criteria, including data and information supporting the rationale.

(iii) A summarizing discussion and analysis of the pharmacokinetics and metabolism of the active ingredients and the bioavailability or bioequivalence, or both, of the drug product.

(4) *Microbiology section*. If the drug is an anti-infective drug, a section describing the microbiology data, including the following:

(i) A description of the biochemical basis of the drug's action on microbial physiology.

(ii) A description of the antimicrobial spectra of the drug, including results of in vitro preclinical studies to demonstrate concentrations of the drug required for effective use.

(iii) A description of any known mechanisms of resistance to the drug, including results of any known epidemiologic studies to demonstrate prevalence of resistance factors.

(iv) A description of clinical microbiology laboratory procedures (for example, in vitro sensitivity discs) needed for effective use of the drug.

(5) *Clinical data section*. A section describing the clinical investigations of the drug, including the following:

(i) A description and analysis of each clinical pharmacology study of the drug, including a brief comparison of the results of the human studies with the animal pharmacology and toxicology data.

(ii) A description and analysis of each controlled clinical study pertinent to a proposed use of the drug, including the protocol and a description of the statistical analyses used to evaluate the study. If the study report is an interim analysis, this is to be noted and a projected completion date provided. Controlled clinical studies that have not been analyzed in detail for any reason (e.g., because they have been discontinued or are incomplete) are to be included in this section, including a copy of the protocol and a brief description of the results and status of the study.

(iii) A description of each uncontrolled clinical study, a summary of the results, and a brief statement explaining why the study is classified as uncontrolled.

(iv) A description and analysis of any other data or information relevant to an evaluation of the safety and effectiveness of the drug product obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from clinical investigations, including controlled and uncontrolled studies of uses of the drug other than those proposed in the NDA, commercial marketing experience, reports in the scientific literature, and unpublished scientific papers.

(v) An integrated summary of the data demonstrating substantial evidence of effectiveness for the claimed indications. Evidence is also required to support the dosage and administration section of the labeling, including support for the dosage and dose interval recommended. The effectiveness data must be presented by gender, age, and racial subgroups and must identify any modifications of dose or dose interval needed for specific subgroups. Effectiveness data from other subgroups of the population of patients treated, when appropriate, such as patients with renal failure or patients with different levels of severity of the disease, also must be presented.

(vi) A summary and updates of safety information, as follows:

(a) The applicant must submit an integrated summary of all available information about the safety of the drug product, including pertinent animal data, demonstrated or potential adverse effects of the drug, clinically significant drug/drug interactions, and other safety considerations, such as data from epidemiological studies of related drugs. The safety data must be presented by gender, age, and racial subgroups. When appropriate, safety data from other subgroups of the population of patients treated also must be presented, such as for patients with renal failure or patients with different levels of severity of the disease. A description of any statistical analyses performed in analyzing safety data should also be included, unless already included under paragraph (d)(5)(ii) of this section.

(b) The applicant must, under section 505(i) of the Federal Food, Drug, and Cosmetic Act, update periodically its pending NDA with new safety information learned about the drug that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling and, if applicable, any Medication Guide required under part 208 of this chapter. These "safety update reports" must include the same kinds of information (from clinical studies, animal studies, and other sources) and must be submitted in the same format as the integrated summary in paragraph (d)(5)(vi)(a) of this section. In addition, the reports must include the case report forms for each patient who died during a clinical study or who did not complete the study because of an adverse event (unless this requirement is waived). The applicant must submit these reports (1) 4 months after the initial submission; (2) in a resubmission following receipt of a complete response letter; and (3) at other times as requested by FDA. Before submitting the first such report, applicants are encouraged to consult with FDA regarding further details on its form and content.

(vii) If the drug has a potential for abuse, a description and analysis of studies or information related to abuse of the drug, including a proposal for scheduling under the Controlled Substances Act. A description of any studies related to overdosage is also required, including information on dialysis, antidotes, or other treatments, if known.

(viii) An integrated summary of the benefits and risks of the drug, including a discussion of why the benefits exceed the risks under the conditions stated in the labeling.

(ix) A statement with respect to each clinical study involving human subjects that it either was conducted in compliance with the institutional review board regulations in part 56, or was not subject to the regulations under § 56.104 or § 56.105, and that it was conducted in compliance with the informed consent regulations in part 50.

(x) If a sponsor has transferred any obligations for the conduct of any clinical study to a contract research organization, a statement containing the name and address of the contract research organization, identification of the clinical study, and a listing of the obligations transferred. If all obligations governing the conduct of the study have been transferred, a general statement of this transfer—in lieu of a listing of the specific obligations transferred—may be submitted.

(xi) If original subject records were audited or reviewed by the sponsor in the course of monitoring any clinical study to verify the accuracy of the case reports submitted to the sponsor, a list identifying each clinical study so audited or reviewed.

(6) *Statistical section*. A section describing the statistical evaluation of clinical data, including the following:

(i) A copy of the information submitted under paragraph (d)(5)(ii) of this section concerning the description and analysis of each controlled clinical study, and the documentation and supporting statistical analyses used in evaluating the controlled clinical studies.

(ii) A copy of the information submitted under paragraph (d)(5)(vi)(a) of this section concerning a summary of information about the safety of the drug product, and the documentation and supporting statistical analyses used in evaluating the safety information.

(7) *Pediatric use section.* A section describing the investigation of the drug for use in pediatric populations, including an integrated summary of the information (the clinical pharmacology studies, controlled clinical studies, or uncontrolled clinical studies, or other data or information) that is relevant to the safety and effectiveness and benefits and risks of the drug in pediatric populations for the claimed indications, a reference to the full descriptions of such studies provided under paragraphs (d)(3) and (d)(5) of this section, and information required to be submitted under § 314.55.

(e) *Samples and labeling.* (1) Upon request from FDA, the applicant must submit the samples described below to the places identified in the Agency's request. FDA generally will ask applicants to submit samples directly to two or more Agency laboratories that will perform all necessary tests on the samples and validate the applicant's analytical procedures.

(i) Four representative samples of the following, each sample in sufficient quantity to permit FDA to perform three times each test described in the NDA to determine whether the drug substance and the drug product meet the specifications given in the NDA:

(a) The drug product proposed for marketing;

(b) The drug substance used in the drug product from which the samples of the drug product were taken; and

(c) Reference standards and blanks (except that reference standards recognized in an official compendium need not be submitted).

(ii) Samples of the finished market package, if requested by FDA.

(2) The applicant must submit the following in the archival copy of the NDA:

(i) Three copies of the analytical procedures and related descriptive information contained in the chemistry, manufacturing, and controls section under paragraph (d)(1) of this section for the drug substance and the drug product that are necessary for FDA's laboratories to perform all necessary tests on the samples and to validate the applicant's analytical procedures. The related descriptive information includes a description of each sample; the proposed regulatory specifications for the drug; a detailed description of the methods of analysis; supporting data for accuracy, specificity, precision and ruggedness; and complete results of the applicant's tests on each sample.

(ii) Copies of the label and all labeling for the drug product (including, if applicable, any Medication Guide required under part 208 of this chapter) for the drug product (4 copies of draft labeling or 12 copies of final printed labeling).

(f) *Case report forms and tabulations.* The archival copy of the NDA is required to contain the following case report tabulations and case report forms:

(1) *Case report tabulations.* The NDA is required to contain tabulations of the data from each adequate and well-controlled study under § 314.126 (Phase 2 and Phase 3 studies as described in §§ 312.21 (b) and (c) of this chapter), tabulations of the data from the earliest clinical pharmacology studies (Phase 1 studies as described in § 312.21(a) of this chapter), and tabulations of the safety data from other clinical studies. Routine submission of other patient data from uncontrolled studies is not required. The tabulations are required to include the data on each patient in each study, except that the applicant may delete those tabulations which the agency agrees, in advance, are not pertinent to a review of the drug's safety or effectiveness. Upon request, FDA will discuss with the applicant in a "pre-NDA" conference those tabulations that may be appropriate for such deletion. Barring unforeseen circumstances, tabulations agreed to be deleted at such a conference will not be requested during the conduct of FDA's review of the NDA. If such unforeseen circumstances do occur, any request for deleted tabulations will be made by the director of the FDA division responsible for reviewing the NDA, in accordance with paragraph (f)(3) of this section.

(2) *Case report forms.* The NDA is required to contain copies of individual case report forms for each patient who died during a clinical study or who did not complete the study because of an adverse event, whether believed to be drug related or not, including patients receiving reference drugs or placebo. This requirement may be waived by FDA for specific studies if the case report forms are unnecessary for a proper review of the study.

(3) *Additional data.* The applicant must submit to FDA additional case report forms and tabulations needed to conduct a proper review of the NDA, as requested by the director of the FDA division responsible for reviewing the NDA. The applicant's failure to submit information requested by FDA within 30 days after receipt of the request may result in the agency viewing any eventual submission as a major amendment under § 314.60 and extending the review period as necessary. If desired by the applicant, the FDA division director will verify in writing any request for additional data that was made orally.

(4) *Presentation and format.* Applicants are invited to meet with FDA before submitting an NDA to discuss the presentation and format of supporting information. If the applicant and FDA agree, the applicant may submit tabulations of patient data and case report forms in an alternate form.

(g) *Other.* The following general requirements apply to the submission of information within the summary under paragraph (c) of this section and within the technical sections under paragraph (d) of this section.

(1) The applicant ordinarily is not required to resubmit information previously submitted, but may incorporate the information by reference. A reference to information submitted previously is required to identify the file by name, reference number, volume, and page number in the agency's records where the information can be found. A reference to information submitted to the agency

by a person other than the applicant is required to contain a written statement that authorizes the reference and that is signed by the person who submitted the information.

(2) The applicant must submit an accurate and complete English translation of each part of the NDA that is not in English. The applicant must submit a copy of each original literature publication for which an English translation is submitted.

(3) If an applicant who submits an NDA under section 505(b) of the Federal Food, Drug, and Cosmetic Act obtains a "right of reference or use," as defined under §314.3(b), to an investigation described in clause (A) of section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, the applicant must include in its NDA a written statement signed by the owner of the data from each such investigation that the applicant may rely on in support of the approval of its NDA, and provide FDA access to, the underlying raw data that provide the basis for the report of the investigation submitted in its NDA.

(h) *Patent information.* The NDA is required to contain the patent information described under §314.53.

(i) *Patent certification*—(1) *Contents*. A 505(b)(2) application is required to contain the following:

(i) *Patents claiming drug substance, drug product, or method of use.* (A) An appropriate patent certification or statement with respect to each patent issued by the U.S. Patent and Trademark Office that, in the opinion of the applicant and to the best of its knowledge, claims the drug substance or drug product on which investigations that are relied upon by the applicant for approval of its 505(b)(2) application were conducted or that claims an approved use for such drug and for which information is required to be filed under section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act and §314.53. For each such patent, the applicant must provide the patent number and certify, in its opinion and to the best of its knowledge, one of the following circumstances:

(1) That the patent information has not been submitted to FDA. The applicant must entitle such a certification "Paragraph I Certification";

(2) That the patent has expired. The applicant must entitle such a certification "Paragraph II Certification";

(3) The date on which the patent will expire. The applicant must entitle such a certification "Paragraph III Certification"; or

(4)(i) That the patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the 505(b)(2) application is submitted. The applicant must entitle such a certification "Paragraph IV Certification". This certification must be submitted in the following form:

> I, (name of applicant), certify that Patent No. _____ (*is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of*) (*name of proposed drug product*) for which this 505(b)(2) application is submitted.

(ii) The certification must be accompanied by a statement that the applicant will comply with the requirements under §314.52(a) with respect to providing a notice to each owner of the patent or its representative and to the NDA holder (or, if the NDA holder does not reside or maintain a place of business within the United States, its attorney, agent, or other authorized official) for the drug product that is claimed by the patent or a use of which is claimed by the patent and with the requirements under §314.52(b) with respect to sending the notice and under §314.52(c) with respect to the content of the notice.

(B) If the drug on which investigations that are relied upon by the applicant were conducted is itself a licensed generic drug of a patented drug first approved under section 505(b) of the Federal Food, Drug, and Cosmetic Act, an appropriate patent certification or statement under this section

with respect to each patent that claims the first-approved patented drug or that claims an approved use for such a drug.

(C) If, before the date of submission of an original 505(b)(2) application, there is a drug product approved in an NDA that is pharmaceutically equivalent to the drug product for which the original 505(b)(2) application is submitted, an appropriate patent certification or statement under this section with respect to each patent that claims the drug substance or drug product or that claims an approved use for one such drug product.

(ii) *No relevant patents*. If, in the opinion of the applicant and to the best of its knowledge, there are no patents described in paragraph (i)(1)(i) of this section, a certification in the following form:

> In the opinion and to the best knowledge of (name of applicant), there are no patents that claim the drug or drugs on which investigations that are relied upon in this 505(b)(2) application were conducted or that claim a use of such drug or drugs.

(iii) *Method-of-use patent.* (A) If information that is submitted under section 505(b) or (c) of the Federal Food, Drug, and Cosmetic Act and §314.53 is for a method-of-use patent, and the labeling for the drug product for which the applicant is seeking approval does not include an indication or other condition of use that is covered by the method-of-use patent, a statement explaining that the method-of-use patent does not claim a proposed indication or other condition of use.

(B) If the labeling of the drug product for which the applicant is seeking approval includes an indication or other condition of use that, according to the patent information submitted under section 505(b) or (c) of the Federal Food, Drug, and Cosmetic Act and §314.53 or in the opinion of the applicant, is claimed by a method-of-use patent, the applicant must submit an applicable certification under paragraph (i)(1)(i) of this section.

(2) [Reserved]

(3) *Licensing agreements.* If a 505(b)(2) application is submitted for a drug or method of using a drug claimed by a patent and the applicant has a licensing agreement with the patent owner, the applicant must submit a paragraph IV certification as to that patent and a statement that the applicant has been granted a patent license. If the patent owner consents to approval of the 505(b)(2) application (if otherwise eligible for approval) as of a specific date, the 505(b)(2) application must contain a written statement from the patent owner that it has a licensing agreement with the applicant and that it consents to approval of the 505(b)(2) application as of a specific date.

(4) *Untimely filing of patent information.* (i) If a patent described in paragraph (i)(1)(i)(A) of this section is issued and the holder of the approved NDA for the patented drug does not file with FDA the required information on the patent within 30 days of issuance of the patent, an applicant who submitted a 505(b)(2) application that, before the submission of the patent information, contained an appropriate patent certification or statement is not required to submit a patent certification or statement to address the patent or patent information that is late-listed with respect to the pending 505(b)(2) application. Except as provided in §314.53(f)(1), an NDA holder's amendment to the description of the approved method(s) of use claimed by the patent will be considered untimely filing of patent information unless:

(A) The amendment to the description of the approved method(s) of use claimed by the patent is submitted within 30 days of patent issuance;

(B) The amendment to the description of the approved method(s) of use claimed by the patent is submitted within 30 days of approval of a corresponding change to product labeling; or

(C) The amendment to the description of the approved method(s) of use claimed by the patent is submitted within 30 days of a decision by the U.S. Patent and Trademark Office or by a Federal district court, the Court of Appeals for the Federal Circuit, or the U.S. Supreme Court that is specific

to the patent and alters the construction of a method-of-use claim(s) of the patent, and the amendment contains a copy of the decision.

(ii) An applicant whose 505(b)(2) application is submitted after the NDA holder's untimely filing of patent information or whose 505(b)(2) application was previously filed but did not contain an appropriate patent certification or statement at the time of the patent submission must submit a certification under paragraph (i)(1)(i) of this section and/or a statement under paragraph (i)(1)(iii) of this section as to that patent.

(5) *Disputed patent information*. If an applicant disputes the accuracy or relevance of patent information submitted to FDA, the applicant may seek a confirmation of the correctness of the patent information in accordance with the procedures under §314.53(f). Unless the patent information is withdrawn, the applicant must submit an appropriate certification or statement for each listed patent.

(6) *Amended certifications*. A patent certification or statement submitted under paragraphs (i)(1)(i) through (iii) of this section may be amended at any time before the approval of the 505(b)(2) application. An applicant must submit an amended certification as an amendment to a pending 505(b)(2) application. If an applicant with a pending 505(b)(2) application voluntarily makes a patent certification for an untimely filed patent, the applicant may withdraw the patent certification for the untimely filed patent. Once an amendment is submitted to change the certification, the 505(b)(2) application will no longer be considered to contain the prior certification.

(i) *After finding of infringement.* An applicant who has submitted a paragraph IV certification and is sued for patent infringement must submit an amendment to change its certification if a court enters a final decision from which no appeal has been or can be taken, or signs and enters a settlement order or consent decree in the action that includes a finding that the patent is infringed, unless the final decision, settlement order, or consent decree also finds the patent to be invalid. In its amendment, the applicant must certify under paragraph (i)(1)(i)(A)(3) of this section that the patent will expire on a specific date or, with respect to a patent claiming a method of use, the applicant may instead provide a statement under paragraph (i)(1)(iii) of this section if the applicant amends its 505(b)(2) application such that the applicant is no longer seeking approval for a method of use claimed by the patent. Once an amendment for the change has been submitted, the 505(b)(2) application will no longer be considered to contain a paragraph IV certification to the patent. If a final decision finds the patent to be invalid and infringed, an amended certification is not required.

(ii) *After request to remove a patent or patent information from the list.* If the list reflects that an NDA holder has requested that a patent or patent information be removed from the list and no ANDA applicant is eligible for 180-day exclusivity based on a paragraph IV certification to that patent, the patent or patent information will be removed and any applicant with a pending 505(b)(2) application (including a tentatively approved 505(b)(2) application) who has made a certification with respect to such patent must submit an amendment to withdraw its certification. In the amendment, the applicant must state the reason for withdrawing the certification or statement (that the patent has been removed from the list). If the list reflects that an NDA holder has requested that a patent or patent information be removed from the list and one or more first applicants are eligible for 180-day exclusivity based on a paragraph IV certification to that patent, the patent will remain listed until any 180-day exclusivity based on that patent has expired or has been extinguished. A 505(b)(2) applicant is not required to provide or maintain a certification to a patent or patent information that remains listed only for purposes of a first applicant's 180-day exclusivity for its ANDA. Once an amendment to withdraw the certification has been submitted, the 505(b)(2) application will no longer be considered to contain a paragraph IV certification to the patent. If removal of a patent from the list results in there being no patents listed for the listed drug(s) identified in the 505(b)(2) application, the applicant must submit an amended certification reflecting that there are no listed patents.

(iii) *Other amendments*. (A) Except as provided in paragraphs (i)(4) and (i)(6)(iii)(B) of this section:

(1) An applicant must amend a submitted certification or statement if, at any time before the approval of the 505(b)(2) application, the applicant learns that the submitted certification or statement is no longer accurate; and

(2) An applicant must submit an appropriate patent certification or statement under paragraph (i)(1) of this section if, after submission of the 505(b)(2) application, a new patent is issued by the U.S. Patent and Trademark Office that, in the opinion of the applicant and to the best of its knowledge, claims a listed drug relied upon or that claims an approved use for such listed drug for which information is required to be filed under section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act and §314.53.

(B) An applicant is not required to submit a supplement to change a submitted certification when information on an otherwise applicable patent is submitted after the approval of the 505(b)(2) application.

(j) *Claimed exclusivity*. A new drug product, upon approval, may be entitled to a period of marketing exclusivity under the provisions of §314.108. If an applicant believes its drug product is entitled to a period of exclusivity, it must submit with the NDA prior to approval the following information:

(1) A statement that the applicant is claiming exclusivity.

(2) A reference to the appropriate paragraph under §314.108 that supports its claim.

(3) If the applicant claims exclusivity under §314.108(b)(2), information to show that, to the best of its knowledge or belief, a drug has not previously been approved under section 505(b) of the Federal Food, Drug, and Cosmetic Act containing any active moiety in the drug for which the applicant is seeking approval.

(4) If the applicant claims exclusivity under §314.108(b)(4) or (b)(5), the following information to show that the NDA contains "new clinical investigations" that are "essential to approval of the NDA or supplement" and were "conducted or sponsored by the applicant:"

(i) *"New clinical investigations."* A certification that to the best of the applicant's knowledge each of the clinical investigations included in the NDA meets the definition of "new clinical investigation" set forth in §314.108(a).

(ii) *"Essential to approval."* A list of all published studies or publicly available reports of clinical investigations known to the applicant through a literature search that are relevant to the conditions for which the applicant is seeking approval, a certification that the applicant has thoroughly searched the scientific literature and, to the best of the applicant's knowledge, the list is complete and accurate and, in the applicant's opinion, such published studies or publicly available reports do not provide a sufficient basis for the approval of the conditions for which the applicant is seeking approval without reference to the new clinical investigation(s) in the NDA, and an explanation as to why the studies or reports are insufficient.

(iii) *"Conducted or sponsored by."* If the applicant was the sponsor named in the Form FDA 1571 for an IND under which the new clinical investigation(s) that is essential to the approval of its NDA was conducted, identification of the IND by number. If the applicant was not the sponsor of the IND under which the clinical investigation(s) was conducted, a certification that the applicant or its predecessor in interest provided substantial support for the clinical investigation(s) that is essential to the approval of its NDA, and information supporting the certification. To demonstrate "substantial support," an applicant must either provide a certified statement from a certified public accountant that the applicant provided 50 percent or more of the cost of conducting the study or provide an explanation of why FDA should consider the applicant to have conducted or sponsored the study if the applicant's financial contribution to the study is less than 50 percent or the applicant did not sponsor the investigational new drug. A predecessor in interest is an entity, e.g., a corporation, that

the applicant has taken over, merged with, or purchased, or from which the applicant has purchased all rights to the drug. Purchase of nonexclusive rights to a clinical investigation after it is completed is not sufficient to satisfy this definition.

(k) *Financial certification or disclosure statement.* The NDA must contain a financial certification or disclosure statement or both as required by part 54 of this chapter.

(l) *Format of an original NDA*—(1) *Archival copy.* The applicant must submit a complete archival copy of the NDA that contains the information required under paragraphs (a) through (f) of this section. FDA will maintain the archival copy during the review of the NDA to permit individual reviewers to refer to information that is not contained in their particular technical sections of the NDA, to give other agency personnel access to the NDA for official business, and to maintain in one place a complete copy of the NDA. Except as required by paragraph (l)(1)(i) of this section, applicants may submit the archival copy on paper or in electronic format provided that electronic submissions are made in accordance with part 11 of this chapter.

(i) *Labeling*. The content of labeling required under § 201.100(d)(3) of this chapter (commonly referred to as the package insert or professional labeling), including all text, tables, and figures, must be submitted to the agency in electronic format as described in paragraph (l)(5) of this section. This requirement is in addition to the requirements of paragraph (e)(2)(ii) of this section that copies of the formatted label and all labeling be submitted. Submissions under this paragraph must be made in accordance with part 11 of this chapter, except for the requirements of § 11.10(a), (c) through (h), and (k), and the corresponding requirements of § 11.30.

(ii) [Reserved]

(2) *Review copy.* The applicant must submit a review copy of the NDA. Each of the technical sections, described in paragraphs (d)(1) through (6) of this section, in the review copy is required to be separately bound with a copy of the application form required under paragraph (a) of this section and a copy of the summary required under paragraph (c) of this section.

(3) *Field copy.* The applicant must submit a field copy of the NDA that contains the technical section described in paragraph (d)(1) of this section, a copy of the application form required under paragraph (a) of this section, a copy of the summary required under paragraph (c) of this section, and a certification that the field copy is a true copy of the technical section described in paragraph (d)(1) of this section contained in the archival and review copies of the NDA.

(4) *Binding folders.* The applicant may obtain from FDA sufficient folders to bind the archival, the review, and the field copies of the NDA.

(5) *Electronic format submissions.* Electronic format submissions must be in a form that FDA can process, review, and archive. FDA will periodically issue guidance on how to provide the electronic submission (e.g., method of transmission, media, file formats, preparation and organization of files).

[50 FR 7493, Feb. 22, 1985]

Editorial note: For Federal Register citations affecting § 314.50, see the List of CFR Sections Affected, which appears in the Finding Aids section of the printed volume and at *www.fdsys.gov*.

§ 314.52 Notice of certification of invalidity, unenforceability, or noninfringement of a patent.

(a) Notice of certification. For each patent that claims the listed drug or drugs relied upon or that claims a use for such listed drug or drugs and for which the 505(b)(2) applicant submits a paragraph IV certification, the applicant must send notice of such certification by registered or certified mail, return receipt requested, or by a designated delivery service, as defined in paragraph (g) of this section, to each of the following persons:

(1) Each owner of the patent that is the subject of the certification or the representative designated by the owner to receive the notice. The name and address of the patent owner or its representative may be obtained from the U.S. Patent and Trademark Office; and

(2) The holder of the approved NDA under section 505(b) of the Federal Food, Drug, and Cosmetic Act for each drug product which is claimed by the patent or a use of which is claimed by the patent and for which the applicant is seeking approval, or, if the NDA holder does not reside or maintain a place of business within the United States, the NDA holder's attorney, agent, or other authorized official. The name and address of the NDA holder or its attorney, agent, or authorized official may be obtained by sending a written or electronic communication to the Orange Book Staff, Office of Generic Drugs, 7620 Standish Pl., Rockville, MD 20855, or to the Orange Book Staff at the email address listed on the Agency's Web site at *http://www.fda.gov*.

(3) This paragraph (a) does not apply to a method-of-use patent that does not claim a use for which the applicant is seeking approval.

(4) An applicant may send notice by an alternative method only if FDA has agreed in advance that the method will produce an acceptable form of documentation.

(b) *Sending the notice.* (1) Except as provided under paragraph (d) of this section, the applicant must send the notice required by paragraph (a) of this section on or after the date of filing described in § 314.101(a)(2) or (3), as applicable, but not later than 20 days after the date of the postmark on the paragraph IV acknowledgment letter. The 20-day clock described in this paragraph (b) begins on the day after the date of the postmark on the paragraph IV acknowledgment letter. When the 20th day falls on Saturday, Sunday, or a Federal holiday, the 20th day will be the next day that is not a Saturday, Sunday, or Federal holiday.

(2) Any notice required by paragraph (a) of this section is invalid if it is sent before the date of filing described in § 314.101(a)(2) or, if FDA notifies the applicant that FDA has refused to file the 505(b)(2) application, before the date described in § 314.101(a)(3) on which the 505(b)(2) application is filed. The applicant will not have complied with this paragraph (b) until it sends valid notice.

(3) The applicant must submit to FDA an amendment to its 505(b)(2) application that includes a statement certifying that the notice has been provided to each person identified under paragraph (a) of this section and that the notice met the content requirement under paragraph (c) of this section. A copy of the notice itself need not be submitted to the Agency.

(c) *Content of a notice.* In the notice, the applicant must cite section 505(b)(3)(D) of the Federal Food, Drug, and Cosmetic Act and the notice must include, but is not limited to, the following information:

(1) A statement that a 505(b)(2) application that contains any required bioavailability or bioequivalence studies has been submitted by the applicant and filed by FDA.

(2) The NDA number.

(3) The established name, if any, as defined in section 502(e)(3) of the Federal Food, Drug, and Cosmetic Act, of the proposed drug product.

(4) The active ingredient, strength, and dosage form of the proposed drug product.

(5) The patent number and expiration date of each patent on the list alleged to be invalid, unenforceable, or not infringed.

(6) A detailed statement of the factual and legal basis of the applicant's opinion that the patent is not valid, unenforceable, or will not be infringed. The applicant must include in the detailed statement:

(i) For each claim of a patent alleged not to be infringed, a full and detailed explanation of why the claim is not infringed.

(ii) For each claim of a patent alleged to be invalid or unenforceable, a full and detailed explanation of the grounds supporting the allegation.

(7) If the applicant alleges that the patent will not be infringed and the applicant seeks to preserve the option to later file a civil action for declaratory judgment in accordance with section 505(c)(3)(D) of the Federal Food, Drug, and Cosmetic Act, then the notice must be accompanied by an offer of confidential access to the 505(b)(2) application for the sole and limited purpose of evaluating possible infringement of the patent that is the subject of the paragraph IV certification.

(8) If the applicant does not reside or have a place of business in the United States, the name and address of an agent in the United States authorized to accept service of process for the applicant.

(d) *Amendment or supplement to a 505(b)(2) application*. (1) If, after the date of filing described in § 314.101(a)(2) or (3), as applicable, an applicant submits an amendment or supplement to its 505(b)(2) application that includes a paragraph IV certification, the applicant must send the notice required by paragraph (a) of this section at the same time that the amendment or supplement to the 505(b)(2) application is submitted to FDA, regardless of whether the applicant has already given notice with respect to another such certification contained in the 505(b)(2) application or in an amendment or supplement to the 505(b)(2) application.

(2) If, before the date of filing described in § 314.101(a)(2) or (3), as applicable, an applicant submits a paragraph IV certification in an amendment, the applicant must send the notice required by paragraph (a) of this section in accordance with the procedures in paragraph (b) of this section.

(3) An applicant that submits an amendment or supplement to seek approval of a different strength must provide notice of any paragraph IV certification in accordance with paragraph (d)(1) or (2) of this section, as applicable.

(e) *Documentation of timely sending and receipt of notice.* The applicant must amend its 505(b)(2) application to provide documentation of the date of receipt of the notice required under paragraph (a) of this section by each person provided the notice. The amendment must be submitted to FDA within 30 days after the last date on which notice was received by a person described in paragraph (a) of this section. The applicant's amendment also must include documentation that its notice was sent on a date that complies with the timeframe required by paragraph (b) or (d) of this section, as applicable. FDA will accept, as adequate documentation of the date the notice was sent, a copy of the registered mail receipt, certified mail receipt, or receipt from a designated delivery service, as defined in paragraph (g) of this section. FDA will accept as adequate documentation of the date of receipt a return receipt, a signature proof of delivery by a designated delivery service, or a letter acknowledging receipt by the person provided the notice. An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance. A copy of the notice itself need not be submitted to the Agency.

(f) *Forty-five day period after receipt of notice.* If the requirements of this section are met, the Agency will presume the notice to be complete and sufficient and will count the day following the date of receipt of the notice by the patent owner or its representative and by the approved NDA holder or its attorney, agent, or other authorized official as the first day of the 45-day period provided for in section 505(c)(3)(C) of the Federal Food, Drug, and Cosmetic Act. FDA may, if the applicant amends its 505(b)(2) application with a written statement that a later date should be used, count from such later date.

(g) *Designated delivery services.* (1) For purposes of this section, the term "designated delivery service" is any delivery service provided by a trade or business that the Agency determines:

(i) Is available to the general public throughout the United States;

(ii) Records electronically to its database, kept in the regular course of its business, or marks on the cover in which any item referred to in this section is to be delivered, the date on which such item was given to such trade or business for delivery; and

(iii) Provides overnight or 2-day delivery service throughout the United States.

(2) FDA may periodically issue guidance regarding designated delivery services.

[81 FR 69641, Oct. 6, 2016]

§ 314.53 Submission of patent information.

(a) *Who must submit patent information*. This section applies to any applicant who submits to FDA an NDA or an amendment to it under section 505(b) of the Federal Food, Drug, and Cosmetic Act and § 314.50 or a supplement to an approved NDA under § 314.70, except as provided in paragraph (d)(2) of this section.

(b) *Patents for which information must be submitted and patents for which information must not be submitted*—(1) *General requirements.* An applicant described in paragraph (a) of this section must submit to its NDA the required information, on the required FDA declaration form, set forth in paragraph (c) of this section for each patent that claims the drug or a method of using the drug that is the subject of the NDA or amendment or supplement to it and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. For purposes of this part, such patents consist of drug substance (active ingredient) patents, drug product (formulation and composition) patents, and method-of-use patents. For patents that claim the drug substance, the applicant must submit information only on those patents that claim the drug substance that is the subject of the pending or approved NDA or that claim a drug substance that is the same as the active ingredient that is the subject of the approved or pending NDA. For patents that claim only a polymorph that is the same as the active ingredient described in the approved or pending NDA, the applicant must certify in the required FDA declaration form that the applicant has test data, as set forth in paragraph (b)(2) of this section, demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA. For patents that claim a drug product, the applicant must submit information only on those patents that claim the drug product, as is defined in § 314.3, that is described in the pending or approved NDA. For patents that claim a method of use, the applicant must submit information only on those patents that claim indications or other conditions of use for which approval is sought or has been granted in the NDA. The applicant must separately identify each pending or approved method of use and related patent claim(s). For approved NDAs, the NDA holder's description of the patented method of use required by paragraph (c)(2)(ii)(P)(3) of this section must describe only the approved method(s) of use claimed by the patent for which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. If the method(s) of use claimed by the patent does not cover an indication or other approved condition of use in its entirety, the applicant must describe only the specific approved method of use claimed by the patent for which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. For approved NDAs, the NDA holder submitting information on the method-of-use patent must identify with specificity the section(s) and subsection(s) of the approved labeling that describes the method(s) of use claimed by the patent submitted. Process patents, patents claiming packaging, patents claiming metabolites, and patents claiming intermediates are not covered by this section, and information on these patents must not be submitted to FDA.

(2) *Test data for submission of patent information for patents that claim only a polymorph*. The test data, referenced in paragraph (b)(1) of this section, must include the following:

(i) A full description of the polymorphic form of the drug substance, including its physical and chemical characteristics and stability; the method of synthesis (or isolation) and purification of the drug substance; the process controls used during manufacture and packaging; and such specifications and analytical methods as are necessary to assure the identity, strength, quality, and purity of the polymorphic form of the drug substance;

(ii) The executed batch record for a drug product containing the polymorphic form of the drug substance and documentation that the batch was manufactured under current good manufacturing practice requirements;

(iii) Demonstration of bioequivalence between the executed batch of the drug product that contains the polymorphic form of the drug substance and the drug product as described in the NDA;

(iv) A list of all components used in the manufacture of the drug product containing the polymorphic form and a statement of the composition of the drug product; a statement of the specifications and analytical methods for each component; a description of the manufacturing and packaging procedures and in-process controls for the drug product; such specifications and analytical methods as are necessary to assure the identity, strength, quality, purity, and bioavailability of the drug product, including release and stability data complying with the approved product specifications to demonstrate pharmaceutical equivalence and comparable product stability; and

(v) Comparative in vitro dissolution testing on 12 dosage units each of the executed test batch and the NDA product.

(c) *Reporting requirements*—(1) *General requirements.* An applicant described in paragraph (a) of this section must submit the required patent information described in paragraph (c)(2) of this section for each patent that meets the requirements described in paragraph (b) of this section. We will not accept the patent information unless it is submitted on the appropriate form, Form FDA 3542 or 3542a, and contains the information required in paragraph (c)(2) of this section. These forms may be obtained on the Internet at *http://www.fda.gov* by searching for "forms".

(2) *Drug substance (active ingredient), drug product (formulation or composition), and method-of-use patents*—(i) *Original declaration.* For each patent that claims a drug substance (active ingredient), drug product (formulation and composition), or method of use, the applicant must submit Form FDA 3542a. The following information and verification is required, subject to the exceptions listed in paragraph (c)(2)(i)(S) of this section:

(A) NDA number;

(B) The NDA applicant's name, full address, phone number and, if available, fax number and email address;

(C) Trade name (or proposed trade name) of new drug;

(D) Active ingredient(s) of new drug;

(E) Strength(s) of new drug;

(F) Dosage form(s) and route(s) of administration of new drug, and whether the applicant proposes to market the new drug for prescription use or over-the-counter use;

(G) U.S. patent number, issue date, and expiration date of patent submitted;

(H) The patent owner's name, full address, phone number and, if available, fax number and email address;

(I) The name, full address, phone number and, if available, fax number and email address of an agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and §§ 314.52 and 314.95 (if patent owner or NDA applicant or holder does not reside or have a place of business within the United States);

(J) Information on whether the patent has been submitted previously for the NDA or supplement;

(K) If the patent has been submitted previously for listing, identify all change(s) from the previously submitted patent information and specify whether the change is related to the patent or related to an FDA action or procedure;

(L) Information on whether the patent is a product-by-process patent in which the product claimed is novel;

(M) Information on the drug substance (active ingredient) patent, including the following:

(1) Whether the patent claims a drug substance that is an active ingredient in the drug product described in the NDA or supplement;

(2) Whether the patent claims only a polymorph that is the same active ingredient that is described in the pending NDA or supplement;

(3) Whether the applicant has test data, described in paragraph (b)(2) of this section, demonstrating that a drug product containing only the polymorph will perform the same as the drug product described in the NDA or supplement, and a description of the polymorphic form(s) claimed by the patent for which such test data exist;

(4) Whether the patent claims only a metabolite of the active ingredient; and

(5) Whether the patent claims only an intermediate;

(N) Information on the drug product (composition/formulation) patent, including the following:

(1) Whether the patent claims the drug product for which approval is being sought, as defined in §314.3; and

(2) Whether the patent claims only an intermediate;

(O) Information on each method-of-use patent, including the following:

(1) Whether the patent claims one or more methods of using the drug product for which approval is being sought and a description of each pending method of use and related patent claim of the patent being submitted;

(2) Identification of the specific section(s) and subsection(s) of the proposed labeling for the drug product that describes the method of use claimed by the patent submitted; and

(3) An applicant that submits information for a patent that claims one or more methods of using the drug product must also submit information described in either paragraph (c)(2)(i)(M) or (N) of this section, regarding whether that patent also claims either the drug substance (active ingredient) or the drug product (composition/formulation).

(P) Whether there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition), or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product;

(Q) A signed verification that states:

The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

(R) Information on whether the applicant, patent owner or attorney, agent, representative, or other authorized official signed the form; the name of the person; and the full address, phone number and, if available, the fax number and email address; and

(S) Exceptions to required submission of patent information:

(1) If an applicant submits the information described in paragraph (c)(2)(i)(M) of this section for a patent that claims the drug substance (active ingredient) and meets the requirements for listing on that basis, then the applicant is not required to provide the information described in paragraph (c)(2)(i)(N) of this section on whether that patent also claims the drug product (composition/formulation);

(2) If an applicant submits the information described in paragraph (c)(2)(i)(N) of this section for a patent that claims the drug product (composition/formulation) and meets the requirements for listing on that basis, then the applicant is not required to provide the information described in paragraph (c)(2)(i)(M) of this section on whether that patent also claims the drug substance (active ingredient);

(3) If the applicant submits a supplement for a change other than one of the changes listed under paragraph (d)(2)(i) of this section, then the patent information submission requirements of paragraph (d)(2)(ii) of this section apply.

(ii) *Submission of patent information upon and after approval.* Within 30 days after the date of approval of its NDA or supplement, the applicant must submit Form FDA 3542 for each patent that claims the drug substance (active ingredient), drug product (formulation and composition), or approved method of use. FDA will not list or publish patent information if it is not provided on this form or if the patent declaration does not contain the required information or indicates the patent is not eligible for listing. Patent information must also be submitted for patents issued after the date of approval of the NDA as required in paragraph (c)(2)(ii) of this section. As described in paragraph (d)(3) of this section, to be timely filed, patent information for patents issued after the date of approval of the NDA must be submitted to FDA within 30 days of the date of issuance of the patent. If the applicant submits the required patent information within the 30 days, but we notify an applicant that a declaration form is incomplete or shows that the patent is not eligible for listing, the applicant must submit an acceptable declaration form within 15 days of FDA notification to be considered timely filed. The following information and verification statement is required, subject to the exceptions listed in paragraph (c)(2)(ii)(T) of this section:

(A) NDA number;

(B) The NDA holder's name, full address, phone number and, if available, fax number and email address;

(C) Trade name of new drug;

(D) Active ingredient(s) of new drug;

(E) Strength(s) of new drug;

(F) Dosage form(s) and route(s) of administration of new drug, and whether the new drug is approved for prescription use or over-the-counter use;

(G) Approval date of NDA or supplement;

(H) U.S. patent number, issue date, and expiration date of patent submitted;

(I) The patent owner's name, full address, phone number and, if available, fax number and email address;

(J) The name, full address, phone number and, if available, fax number and email address of an agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and §§ 314.52 and 314.95 (if patent owner or NDA applicant or holder does not reside or have a place of business within the United States);

(K) Information on whether the patent has been submitted previously for the NDA or supplement;

(L) If the patent has been submitted previously for listing, identify all change(s) from the previously submitted patent information and specify whether the change is related to the patent or related to an FDA action or procedure;

(M) Information on whether the patent is a product-by-process patent in which the product claimed is novel;

(N) Information on the drug substance (active ingredient) patent, including the following:

(1) Whether the patent claims a drug substance that is an active ingredient in the drug product described in the approved NDA;

(2) Whether the patent claims only a polymorph that is the same as the active ingredient that is described in the approved NDA;

(3) Whether the applicant has test data, described in paragraph (b)(2) of this section, demonstrating that a drug product containing only the polymorph will perform the same as the drug product described in the approved NDA and a description of the polymorphic form(s) claimed by the patent for which such test data exist;

(4) Whether the patent claims only a metabolite of the active ingredient; and

(5) Whether the patent claims only an intermediate;

(O) Information on the drug product (composition/formulation) patent, including the following:

(1) Whether the patent claims the approved drug product as defined in § 314.3; and

(2) Whether the patent claims only an intermediate;

(P) Information on each method-of-use patent, including the following:

(1) Whether the patent claims one or more approved methods of using the approved drug product and a description of each approved method of use and related patent claim of the patent being submitted;

(2) Identification of the specific section(s) and subsection(s) of the approved labeling for the drug product that describes the method of use claimed by the patent submitted;

(3) The description of the patented method of use as required for publication, which must contain adequate information to assist 505(b)(2) and ANDA applicants in determining whether a listed method-of-use patent claims a use for which the 505(b)(2) or ANDA applicant is not seeking approval (for example, if the method(s) of use claimed by the patent does not cover an indication or other approved condition of use in its entirety, then the applicant must describe only the specific approved method of use claimed by the patent for which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product); and

(4) An applicant that submits information for a patent that claims one or more methods of using the drug product must also submit information described in either paragraph (c)(2)(ii)(N) or (O) of this section, regarding whether that patent also claims either the drug substance (active ingredient) or the drug product (composition/formulation).

(Q) Whether there are no relevant patents that claim the approved drug substance (active ingredient), the approved drug product (formulation or composition), or approved method(s) of use and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product;

(R) A signed verification that states:

The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement approved under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information or response to a request under 21 CFR

314.53(f)(1) is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

(S) Information on whether the applicant, patent owner or attorney, agent, representative, or other authorized official signed the form; the name of the person; and the full address, phone number and, if available, the fax number and email address; and

(T) Exceptions to required submission of patent information:

(1) If an applicant submits the information described in paragraph (c)(2)(ii)(N) of this section for a patent that claims the drug substance (active ingredient) and meets the requirements for listing on that basis, then the applicant is not required to provide the information described in paragraph (c)(2)(ii)(O) of this section on whether that patent also claims the drug product (composition/formulation).

(2) If an applicant submits the information described in paragraph (c)(2)(ii)(O) of this section for a patent that claims the drug product (composition/formulation) and meets the requirements for listing on that basis, then the applicant is not required to provide the information described in paragraph (c)(2)(ii)(N) of this section on whether that patent also claims the drug substance (active ingredient).

(3) If the applicant submits a supplement for a change other than one of the changes listed under paragraph (d)(2)(i) of this section, then the patent information submission requirements of paragraph (d)(2)(ii) of this section apply.

(3) *No relevant patents.* If the applicant believes that there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition), or the method(s) of use for which the applicant has received approval, and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product, the applicant will verify this information in the appropriate form, Form FDA 3542 or 3542a.

(4) *Authorized signature.* The declarations required by this section must be signed by the applicant or patent owner, or the applicant's or patent owner's attorney, agent (representative), or other authorized official.

(d) *When and where to submit patent information*—(1) *Original NDA.* An applicant must submit with its original NDA submitted under this part, the information described in paragraph (c) of this section on each drug substance (active ingredient), drug product (formulation and composition), and method-of-use patent issued before the NDA is filed with FDA and for which patent information is required to be submitted under this section. If a patent is issued after the NDA is filed with FDA but before the NDA is approved, the applicant must, within 30 days of the date of issuance of the patent, submit the required patent information in an amendment to the NDA under § 314.60.

(2) *Supplements*. (i) An applicant must submit patent information required under paragraph (c) of this section for a patent that claims the drug substance, drug product, or method of use for which approval is sought in any of the following supplements:

(A) To add or change the dosage form or route of administration;

(B) To add or change the strength; or

(C) To change the drug product from prescription use to over-the-counter use.

(ii) If the applicant submits a supplement for a change other than one of the changes listed under paragraph (d)(2)(i) of this section (for example, to change the formulation, to add a new indication or other condition of use, or to make any other patented change regarding the drug substance, drug product, or any method of use), the following patent information submission requirements apply:

(A) If existing patents for which information required by paragraph (c) of this section has already been submitted to FDA for the product approved in the original NDA claim the changed product, the applicant is not required to resubmit this patent information pursuant to paragraph (c) of this section unless the published description of the patented method of use would change upon approval of the supplement, and FDA will continue to list this patent information for the product;

(B) If one or more existing patents for which information has already been submitted to FDA no longer claim the changed product, the applicant must submit a request under paragraph (f)(2)(iv) of this section to remove that patent information from the list at the time of approval of the supplement;

(C) If one or more existing drug substance (active ingredient), drug product (formulation and composition), or method-of-use patents claim the changed product for which approval is sought in the supplement and such patent information has not been submitted to FDA, the applicant must submit the patent information required under paragraph (c) of this section.

(3) *Newly issued patents.* If a patent is issued for a drug substance, drug product, or method of use after an NDA is approved, the applicant must submit to FDA, as described in paragraph (d)(4) of this section, the required patent information within 30 days of the date of issuance of the patent. If the required patent information is not submitted within 30 days of the issuance of the patent, FDA will list the patent, but patent certifications or statements will be governed by the provisions regarding untimely filed patent information at §§ 314.50(i)(4) and (6) and 314.94(a)(12)(vi) and (viii).

(4) *Submission of Forms FDA 3542a and 3542*—(i) *Patent information submitted with the filing of an NDA, amendment, or supplement.* The applicant must submit patent information required by paragraphs (c)(1) and (c)(2)(i) of this section and § 314.50(h) or § 314.70(f) on Form FDA 3542a to the Central Document Room, Center for Drug Evaluation and Research, Food and Drug Administration, 5901-B Ammendale Rd., Beltsville, MD 20705-1266, or to FDA in an electronic format submission that complies with § 314.50(l)(5). Form FDA 3542a should not be submitted to the Orange Book Staff in the Office of Generic Drugs.

(ii) *Patent information submitted upon and after approval of an NDA or supplement.* The applicant must submit patent information required by paragraphs (c)(1) and (c)(2)(ii) of this section on Form FDA 3542 to the Central Document Room, Center for Drug Evaluation and Research, Food and Drug Administration, 5901-B Ammendale Rd., Beltsville, MD 20705-1266, or to FDA in an electronic format submission that complies with § 314.50(l)(5). Form FDA 3542 should not be submitted to the Orange Book Staff in the Office of Generic Drugs.

(5) *Submission date*. Patent information will be considered to be submitted to FDA for purposes of paragraph (d)(3) of this section as of the earlier of the date the information submitted on Form FDA 3542 is date-stamped by the Central Document Room, or officially received by FDA in an electronic format submission that complies with § 314.50(l)(5).

(6) *Identification*. Each submission of patent information, except information submitted with an original NDA, must bear prominent identification as to its contents, i.e., "Patent Information," or, if submitted after approval of an NDA, "Time Sensitive Patent Information."

(e) *Public disclosure of patent information.* FDA will publish in the list the patent number and expiration date of each patent that is required to be, and is, submitted to FDA by an applicant, and for each method-of-use patent, the description of the method of use claimed by the patent as required by § 314.53(c)(2)(ii)(P)(3). FDA will publish such patent information upon approval of the NDA, or, if the patent information is submitted by the applicant after approval of an NDA as provided under paragraph (d)(2) of this section, as soon as possible after the submission to the Agency of the patent information. A request for copies of the submitted patent information must be sent in writing to the Freedom of Information Staff at the address listed on the Agency's Web site at *http://www.fda.gov.*

The submitted patent information, and requests to remove a patent or patent information from the list, may be subject to public disclosure.

(f) *Correction of patent information errors*—(1) *Requests by persons other than the NDA holder.* If any person disputes the accuracy or relevance of patent information submitted to the Agency under this section and published by FDA in the list, or believes that an NDA holder has failed to submit required patent information, that person must first notify the Agency in a written or electronic communication titled "314.53(f) Patent Listing Dispute." The patent listing dispute communication must include a statement of dispute that describes the specific grounds for disagreement regarding the accuracy or relevance of patent information for FDA to send to the applicable NDA holder. For a dispute regarding the accuracy or relevance of patent information regarding an approved method of using the drug product, this statement of dispute must be only a narrative description (no more than 250 words) of the person's interpretation of the scope of the patent. This statement of dispute must only contain information for which the person consents to disclosure because FDA will send the text of the statement to the applicable NDA holder without review or redaction. The patent listing dispute communication should be directed to the Office of Generic Drugs, OGD Document Room, Attention: Orange Book Staff, 7620 Standish Pl., Rockville, MD 20855, or to the Orange Book Staff at the email address listed on the Agency's Web site at *http://www.fda.gov.*

(i) *Communication with the NDA holder*—(A) *Drug substance or drug product claim.* For requests submitted under this paragraph (f)(1) that are directed to the accuracy or relevance of submitted patent information regarding a drug substance or drug product claim, the Agency will send the statement of dispute to the applicable NDA holder. The NDA holder must confirm the correctness of the patent information and include the signed verification required by paragraph (c)(2)(ii)(R) of this section or withdraw or amend the patent information in accordance with paragraph (f)(2) of this section within 30 days of the date on which the Agency sends the statement of dispute. Unless the NDA holder withdraws or amends its patent information in response to the patent listing dispute, the Agency will not change the patent information in the Orange Book.

(B) *Method-of-use claim.* For requests submitted under this paragraph (f)(1) that are directed to the accuracy or relevance of submitted patent information regarding an approved method of using the drug product, FDA will send the statement of dispute to the NDA holder. The NDA holder must confirm the correctness of its description of the approved method of use claimed by the patent that has been included as the "Use Code" in the Orange Book, or withdraw or amend the patent information in accordance with paragraph (f)(2) of this section, provide a narrative description (no more than 250 words) of the NDA holder's interpretation of the scope of the patent that explains why the existing or amended "Use Code" describes only the specific approved method of use claimed by the patent for which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product, and include the signed verification required by paragraph (c)(2)(ii)(R) of this section within 30 days of the date on which the Agency sends the statement of dispute. The narrative description must only contain information for which the NDA holder consents to disclosure because FDA will send the text of the statement to the person who submitted the patent listing dispute without review or redaction.

(1) If the NDA holder confirms the correctness of the patent information, provides the narrative description required by paragraph (f)(1)(i)(B) of this section, and includes the signed verification required by paragraph (c)(2)(ii)(R) of this section within 30 days of the date on which the Agency sends the statement of dispute, the Agency will not change the patent information in the Orange Book.

(2) If the NDA holder responds to the patent listing dispute with amended patent information in accordance with paragraph (f)(2) of this section, provides the narrative description required by paragraph (f)(1)(i)(B) of this section, and includes the signed verification required by paragraph (c)(2)(ii)

(R) of this section within 30 days of the date on which the Agency sends the statement of dispute, FDA will update the Orange Book to reflect the amended patent information.

(ii) *Patent certification or statement during and after patent listing dispute.* A 505(b)(2) application or ANDA must contain an appropriate certification or statement for each listed patent, including the disputed patent, during and after the patent listing dispute.

(iii) *Information on patent listing disputes.* FDA will promptly post information on its Web site regarding whether a patent listing dispute has been submitted for a published description of a patented method of use for a drug product and whether the NDA holder has timely responded to the patent listing dispute.

(2) *Requests by the NDA holder*—(i) *Patents or patent claims that no longer meet the statutory requirements for listing*. If the NDA holder determines that a patent or patent claim no longer meets the requirements for listing in section 505(b)(1) or (c)(2) of the Federal Food, Drug, and Cosmetic Act (including if there has been a judicial finding of invalidity for a listed patent, from which no appeal has been or can be taken), the NDA holder is required to promptly notify FDA to amend the patent information or withdraw the patent or patent information and request that the patent or patent information be removed from the list. If the NDA holder is required by court order to amend patent information or withdraw a patent from the list, it must submit an amendment to its NDA that includes a copy of the order, within 14 days of the date the order was entered, to the Central Document Room, Center for Drug Evaluation and Research, Food and Drug Administration, 5901-B Ammendale Rd., Beltsville, MD 20705-1266. The amendment to the NDA must bear the identification described in paragraph (d)(6) of this section. FDA will remove a patent or patent information from the list if there is no first applicant eligible for 180-day exclusivity based on a paragraph IV certification to that patent or after the 180-day exclusivity period of a first applicant based on that patent has expired or has been extinguished.

(ii) Patent term restoration. If the term of a listed patent is extended pursuant to 35 U.S.C. 156(e), the NDA holder must submit on Form FDA 3542 a correction to the expiration date of the patent. This correction must be submitted within 30 days of receipt of a certificate of extension as described in 35 U.S.C. 156(e)(1) or documentation of an extension of the term of the patent as described in 35 U.S.C. 156(e)(2).

(iii) *Submission of corrections or changes to patent information.* Corrections or changes to previously submitted patent information, other than withdrawal of a patent and requests to remove a patent from the list, must be submitted on Form FDA 3542 or 3542a, as appropriate, in an amendment or supplement to the NDA. The amendment or supplement to the NDA must bear the identification described in paragraph (d)(6) of this section. We will not accept the corrections or changes unless they are submitted on the appropriate forms.

(iv) *Submission of patent withdrawals and requests to remove a patent from the list.* Withdrawal of a patent and requests to remove a patent from the list must be submitted to the same addresses described in paragraph (d)(4)(ii) of this section, except that the withdrawal or request to remove a patent from the list is not required to be submitted on Form FDA 3542 and may be submitted by letter. Withdrawal of a patent and a request to remove a patent from the list must contain the following information:

(A) The NDA number to which the request applies;

(B) Each product(s) approved in the NDA to which the request applies; and

(C) The patent number.

[81 FR 69643, Oct. 6, 2016]

§ 314.54 Procedure for submission of a 505(b)(2) application requiring investigations for approval of a new indication for, or other change from, a listed drug.

(a) The Federal Food, Drug, and Cosmetic Act does not permit approval of an ANDA for a new indication, nor does it permit approval of other changes in a listed drug if investigations, other than bioavailability or bioequivalence studies, are essential to the approval of the change. Any person seeking approval of a drug product that represents a modification of a listed drug (e.g., a new indication or new dosage form) and for which investigations, other than bioavailability or bioequivalence studies, are essential to the approval of the changes may, except as provided in paragraph (b) of this section, submit a 505(b)(2) application. This 505(b)(2) application need contain only that information needed to support the modification(s) of the listed drug.

(1) The applicant must submit a complete archival copy of the application that contains the following:

(i) The information required under § 314.50(a), (b), (c), (d)(1), (d)(3), (e), and (g), except that § 314.50(d)(1)(ii)(c) must contain the proposed or actual master production record, including a description of the equipment, to be used for the manufacture of a commercial lot of the drug product.

(ii) The information required under § 314.50 (d)(2), (d)(4) (if an anti-infective drug), (d)(5), (d)(6), and (f) as needed to support the safety and effectiveness of the drug product.

(iii) Identification of each listed drug for which FDA has made a finding of safety and effectiveness and on which finding the applicant relies in seeking approval of its proposed drug product by established name, if any, proprietary name, dosage form, strength, route of administration, name of listed drug's application holder, and listed drug's approved NDA number. The listed drug(s) identified as relied upon must include a drug product approved in an NDA that:

(A) Is pharmaceutically equivalent to the drug product for which the original 505(b)(2) application is submitted; and

(B) Was approved before the original 505(b)(2) application was submitted.

(iv) If the applicant is seeking approval only for a new indication and not for the indications approved for the listed drug on which the applicant relies, a certification so stating.

(v) Any patent information required under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act with respect to any patent which claims the drug for which approval is sought or a method of using such drug and to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.

(vi) Any patent certification or statement required under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act with respect to any relevant patents that claim the listed drug(s) on which investigations relied on by the applicant for approval of the application were conducted, or that claim a use for the listed drug(s). A 505(b)(2) applicant seeking approval of a drug that is pharmaceutically equivalent to a listed drug approved in an NDA implicitly relies upon one such pharmaceutically equivalent listed drug.

(vii) If the applicant believes the change for which it is seeking approval is entitled to a period of exclusivity, the information required under § 314.50(j).

(2) The applicant must submit a review copy that contains the technical sections described in § 314.50(d)(1), except that the section described in § 314.50(d)(1)(ii)(c) must contain the proposed or actual master production record, including a description of the equipment, to be used for the manufacture of a commercial lot of the drug product, and § 314.50(d)(3), and the technical sections described in § 314.50(d)(2), (d)(4) through (6), and (f) when needed to support the modification. Each of the technical sections in the review copy is required to be separately bound with a copy of the information required under § 314.50(a), (b), and (c) and a copy of the proposed labeling.

(3) The information required by §314.50 (d)(2), (d)(4) (if an anti-infective drug), (d)(5), (d)(6), and (f) for the listed drug on which the applicant relies must be satisfied by reference to the listed drug under paragraph (a)(1)(iii) of this section.

(4) The applicant must submit a field copy of the 505(b)(2) application that contains the technical section described in §314.50(d)(1), a copy of the information required under §314.50(a) and (c), and certification that the field copy is a true copy of the technical section described in §314.50(d)(1) contained in the archival and review copies of the 505(b)(2) application.

(b) A 505(b)(2) application may not be submitted under this section for a drug product whose only difference from a listed drug is that:

(1) The extent to which its active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the listed drug; or

(2) The rate at which its active ingredient(s) is absorbed or otherwise made available to the site of action is unintentionally less than that of the listed drug.

[57 FR 17982, Apr. 28, 1992; 57 FR 61612, Dec. 28, 1992, as amended at 58 FR 47351, Sept. 8, 1993; 59 FR 50364, Oct. 3, 1994; 81 FR 69647, Oct. 6, 2016]

§314.55 Pediatric use information.

(a) *Required assessment.* Except as provided in paragraphs (b), (c), and (d) of this section, each application for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration shall contain data that are adequate to assess the safety and effectiveness of the drug product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the drug is safe and effective. Where the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, FDA may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies. Studies may not be needed in each pediatric age group, if data from one age group can be extrapolated to another. Assessments of safety and effectiveness required under this section for a drug product that represents a meaningful therapeutic benefit over existing treatments for pediatric patients must be carried out using appropriate formulations for each age group(s) for which the assessment is required.

(b) *Deferred submission.* (1) FDA may, on its own initiative or at the request of an applicant, defer submission of some or all assessments of safety and effectiveness described in paragraph (a) of this section until after approval of the drug product for use in adults. Deferral may be granted if, among other reasons, the drug is ready for approval in adults before studies in pediatric patients are complete, or pediatric studies should be delayed until additional safety or effectiveness data have been collected. If an applicant requests deferred submission, the request must provide a certification from the applicant of the grounds for delaying pediatric studies, a description of the planned or ongoing studies, and evidence that the studies are being or will be conducted with due diligence and at the earliest possible time.

(2) If FDA determines that there is an adequate justification for temporarily delaying the submission of assessments of pediatric safety and effectiveness, the drug product may be approved for use in adults subject to the requirement that the applicant submit the required assessments within a specified time.

(c) *Waivers*—(1) *General*. FDA may grant a full or partial waiver of the requirements of paragraph (a) of this section on its own initiative or at the request of an applicant. A request for a waiver must provide an adequate justification.

(2) *Full waiver.* An applicant may request a waiver of the requirements of paragraph (a) of this section if the applicant certifies that:

(i) The drug product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is not likely to be used in a substantial number of pediatric patients;

(ii) Necessary studies are impossible or highly impractical because, e.g., the number of such patients is so small or geographically dispersed; or

(iii) There is evidence strongly suggesting that the drug product would be ineffective or unsafe in all pediatric age groups.

(3) *Partial waiver.* An applicant may request a waiver of the requirements of paragraph (a) of this section with respect to a specified pediatric age group, if the applicant certifies that:

(i) The drug product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients in that age group, and is not likely to be used in a substantial number of patients in that age group;

(ii) Necessary studies are impossible or highly impractical because, e.g., the number of patients in that age group is so small or geographically dispersed;

(iii) There is evidence strongly suggesting that the drug product would be ineffective or unsafe in that age group; or

(iv) The applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed.

(4) *FDA action on waiver.* FDA shall grant a full or partial waiver, as appropriate, if the agency finds that there is a reasonable basis on which to conclude that one or more of the grounds for waiver specified in paragraphs (c)(2) or (c)(3) of this section have been met. If a waiver is granted on the ground that it is not possible to develop a pediatric formulation, the waiver will cover only those pediatric age groups requiring that formulation. If a waiver is granted because there is evidence that the product would be ineffective or unsafe in pediatric populations, this information will be included in the product's labeling.

(5) *Definition of "meaningful therapeutic benefit".* For purposes of this section and § 201.23 of this chapter, a drug will be considered to offer a meaningful therapeutic benefit over existing therapies if FDA estimates that:

(i) If approved, the drug would represent a significant improvement in the treatment, diagnosis, or prevention of a disease, compared to marketed products adequately labeled for that use in the relevant pediatric population. Examples of how improvement might be demonstrated include, for example, evidence of increased effectiveness in treatment, prevention, or diagnosis of disease, elimination or substantial reduction of a treatment-limiting drug reaction, documented enhancement of compliance, or evidence of safety and effectiveness in a new subpopulation; or

(ii) The drug is in a class of drugs or for an indication for which there is a need for additional therapeutic options.

(d) Exemption for orphan drugs. This section does not apply to any drug for an indication or indications for which orphan designation has been granted under part 316, subpart C, of this chapter.

[63 FR 66670, Dec. 2, 1998]

§ 314.60 Amendments to an unapproved NDA, supplement, or resubmission.

(a) *Submission of NDA*. FDA generally assumes that when an original NDA, supplement to an approved NDA, or resubmission of an NDA or supplement is submitted to the Agency for review, the applicant believes that the Agency can approve the NDA, supplement, or resubmission as submitted. However, the applicant may submit an amendment to an NDA, supplement, or resubmission that has been filed under § 314.101 but is not yet approved.

(b) Submission of major amendment. (1) Submission of a major amendment to an original NDA, efficacy supplement, or resubmission of an NDA or efficacy supplement within 3 months of the end of the initial review cycle constitutes an agreement by the applicant under section 505(c) of the Federal Food, Drug, and Cosmetic Act to extend the initial review cycle by 3 months. (For references to a resubmission of an NDA or efficacy supplement in paragraph (b) of this section, the timeframe for reviewing the resubmission is the "review cycle" rather than the "initial review cycle.") FDA may instead defer review of the amendment until the subsequent review cycle. If the agency extends the initial review cycle for an original NDA, efficacy supplement, or resubmission under this paragraph, the division responsible for reviewing the NDA, supplement, or resubmission will notify the applicant of the extension. The initial review cycle for an original NDA, efficacy supplement, or resubmission of an NDA or efficacy supplement may be extended only once due to submission of a major amendment. FDA may, at its discretion, review any subsequent major amendment during the initial review cycle (as extended) or defer review until the subsequent review cycle.

(2) Submission of a major amendment to an original NDA, efficacy supplement, or resubmission of an NDA or efficacy supplement more than 3 months before the end of the initial review cycle will not extend the cycle. FDA may, at its discretion, review such an amendment during the initial review cycle or defer review until the subsequent review cycle.

(3) Submission of an amendment to an original NDA, efficacy supplement, or resubmission of an NDA or efficacy supplement that is not a major amendment will not extend the initial review cycle. FDA may, at its discretion, review such an amendment during the initial review cycle or defer review until the subsequent review cycle.

(4) Submission of a major amendment to a manufacturing supplement within 2 months of the end of the initial review cycle constitutes an agreement by the applicant under section 505(c) of the Federal Food, Drug, and Cosmetic Act to extend the initial review cycle by 2 months. FDA may instead defer review of the amendment until the subsequent review cycle. If the agency extends the initial review cycle for a manufacturing supplement under this paragraph, the division responsible for reviewing the supplement will notify the applicant of the extension. The initial review cycle for a manufacturing supplement may be extended only once due to submission of a major amendment. FDA may, at its discretion, review any subsequent major amendment during the initial review cycle (as extended) or defer review until the subsequent review cycle.

(5) Submission of an amendment to a supplement other than an efficacy or manufacturing supplement will not extend the initial review cycle. FDA may, at its discretion, review such an amendment during the initial review cycle or defer review until the subsequent review cycle.

(6) A major amendment may not include data to support an indication or claim that was not included in the original NDA, supplement, or resubmission, but it may include data to support a minor modification of an indication or claim that was included in the original NDA, supplement, or resubmission.

(7) When FDA defers review of an amendment until the subsequent review cycle, the agency will notify the applicant of the deferral in the complete response letter sent to the applicant under §314.110 of this part.

(c) *Limitation on certain amendments.* (1) An unapproved NDA may not be amended if all of the following conditions apply:

(i) The unapproved NDA is for a drug for which a previous NDA has been approved and granted a period of exclusivity in accordance with section 505(c)(3)(E)(ii) of the Federal Food, Drug, and Cosmetic Act that has not expired;

(ii) The applicant seeks to amend the unapproved NDA to include a published report of an investigation that was conducted or sponsored by the applicant entitled to exclusivity for the drug;

(iii) The applicant has not obtained a right of reference or use to the investigation described in paragraph (c)(1)(ii) of this section; and

(iv) The report of the investigation described in paragraph (c)(1)(ii) of this section would be essential to the approval of the unapproved NDA.

(2) The submission of an amendment described in paragraph (c)(1) of this section will cause the unapproved NDA to be deemed to be withdrawn by the applicant under § 314.65 on the date of receipt by FDA of the amendment. The amendment will be considered a resubmission of the NDA, which may not be accepted except as provided in accordance with section 505(c)(3)(E)(ii) of the Federal Food, Drug, and Cosmetic Act.

(d) *Field copy.* The applicant must submit a field copy of each amendment to a section of the NDA described in § 314.50(d)(1). The applicant must include in its submission of each such amendment to FDA a statement certifying that a field copy of the amendment has been sent to the applicant's home FDA district office.

(e) Different drug. An applicant may not amend a 505(b)(2) application to seek approval of a drug that is a different drug from the drug in the original submission of the 505(b)(2) application. For purposes of this paragraph (e), a drug is a different drug if it has been modified to have a different active ingredient, different route of administration, different dosage form, or difference in excipients that requires either a separate clinical study to establish safety or effectiveness or, for topical products, that requires a separate in vivo demonstration of bioequivalence. However, notwithstanding the limitation described in this paragraph (e), an applicant may amend the 505(b)(2) application to seek approval of a different strength.

(f) *Patent certification requirements.* (1) An amendment to a 505(b)(2) application is required to contain an appropriate patent certification or statement described in § 314.50(i) or a recertification for a previously submitted paragraph IV certification if approval is sought for any of the following types of amendments:

(i) To add a new indication or other condition of use;

(ii) To add a new strength;

(iii) To make other than minor changes in product formulation; or

(iv) To change the physical form or crystalline structure of the active ingredient.

(2) If the amendment to the 505(b)(2) application does not contain a patent certification or statement, the applicant must verify that the proposed change described in the amendment is not one of the types of amendments described in paragraph (f)(1) of this section.

[50 FR 7493, Feb. 22, 1985, as amended at 57 FR 17983, Apr. 28, 1992; 58 FR 47352, Sept. 8, 1993; 63 FR 5252, Feb. 2, 1998; 69 FR 18764, Apr. 8, 2004; 73 FR 39608, July 10, 2008; 81 FR 69648, Oct. 6, 2016]

§ 314.65 Withdrawal by the applicant of an unapproved application.

An applicant may at any time withdraw an application that is not yet approved by notifying the Food and Drug Administration in writing. If, by the time it receives such notice, the agency has identified any deficiencies in the application, we will list such deficiencies in the letter we send the applicant acknowledging the withdrawal. A decision to withdraw the application is without prejudice to refiling. The agency will retain the application and will provide a copy to the applicant on request under the fee schedule in § 20.45 of FDA's public information regulations.

[50 FR 7493, Feb. 22, 1985, as amended at 68 FR 25287, May 12, 2003; 73 FR 39609, July 10, 2008]

§ 314.70 Supplements and other changes to an approved NDA.

(a) *Changes to an approved NDA.* (1)(i) Except as provided in paragraph (a)(1)(ii) of this section, the applicant must notify FDA about each change in each condition established in an approved

NDA beyond the variations already provided for in the NDA. The notice is required to describe the change fully. Depending on the type of change, the applicant must notify FDA about the change in a supplement under paragraph (b) or (c) of this section or by inclusion of the information in the annual report to the NDA under paragraph (d) of this section.

(ii) The submission and grant of a written request for an exception or alternative under § 201.26 of this chapter satisfies the applicable requirements in paragraphs (a) through (c) of this section. However, any grant of a request for an exception or alternative under § 201.26 of this chapter must be reported as part of the annual report to the NDA under paragraph (d) of this section.

(2) The NDA holder must assess the effects of the change before distributing a drug product made with a manufacturing change.

(3) Notwithstanding the requirements of paragraphs (b) and (c) of this section, an applicant must make a change provided for in those paragraphs in accordance with a regulation or guidance that provides for a less burdensome notification of the change (for example, by submission of a supplement that does not require approval prior to distribution of the product or in an annual report).

(4) The applicant must promptly revise all promotional labeling and advertising to make it consistent with any labeling change implemented in accordance with paragraphs (b) and (c) of this section.

(5) Except for a supplement providing for a change in the labeling, the applicant must include in each supplement and amendment to a supplement providing for a change under paragraph (b) or (c) of this section a statement certifying that a field copy has been provided in accordance with § 314.440(a)(4).

(6) A supplement or annual report must include a list of all changes contained in the supplement or annual report. For supplements, this list must be provided in the submission.

(b) *Changes requiring supplement submission and approval prior to distribution of the product made using the change (major changes).* (1) A supplement must be submitted for any change in the drug substance, drug product, production process, quality controls, equipment, or facilities that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product.

(2) These changes include, but are not limited to:

(i) Except those described in paragraphs (c) and (d) of this section, changes in the qualitative or quantitative formulation of the drug product, including inactive ingredients, or in the specifications provided in the approved NDA;

(ii) Changes requiring completion of studies in accordance with part 320 of this chapter to demonstrate the equivalence of the drug product to the drug product as manufactured without the change or to the reference listed drug;

(iii) Changes that may affect drug substance or drug product sterility assurance, such as changes in drug substance, drug product, or component sterilization method(s) or an addition, deletion, or substitution of steps in an aseptic processing operation;

(iv) Changes in the synthesis or manufacture of the drug substance that may affect the impurity profile and/or the physical, chemical, or biological properties of the drug substance;

(v) The following labeling changes:

(A) Changes in labeling, except those described in paragraphs (c)(6)(iii), (d)(2)(ix), or (d)(2)(x) of this section;

(B) If applicable, any change to a Medication Guide required under part 208 of this chapter, except for changes in the information specified in § 208.20(b)(8)(iii) and (b)(8)(iv) of this chapter; and

(C) Any change to the information required by § 201.57(a) of this chapter, with the following exceptions that may be reported in an annual report under paragraph (d)(2)(x) of this section:

(1) Removal of a listed section(s) specified in § 201.57(a)(5) of this chapter; and

(2) Changes to the most recent revision date of the labeling as specified in § 201.57(a)(15) of this chapter.

(vi) Changes in a drug product container closure system that controls the drug product delivered to a patient or changes in the type (e.g., glass to high density polyethylene (HDPE), HDPE to polyvinyl chloride, vial to syringe) or composition (e.g., one HDPE resin to another HDPE resin) of a packaging component that may affect the impurity profile of the drug product.

(vii) Changes solely affecting a natural product, a recombinant DNA-derived protein/polypeptide, or a complex or conjugate of a drug substance with a monoclonal antibody for the following:

(A) Changes in the virus or adventitious agent removal or inactivation method(s);

(B) Changes in the source material or cell line; and

(C) Establishment of a new master cell bank or seed.

(viii) Changes to a drug product under an NDA that is subject to a validity assessment because of significant questions regarding the integrity of the data supporting that NDA.

(3) The applicant must obtain approval of a supplement from FDA prior to distribution of a drug product made using a change under paragraph (b) of this section. Except for submissions under paragraph (e) of this section, the following information must be contained in the supplement:

(i) A detailed description of the proposed change;

(ii) The drug product(s) involved;

(iii) The manufacturing site(s) or area(s) affected;

(iv) A description of the methods used and studies performed to assess the effects of the change;

(v) The data derived from such studies;

(vi) For a natural product, a recombinant DNA-derived protein/polypeptide, or a complex or conjugate of a drug substance with a monoclonal antibody, relevant validation protocols and a list of relevant standard operating procedures must be provided in addition to the requirements in paragraphs (b)(3)(iv) and (b)(3)(v) of this section; and

(vii) For sterilization process and test methodologies related to sterilization process validation, relevant validation protocols and a list of relevant standard operating procedures must be provided in addition to the requirements in paragraphs (b)(3)(iv) and (b)(3)(v) of this section.

(4) An applicant may ask FDA to expedite its review of a supplement for public health reasons or if a delay in making the change described in it would impose an extraordinary hardship on the applicant. Such a supplement should be plainly marked: "Prior Approval Supplement-Expedited Review Requested."

(c) *Changes requiring supplement submission at least 30 days prior to distribution of the drug product made using the change (moderate changes).* (1) A supplement must be submitted for any change in the drug substance, drug product, production process, quality controls, equipment, or facilities that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product. If the supplement provides for a labeling change under paragraph (c)(6)(iii) of this section, 12 copies of the final printed labeling must be included.

(2) These changes include, but are not limited to:

(i) A change in the container closure system that does not affect the quality of the drug product, except those described in paragraphs (b) and (d) of this section; and

(ii) Changes solely affecting a natural protein, a recombinant DNA-derived protein/polypeptide or a complex or conjugate of a drug substance with a monoclonal antibody, including:

(A) An increase or decrease in production scale during finishing steps that involves different equipment; and

(B) Replacement of equipment with that of a different design that does not affect the process methodology or process operating parameters.

(iii) Relaxation of an acceptance criterion or deletion of a test to comply with an official compendium that is consistent with FDA statutory and regulatory requirements.

(3) A supplement submitted under paragraph (c)(1) of this section is required to give a full explanation of the basis for the change and identify the date on which the change is to be made. The supplement must be labeled "Supplement—Changes Being Effected in 30 Days" or, if applicable under paragraph (c)(6) of this section, "Supplement—Changes Being Effected."

(4) Pending approval of the supplement by FDA, except as provided in paragraph (c)(6) of this section, distribution of the drug product made using the change may begin not less than 30 days after receipt of the supplement by FDA. The information listed in paragraphs (b)(3)(i) through (b)(3)(vii) of this section must be contained in the supplement.

(5) The applicant must not distribute the drug product made using the change if within 30 days following FDA's receipt of the supplement, FDA informs the applicant that either:

(i) The change requires approval prior to distribution of the drug product in accordance with paragraph (b) of this section; or

(ii) Any of the information required under paragraph (c)(4) of this section is missing; the applicant must not distribute the drug product made using the change until the supplement has been amended to provide the missing information.

(6) The agency may designate a category of changes for the purpose of providing that, in the case of a change in such category, the holder of an approved NDA may commence distribution of the drug product involved upon receipt by the agency of a supplement for the change. These changes include, but are not limited to:

(i) Addition to a specification or changes in the methods or controls to provide increased assurance that the drug substance or drug product will have the characteristics of identity, strength, quality, purity, or potency that it purports or is represented to possess;

(ii) A change in the size and/or shape of a container for a nonsterile drug product, except for solid dosage forms, without a change in the labeled amount of drug product or from one container closure system to another;

(iii) Changes in the labeling to reflect newly acquired information, except for changes to the information required in § 201.57(a) of this chapter (which must be made under paragraph (b)(2)(v)(C) of this section), to accomplish any of the following:

(A) To add or strengthen a contraindication, warning, precaution, or adverse reaction for which the evidence of a causal association satisfies the standard for inclusion in the labeling under § 201.57(c) of this chapter;

(B) To add or strengthen a statement about drug abuse, dependence, psychological effect, or overdosage;

(C) To add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product;

(D) To delete false, misleading, or unsupported indications for use or claims for effectiveness; or

(E) Any labeling change normally requiring a supplement submission and approval prior to distribution of the drug product that FDA specifically requests be submitted under this provision.

(7) If the agency disapproves the supplemental NDA, it may order the manufacturer to cease distribution of the drug product(s) made with the manufacturing change.

(d) *Changes to be described in an annual report (minor changes).* (1) Changes in the drug substance, drug product, production process, quality controls, equipment, or facilities that have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product must be documented by the applicant in the next annual report in accordance with § 314.81(b)(2).

(2) These changes include, but are not limited to:

(i) Any change made to comply with a change to an official compendium, except a change described in paragraph (c)(2)(iii) of this section, that is consistent with FDA statutory and regulatory requirements.

(ii) The deletion or reduction of an ingredient intended to affect only the color of the drug product;

(iii) Replacement of equipment with that of the same design and operating principles except those equipment changes described in paragraph (c) of this section;

(iv) A change in the size and/or shape of a container containing the same number of dosage units for a nonsterile solid dosage form drug product, without a change from one container closure system to another;

(v) A change within the container closure system for a nonsterile drug product, based upon a showing of equivalency to the approved system under a protocol approved in the NDA or published in an official compendium;

(vi) An extension of an expiration dating period based upon full shelf life data on production batches obtained from a protocol approved in the NDA;

(vii) The addition or revision of an alternative analytical procedure that provides the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved NDA, or deletion of an alternative analytical procedure;

(viii) The addition by embossing, debossing, or engraving of a code imprint to a solid oral dosage form drug product other than a modified release dosage form, or a minor change in an existing code imprint;

(ix) A change in the labeling concerning the description of the drug product or in the information about how the drug product is supplied, that does not involve a change in the dosage strength or dosage form; and

(x) An editorial or similar minor change in labeling, including a change to the information allowed by paragraphs (b)(2)(v)(C)(1) and (2) of this section.

(3) For changes under this category, the applicant is required to submit in the annual report:

(i) A statement by the holder of the approved NDA that the effects of the change have been assessed;

(ii) A full description of the manufacturing and controls changes, including the manufacturing site(s) or area(s) involved;

(iii) The date each change was implemented;

(iv) Data from studies and tests performed to assess the effects of the change; and,

(v) For a natural product, recombinant DNA-derived protein/polypeptide, complex or conjugate of a drug substance with a monoclonal antibody, sterilization process or test methodology related

to sterilization process validation, a cross-reference to relevant validation protocols and/or standard operating procedures.

(e) *Protocols*. An applicant may submit one or more protocols describing the specific tests and studies and acceptance criteria to be achieved to demonstrate the lack of adverse effect for specified types of manufacturing changes on the identity, strength, quality, purity, and potency of the drug product as these factors may relate to the safety or effectiveness of the drug product. Any such protocols, if not included in the approved NDA, or changes to an approved protocol, must be submitted as a supplement requiring approval from FDA prior to distribution of a drug product produced with the manufacturing change. The supplement, if approved, may subsequently justify a reduced reporting category for the particular change because the use of the protocol for that type of change reduces the potential risk of an adverse effect.

(f) *Patent information.* The applicant must comply with the patent information requirements under section 505(c)(2) of the Federal Food, Drug, and Cosmetic Act and § 314.53.

(g) *Claimed exclusivity.* If an applicant claims exclusivity under § 314.108 upon approval of a supplement for change to its previously approved drug product, the applicant must include with its supplement the information required under § 314.50(j).

(h) *Different drug.* An applicant may not supplement a 505(b)(2) application to seek approval of a drug that is a different drug from the drug in the approved 505(b)(2) application. For purposes of this paragraph (h), a drug is a different drug if it has been modified to have a different active ingredient, different route of administration, different dosage form, or difference in excipients that requires either a separate clinical study to establish safety or effectiveness or, for topical products, that requires a separate in vivo demonstration of bioequivalence. However, notwithstanding the limitation described in this paragraph (h), an applicant may supplement the 505(b)(2) application to seek approval of a different strength.

[69 FR 18764, Apr. 8, 2004, as amended at 71 FR 3997, Jan. 24, 2006; 72 FR 73600, Dec. 28, 2007; 73 FR 49609, Aug. 22, 2008; 81 FR 69648, Oct. 6, 2016]

§ 314.71 Procedures for submission of a supplement to an approved application.

(a) Only the applicant may submit a supplement to an application.

(b) All procedures and actions that apply to an application under § 314.50 also apply to supplements, except that the information required in the supplement is limited to that needed to support the change. A supplement is required to contain an archival copy and a review copy that include an application form and appropriate technical sections, samples, and labeling; except that a supplement for a change other than a change in labeling is required also to contain a field copy.

(c) All procedures and actions that apply to applications under this part, including actions by applicants and the Food and Drug Administration, also apply to supplements except as specified otherwise in this part.

[50 FR 7493, Feb. 22, 1985, as amended at 50 FR 21238, May 23, 1985; 58 FR 47352, Sept. 8, 1993; 67 FR 9586, Mar. 4, 2002; 73 FR 39609, July 10, 2008]

§ 314.72 Change in ownership of an application.

(a) An applicant may transfer ownership of its application. At the time of transfer the new and former owners are required to submit information to the Food and Drug Administration as follows:

(1) The former owner shall submit a letter or other document that states that all rights to the application have been transferred to the new owner.

(2) The new owner shall submit an application form signed by the new owner and a letter or other document containing the following:

(i) The new owner's commitment to agreements, promises, and conditions made by the former owner and contained in the application;

(ii) The date that the change in ownership is effective; and

(iii) Either a statement that the new owner has a complete copy of the approved application, including supplements and records that are required to be kept under §314.81, or a request for a copy of the application from FDA's files. FDA will provide a copy of the application to the new owner under the fee schedule in §20.45 of FDA's public information regulations.

(b) The new owner shall advise FDA about any change in the conditions in the approved application under §314.70, except the new owner may advise FDA in the next annual report about a change in the drug product's label or labeling to change the product's brand or the name of its manufacturer, packer, or distributor.

[50 FR 7493, Feb. 22, 1985; 50 FR 14212, Apr. 11, 1985, as amended at 50 FR 21238, May 23, 1985; 67 FR 9586, Mar. 4, 2002; 68 FR 25287, May 12, 2003]

§314.80 Postmarketing reporting of adverse drug experiences.

(a) *Definitions*. The following definitions of terms apply to this section:

Adverse drug experience. Any adverse event associated with the use of a drug in humans, whether or not considered drug related, including the following: An adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from drug overdose whether accidental or intentional; an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action.

Individual case safety report (ICSR). A description of an adverse drug experience related to an individual patient or subject.

ICSR attachments. Documents related to the adverse drug experience described in an ICSR, such as medical records, hospital discharge summaries, or other documentation.

Disability. A substantial disruption of a person's ability to conduct normal life functions.

Life-threatening adverse drug experience. Any adverse drug experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse drug experience as it occurred, i.e., it does not include an adverse drug experience that, had it occurred in a more severe form, might have caused death.

Serious adverse drug experience. Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Unexpected adverse drug experience. Any adverse drug experience that is not listed in the current labeling for the drug product. This includes events that may be symptomatically and pathophysiologically related to an event listed in the labeling, but differ from the event because of greater severity or specificity. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the labeling only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the labeling only listed cerebral vascular accidents. "Unexpected," as used in this defini-

tion, refers to an adverse drug experience that has not been previously observed (i.e., included in the labeling) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

(b) Review of adverse drug experiences. Each applicant having an approved application under §314.50 or, in the case of a 505(b)(2) application, an effective approved application, must promptly review all adverse drug experience information obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from commercial marketing experience, postmarketing clinical investigations, postmarketing epidemiological/surveillance studies, reports in the scientific literature, and unpublished scientific papers. Applicants are not required to resubmit to FDA adverse drug experience reports forwarded to the applicant by FDA; however, applicants must submit all followup information on such reports to FDA. Any person subject to the reporting requirements under paragraph (c) of this section must also develop written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences to FDA.

(c) Reporting requirements. The applicant must submit to FDA adverse drug experience information as described in this section. Except as provided in paragraph (g)(2) of this section, these reports must be submitted to the Agency in electronic format as described in paragraph (g)(1) of this section.

(1)(i) Postmarketing 15-day "Alert reports". The applicant must report each adverse drug experience that is both serious and unexpected, whether foreign or domestic, as soon as possible but no later than 15 calendar days from initial receipt of the information by the applicant.

(ii) Postmarketing 15-day "Alert reports"—followup. The applicant must promptly investigate all adverse drug experiences that are the subject of these postmarketing 15-day Alert reports and must submit followup reports within 15 calendar days of receipt of new information or as requested by FDA. If additional information is not obtainable, records should be maintained of the unsuccessful steps taken to seek additional information.

(iii) Submission of reports. The requirements of paragraphs (c)(1)(i) and (c)(1)(ii) of this section, concerning the submission of postmarketing 15-day Alert reports, also apply to any person other than the applicant whose name appears on the label of an approved drug product as a manufacturer, packer, or distributor (nonapplicant). To avoid unnecessary duplication in the submission to FDA of reports required by paragraphs (c)(1)(i) and (c)(1)(ii) of this section, obligations of a nonapplicant may be met by submission of all reports of serious adverse drug experiences to the applicant. If a nonapplicant elects to submit adverse drug experience reports to the applicant rather than to FDA, the nonapplicant must submit, by any appropriate means, each report to the applicant within 5 calendar days of initial receipt of the information by the nonapplicant, and the applicant must then comply with the requirements of this section. Under this circumstance, the nonapplicant must maintain a record of this action which must include:

(A) A copy of each adverse drug experience report;

(B) The date the report was received by the nonapplicant;

(C) The date the report was submitted to the applicant; and

(D) The name and address of the applicant.

(2) Periodic adverse drug experience reports. (i) The applicant must report each adverse drug experience not reported under paragraph (c)(1)(i) of this section at quarterly intervals, for 3 years from the date of approval of the application, and then at annual intervals. The applicant must submit each quarterly report within 30 days of the close of the quarter (the first quarter beginning on the date of approval of the application) and each annual report within 60 days of the anniversary date of approval of the application. Upon written notice, FDA may extend or reestablish the requirement

that an applicant submit quarterly reports, or require that the applicant submit reports under this section at different times than those stated. For example, the agency may reestablish a quarterly reporting requirement following the approval of a major supplement. Followup information to adverse drug experiences submitted in a periodic report may be submitted in the next periodic report.

(ii) Each periodic report is required to contain:

(A) Descriptive information. (1) A narrative summary and analysis of the information in the report;

(2) An analysis of the 15-day Alert reports submitted during the reporting interval (all 15-day Alert reports being appropriately referenced by the applicant's patient identification code, adverse reaction term(s), and date of submission to FDA);

(3) A history of actions taken since the last report because of adverse drug experiences (for example, labeling changes or studies initiated); and

(4) An index consisting of a line listing of the applicant's patient identification code, and adverse reaction term(s) for all ICSRs submitted under paragraph (c)(2)(ii)(B) of this section.

(B) ICSRs for serious, expected, and nonserious adverse drug experiences. An ICSR for each adverse drug experience not reported under paragraph (c)(1)(i) of this section (all serious, expected and nonserious adverse drug experiences). All such ICSRs must be submitted to FDA (either individually or in one or more batches) within the timeframe specified in paragraph (c)(2)(i) of this section. ICSRs must only be submitted to FDA once.

(iii) Periodic reporting, except for information regarding 15-day Alert reports, does not apply to adverse drug experience information obtained from postmarketing studies (whether or not conducted under an investigational new drug application), from reports in the scientific literature, and from foreign marketing experience.

(d) Scientific literature. A 15-day Alert report based on information in the scientific literature must be accompanied by a copy of the published article. The 15-day reporting requirements in paragraph (c)(1)(i) of this section (i.e., serious, unexpected adverse drug experiences) apply only to reports found in scientific and medical journals either as case reports or as the result of a formal clinical trial.

(e) Postmarketing studies. An applicant is not required to submit a 15-day Alert report under paragraph (c) of this section for an adverse drug experience obtained from a postmarketing study (whether or not conducted under an investigational new drug application) unless the applicant concludes that there is a reasonable possibility that the drug caused the adverse experience.

(f) Information reported on ICSRs. ICSRs include the following information:

(1) Patient information.

(i) Patient identification code;

(ii) Patient age at the time of adverse drug experience, or date of birth;

(iii) Patient gender; and

(iv) Patient weight.

(2) Adverse drug experience.

(i) Outcome attributed to adverse drug experience;

(ii) Date of adverse drug experience;

(iii) Date of ICSR submission;

(iv) Description of adverse drug experience (including a concise medical narrative);

(v) Adverse drug experience term(s);

(vi) Description of relevant tests, including dates and laboratory data; and

(vii) Other relevant patient history, including preexisting medical conditions.

(3) Suspect medical product(s).

(i) Name;

(ii) Dose, frequency, and route of administration used;

(iii) Therapy dates;

(iv) Diagnosis for use (indication);

(v) Whether the product is a prescription or nonprescription product;

(vi) Whether the product is a combination product as defined in § 3.2(e) of this chapter;

(vii) Whether adverse drug experience abated after drug use stopped or dose reduced;

(viii) Whether adverse drug experience reappeared after reintroduction of drug;

(ix) Lot number;

(x) Expiration date;

(xi) National Drug Code (NDC) number; and

(xii) Concomitant medical products and therapy dates.

(4) Initial reporter information.

(i) Name, address, and telephone number;

(ii) Whether the initial reporter is a health care professional; and

(iii) Occupation, if a health care professional.

(5) Applicant information.

(i) Applicant name and contact office address;

(ii) Telephone number;

(iii) Report source, such as spontaneous, literature, or study;

(iv) Date the report was received by applicant;

(v) Application number and type;

(vi) Whether the ICSR is a 15-day "Alert report";

(vii) Whether the ICSR is an initial report or followup report; and

(viii) Unique case identification number, which must be the same in the initial report and any subsequent followup report(s).

(g) Electronic format for submissions. (1) Safety report submissions, including ICSRs, ICSR attachments, and the descriptive information in periodic reports, must be in an electronic format that FDA can process, review, and archive. FDA will issue guidance on how to provide the electronic submission (e.g., method of transmission, media, file formats, preparation and organization of files).

(2) An applicant or nonapplicant may request, in writing, a temporary waiver of the requirements in paragraph (g)(1) of this section. These waivers will be granted on a limited basis for good cause shown. FDA will issue guidance on requesting a waiver of the requirements in paragraph (g)(1) of this section.

(h) Multiple reports. An applicant should not include in reports under this section any adverse drug experiences that occurred in clinical trials if they were previously submitted as part of the approved application. If a report applies to a drug for which an applicant holds more than one approved application, the applicant should submit the report to the application that was first approved. If a report refers to more than one drug marketed by an applicant, the applicant should submit the report to the application for the drug listed first in the report.

(i) Patient privacy. An applicant should not include in reports under this section the names and addresses of individual patients; instead, the applicant should assign a unique code for identification

of the patient. The applicant should include the name of the reporter from whom the information was received as part of the initial reporter information, even when the reporter is the patient. The names of patients, health care professionals, hospitals, and geographical identifiers in adverse drug experience reports are not releasable to the public under FDA's public information regulations in part 20 of this chapter.

(j) Recordkeeping. The applicant must maintain for a period of 10 years records of all adverse drug experiences known to the applicant, including raw data and any correspondence relating to adverse drug experiences.

(k) Withdrawal of approval. If an applicant fails to establish and maintain records and make reports required under this section, FDA may withdraw approval of the application and, thus, prohibit continued marketing of the drug product that is the subject of the application.

(l) Disclaimer. A report or information submitted by an applicant under this section (and any release by FDA of that report or information) does not necessarily reflect a conclusion by the applicant or FDA that the report or information constitutes an admission that the drug caused or contributed to an adverse effect. An applicant need not admit, and may deny, that the report or information submitted under this section constitutes an admission that the drug caused or contributed to an adverse effect. For purposes of this provision, the term "applicant" also includes any person reporting under paragraph (c)(1)(iii) of this section.

[50 FR 7493, Feb. 22, 1985; 50 FR 14212, Apr. 11, 1985, as amended at 50 FR 21238, May 23, 1985; 51 FR 24481, July 3, 1986; 52 FR 37936, Oct. 13, 1987; 55 FR 11580, Mar. 29, 1990; 57 FR 17983, Apr. 28, 1992; 62 FR 34168, June 25, 1997; 62 FR 52251, Oct. 7, 1997; 63 FR 14611, Mar. 26, 1998; 67 FR 9586, Mar. 4, 2002; 69 FR 13473, Mar. 23, 2004; 74 FR 13113, Mar. 26, 2009; 79 FR 33088, June 10, 2014]

§ 314.81 Other postmarketing reports.

(a) *Applicability*. Each applicant shall make the reports for each of its approved applications and abbreviated applications required under this section and section 505(k) of the act.

(b) *Reporting requirements.* The applicant shall submit to the Food and Drug Administration at the specified times two copies of the following reports:

(1) *NDA—Field alert report.* The applicant shall submit information of the following kinds about distributed drug products and articles to the FDA district office that is responsible for the facility involved within 3 working days of receipt by the applicant. The information may be provided by telephone or other rapid communication means, with prompt written followup. The report and its mailing cover should be plainly marked: "NDA—Field Alert Report."

(i) Information concerning any incident that causes the drug product or its labeling to be mistaken for, or applied to, another article.

(ii) Information concerning any bacteriological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of the drug product to meet the specification established for it in the application.

(2) *Annual report.* The applicant shall submit each year within 60 days of the anniversary date of U.S. approval of the application, two copies of the report to the FDA division responsible for reviewing the application. Each annual report is required to be accompanied by a completed transmittal Form FDA 2252 (Transmittal of Periodic Reports for Drugs for Human Use), and must include all the information required under this section that the applicant received or otherwise obtained during the annual reporting interval that ends on the U.S. anniversary date. The report is required to contain in the order listed:

(i) *Summary*. A brief summary of significant new information from the previous year that might affect the safety, effectiveness, or labeling of the drug product. The report is also required to contain

a brief description of actions the applicant has taken or intends to take as a result of this new information, for example, submit a labeling supplement, add a warning to the labeling, or initiate a new study. The summary shall briefly state whether labeling supplements for pediatric use have been submitted and whether new studies in the pediatric population to support appropriate labeling for the pediatric population have been initiated. Where possible, an estimate of patient exposure to the drug product, with special reference to the pediatric population (neonates, infants, children, and adolescents) shall be provided, including dosage form.

(ii)(a) *Distribution data*. Information about the quantity of the drug product distributed under the approved application, including that distributed to distributors. The information is required to include the National Drug Code (NDC) number, the total number of dosage units of each strength or potency distributed (e.g., 100,000/5 milligram tablets, 50,000/10 milliliter vials), and the quantities distributed for domestic use and the quantities distributed for foreign use. Disclosure of financial or pricing data is not required.

(b) *Authorized generic drugs.* If applicable, the date each authorized generic drug (as defined in § 314.3) entered the market, the date each authorized generic drug ceased being distributed, and the corresponding trade or brand name. Each dosage form and/or strength is a different authorized generic drug and should be listed separately. The first annual report submitted on or after January 25, 2010 must include the information listed in this paragraph for any authorized generic drug that was marketed during the time period covered by an annual report submitted after January 1, 1999. If information is included in the annual report with respect to any authorized generic drug, a copy of that portion of the annual report must be sent to the Food and Drug Administration, Center for Drug Evaluation and Research, Office of New Drug Quality Assessment, Bldg. 21, rm. 2562, 10903 New Hampshire Ave., Silver Spring, MD 20993-0002, and marked "Authorized Generic Submission" or, by e-mail, to the Authorized Generics electronic mailbox at AuthorizedGenerics@fda.hhs.gov with "Authorized Generic Submission" indicated in the subject line. However, at such time that FDA has required that annual reports be submitted in an electronic format, the information required by this paragraph must be submitted as part of the annual report, in the electronic format specified for submission of annual reports at that time, and not as a separate submission under the preceding sentence in this paragraph.

(iii) *Labeling*. (a) Currently used professional labeling, patient brochures or package inserts (if any), and a representative sample of the package labels.

(b) The content of labeling required under § 201.100(d)(3) of this chapter (i.e., the package insert or professional labeling), including all text, tables, and figures, must be submitted in electronic format. Electronic format submissions must be in a form that FDA can process, review, and archive. FDA will periodically issue guidance on how to provide the electronic submission (e.g., method of transmission, media, file formats, preparation and organization of files). Submissions under this paragraph must be made in accordance with part 11 of this chapter, except for the requirements of § 11.10(a), (c) through (h), and (k), and the corresponding requirements of § 11.30.

(c) A summary of any changes in labeling that have been made since the last report listed by date in the order in which they were implemented, or if no changes, a statement of that fact.

(iv) *Chemistry, manufacturing, and controls changes.* (a) Reports of experiences, investigations, studies, or tests involving chemical or physical properties, or any other properties of the drug (such as the drug's behavior or properties in relation to microorganisms, including both the effects of the drug on microorganisms and the effects of microorganisms on the drug). These reports are only required for new information that may affect FDA's previous conclusions about the safety or effectiveness of the drug product.

(b) A full description of the manufacturing and controls changes not requiring a supplemental application under § 314.70 (b) and (c), listed by date in the order in which they were implemented.

(v) *Nonclinical laboratory studies.* Copies of unpublished reports and summaries of published reports of new toxicological findings in animal studies and in vitro studies (e.g., mutagenicity) conducted by, or otherwise obtained by, the applicant concerning the ingredients in the drug product. The applicant shall submit a copy of a published report if requested by FDA.

(vi) *Clinical data.* (a) Published clinical trials of the drug (or abstracts of them), including clinical trials on safety and effectiveness; clinical trials on new uses; biopharmaceutic, pharmacokinetic, and clinical pharmacology studies; and reports of clinical experience pertinent to safety (for example, epidemiologic studies or analyses of experience in a monitored series of patients) conducted by or otherwise obtained by the applicant. Review articles, papers describing the use of the drug product in medical practice, papers and abstracts in which the drug is used as a research tool, promotional articles, press clippings, and papers that do not contain tabulations or summaries of original data should not be reported.

(b) Summaries of completed unpublished clinical trials, or prepublication manuscripts if available, conducted by, or otherwise obtained by, the applicant. Supporting information should not be reported. (A study is considered completed 1 year after it is concluded.)

(c) Analysis of available safety and efficacy data in the pediatric population and changes proposed in the labeling based on this information. An assessment of data needed to ensure appropriate labeling for the pediatric population shall be included.

(vii) *Status reports of postmarketing study commitments.* A status report of each postmarketing study of the drug product concerning clinical safety, clinical efficacy, clinical pharmacology, and nonclinical toxicology that is required by FDA (e.g., accelerated approval clinical benefit studies, pediatric studies) or that the applicant has committed, in writing, to conduct either at the time of approval of an application for the drug product or a supplement to an application, or after approval of the application or a supplement. For pediatric studies, the status report shall include a statement indicating whether postmarketing clinical studies in pediatric populations were required by FDA under § 201.23 of this chapter. The status of these postmarketing studies shall be reported annually until FDA notifies the applicant, in writing, that the agency concurs with the applicant's determination that the study commitment has been fulfilled or that the study is either no longer feasible or would no longer provide useful information.

(a) *Content of status report.* The following information must be provided for each postmarketing study reported under this paragraph:

(1) *Applicant's name.*

(2) *Product name.* Include the approved drug product's established name and proprietary name, if any.

(3) *NDA, ANDA, and supplement number.*

(4) *Date of U.S. approval of NDA or ANDA.*

(5) *Date of postmarketing study commitment.*

(6) *Description of postmarketing study commitment.* The description must include sufficient information to uniquely describe the study. This information may include the purpose of the study, the type of study, the patient population addressed by the study and the indication(s) and dosage(s) that are to be studied.

(7) *Schedule for completion and reporting of the postmarketing study commitment.* The schedule should include the actual or projected dates for submission of the study protocol to FDA, completion of patient accrual or initiation of an animal study, completion of the study, submission of the final study report to FDA, and any additional milestones or submissions for which projected dates were specified as part of the commitment. In addition, it should include a revised schedule, as ap-

propriate. If the schedule has been previously revised, provide both the original schedule and the most recent, previously submitted revision.

(8) *Current status of the postmarketing study commitment.* The status of each postmarketing study should be categorized using one of the following terms that describes the study's status on the anniversary date of U.S. approval of the application or other agreed upon date:

(i) *Pending*. The study has not been initiated, but does not meet the criterion for delayed.

(ii) *Ongoing*. The study is proceeding according to or ahead of the original schedule described under paragraph (b)(2)(vii)(a)(7) of this section.

(iii) *Delayed*. The study is behind the original schedule described under paragraph (b)(2)(vii)(a)(7) of this section.

(iv) *Terminated*. The study was ended before completion but a final study report has not been submitted to FDA.

(v) *Submitted*. The study has been completed or terminated and a final study report has been submitted to FDA.

(9) *Explanation of the study's status.* Provide a brief description of the status of the study, including the patient accrual rate (expressed by providing the number of patients or subjects enrolled to date, and the total planned enrollment), and an explanation of the study's status identified under paragraph (b)(2)(vii)(a)(8) of this section. If the study has been completed, include the date the study was completed and the date the final study report was submitted to FDA, as applicable. Provide a revised schedule, as well as the reason(s) for the revision, if the schedule under paragraph (b)(2)(vii)(a)(7) of this section has changed since the last report.

(b) *Public disclosure of information*. Except for the information described in this paragraph, FDA may publicly disclose any information described in paragraph (b)(2)(vii) of this section, concerning a postmarketing study, if the agency determines that the information is necessary to identify the applicant or to establish the status of the study, including the reasons, if any, for failure to conduct, complete, and report the study. Under this section, FDA will not publicly disclose trade secrets, as defined in § 20.61 of this chapter, or information, described in § 20.63 of this chapter, the disclosure of which would constitute an unwarranted invasion of personal privacy.

(viii) Status of other postmarketing studies. A status report of any postmarketing study not included under paragraph (b)(2)(vii) of this section that is being performed by, or on behalf of, the applicant. A status report is to be included for any chemistry, manufacturing, and controls studies that the applicant has agreed to perform and for all product stability studies.

(ix) *Log of outstanding regulatory business.* To facilitate communications between FDA and the applicant, the report may, at the applicant's discretion, also contain a list of any open regulatory business with FDA concerning the drug product subject to the application (e.g., a list of the applicant's unanswered correspondence with the agency, a list of the agency's unanswered correspondence with the applicant).

(3*) Other reporting*—(i) *Advertisements and promotional labeling.* The applicant shall submit specimens of mailing pieces and any other labeling or advertising devised for promotion of the drug product at the time of initial dissemination of the labeling and at the time of initial publication of the advertisement for a prescription drug product. Mailing pieces and labeling that are designed to contain samples of a drug product are required to be complete, except the sample of the drug product may be omitted. Each submission is required to be accompanied by a completed transmittal Form FDA-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) and is required to include a copy of the product's current professional labeling. Form FDA-2253 is available on the Internet at *http://www.fda.gov/opacom/morechoices/fdaforms/cder.html.*

(ii) *Special reports.* Upon written request the agency may require that the applicant submit the reports under this section at different times than those stated.

(iii) *Notification of a permanent discontinuance or an interruption in manufacturing.* (a) An applicant of a prescription drug product must notify FDA in writing of a permanent discontinuance of manufacture of the drug product or an interruption in manufacturing of the drug product that is likely to lead to a meaningful disruption in supply of that drug in the United States if:

(1) The drug product is life supporting, life sustaining, or intended for use in the prevention or treatment of a debilitating disease or condition, including any such drug used in emergency medical care or during surgery; and

(2) The drug product is not a radiopharmaceutical drug product.

(b) Notifications required by paragraph (b)(3)(iii)(a) of this section must be submitted to FDA electronically in a format that FDA can process, review, and archive:

(1) At least 6 months prior to the date of the permanent discontinuance or interruption in manufacturing; or

(2) If 6 months' advance notice is not possible because the permanent discontinuance or interruption in manufacturing was not reasonably anticipated 6 months in advance, as soon as practicable thereafter, but in no case later than 5 business days after the permanent discontinuance or interruption in manufacturing occurs.

(c) Notifications required by paragraph (b)(3)(iii)(a) of this section must include the following information:

(1) The name of the drug subject to the notification, including the NDC for such drug;

(2) The name of the applicant;

(3) Whether the notification relates to a permanent discontinuance of the drug or an interruption in manufacturing of the drug;

(4) A description of the reason for the permanent discontinuance or interruption in manufacturing; and

(5) The estimated duration of the interruption in manufacturing.

(d)(1) FDA will maintain a publicly available list of drugs that are determined by FDA to be in shortage. This drug shortages list will include the following information:

(i) The names and NDC(s) for such drugs;

(ii) The name of each applicant for such drugs;

(iii) The reason for the shortage, as determined by FDA from the following categories: Requirements related to complying with good manufacturing practices; regulatory delay; shortage of an active ingredient; shortage of an inactive ingredient component; discontinuation of the manufacture of the drug; delay in shipping of the drug; demand increase for the drug; or other reason; and

(iv) The estimated duration of the shortage.

(2) FDA may choose not to make information collected to implement this paragraph available on the drug shortages list or available under section 506C(c) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 356c(c)) if FDA determines that disclosure of such information would adversely affect the public health (such as by increasing the possibility of hoarding or other disruption of the availability of the drug to patients). FDA will also not provide information on the public drug shortages list or under section 506C(c) of the Federal Food, Drug, and Cosmetic Act that is protected by 18 U.S.C. 1905 or 5 U.S.C. 552(b)(4), including trade secrets and commercial or financial information that is considered confidential or privileged under § 20.61 of this chapter.

(e) If an applicant fails to submit a notification as required under paragraph (b)(3)(iii)(a) of this section and in accordance with paragraph (b)(3)(iii)(b) of this section, FDA will issue a letter to the applicant informing it of such failure.

(1) Not later than 30 calendar days after the issuance of such a letter, the applicant must submit to FDA a written response setting forth the basis for noncompliance and providing the required notification under paragraph (b)(3)(iii)(a) of this section and including the information required under paragraph (b)(3)(iii)(c) of this section; and

(2) Not later than 45 calendar days after the issuance of a letter under paragraph (b)(3)(iii)(e) of this section, FDA will make the letter and the applicant's response to the letter public, unless, after review of the applicant's response, FDA determines that the applicant had a reasonable basis for not notifying FDA as required under paragraph (b)(3)(iii)(a) of this section.

(f) The following definitions of terms apply to paragraph (b)(3)(iii) of this section:

Drug shortage or shortage means a period of time when the demand or projected demand for the drug within the United States exceeds the supply of the drug.

Intended for use in the prevention or treatment of a debilitating disease or condition means a drug product intended for use in the prevention or treatment of a disease or condition associated with mortality or morbidity that has a substantial impact on day-to-day functioning.

Life supporting or life sustaining means a drug product that is essential to, or that yields information that is essential to, the restoration or continuation of a bodily function important to the continuation of human life.

Meaningful disruption means a change in production that is reasonably likely to lead to a reduction in the supply of a drug by a manufacturer that is more than negligible and affects the ability of the manufacturer to fill orders or meet expected demand for its product, and does not include interruptions in manufacturing due to matters such as routine maintenance or insignificant changes in manufacturing so long as the manufacturer expects to resume operations in a short period of time.

(iv) Withdrawal of approved drug product from sale. (a) Within 30 calendar days of the withdrawal of an approved drug from sale, applicants who are manufacturers, repackers, or relabelers subject to part 207 of this chapter must submit the following information about the drug, in accordance with the applicable requirements described in §§ 207.61 and 207.65:

(1) The National Drug Code (NDC);

(2) The identity of the drug by established name and by proprietary name, if any;

(3) The new drug application number or abbreviated application number;

(4) The date on which the drug is expected to be no longer in commercial distribution. FDA requests that the reason for withdrawal of the drug from sale be included with the information.

(b) Within 30 calendar days of the withdrawal of an approved drug from sale, applicants who are not subject to part 207 of this chapter must submit the information listed in paragraphs (b)(3)(iv)(a)(1) through (4) of this section. The information must be submitted either electronically or in writing to the Drug Registration and Listing Office, Food and Drug Administration, Center for Drug Evaluation and Research.

(c) Reporting under paragraph (b)(3)(iv)(a) of this section constitutes compliance with the requirements of § 207.57 of this chapter to update drug listing information with respect to the withdrawal from sale.

(c) General requirements—(1) *Multiple applications.* For all reports required by this section, the applicant shall submit the information common to more than one application only to the application first approved, and shall not report separately on each application. The submission is required to identify all the applications to which the report applies.

(2) Patient identification. Applicants should not include in reports under this section the names and addresses of individual patients; instead, the applicant should code the patient names whenever possible and retain the code in the applicant's files. The applicant shall maintain sufficient patient identification information to permit FDA, by using that information alone or along with records maintained by the investigator of a study, to identify the name and address of individual patients; this will ordinarily occur only when the agency needs to investigate the reports further or when there is reason to believe that the reports do not represent actual results obtained.

(d) Withdrawal of approval. If an applicant fails to make reports required under this section, FDA may withdraw approval of the application and, thus, prohibit continued marketing of the drug product that is the subject of the application.

(Collection of information requirements approved by the Office of Management and Budget under control number 0910-0001)

[50 FR 7493, Feb. 22, 1985; 50 FR 14212, Apr. 11, 1985, as amended at 50 FR 21238, May 23, 1985; 55 FR 11580, Mar. 29, 1990; 57 FR 17983, Apr. 28, 1992; 63 FR 66670, Dec. 2, 1998; 64 FR 401, Jan. 5, 1999; 65 FR 64617, Oct. 30, 2000; 66 FR 10815, Feb. 20, 2001; 68 FR 69019, Dec. 11, 2003; 69 FR 18766, Apr. 8, 2004; 69 FR 48775, Aug. 11, 2004; 72 FR 58999, Oct. 18, 2007; 74 FR 13113, Mar. 26, 2009; 74 FR 37167, July 28, 2009; 76 FR 78539, Dec. 19, 2011; 80 FR 38938, July 8, 2015; 81 FR 60221, Aug. 31, 2016]

§ 314.90 Waivers.

(a) An applicant may ask the Food and Drug Administration to waive under this section any requirement that applies to the applicant under §§ 314.50 through 314.81. An applicant may ask FDA to waive under § 314.126(c) any criteria of an adequate and well-controlled study described in § 314.126(b). A waiver request under this section is required to be submitted with supporting documentation in an NDA, or in an amendment or supplement to an NDA. The waiver request is required to contain one of the following:

(1) An explanation why the applicant's compliance with the requirement is unnecessary or cannot be achieved;

(2) A description of an alternative submission that satisfies the purpose of the requirement; or

(3) Other information justifying a waiver.

(b) FDA may grant a waiver if it finds one of the following:

(1) The applicant's compliance with the requirement is unnecessary for the agency to evaluate the NDA or compliance cannot be achieved;

(2) The applicant's alternative submission satisfies the requirement; or

(3) The applicant's submission otherwise justifies a waiver.

(c) If FDA grants the applicant's waiver request with respect to a requirement under §§ 314.50 through 314.81, the waived requirement will not constitute a basis for refusal to approve an NDA under § 314.125.

[50 FR 7493, Feb. 22, 1985, as amended at 50 FR 21238, May 23, 1985; 67 FR 9586, Mar. 4, 2002; 81 FR 69649, Oct. 6, 2016]

Subpart C—Abbreviated Applications

Source: 57 FR 17983, Apr. 28, 1992, unless otherwise noted.

(a) Abbreviated applications are suitable for the following drug products within the limits set forth under § 314.93:

(1) Drug products that are the same as a listed drug. A "listed drug" is defined in § 314.3. For determining the suitability of an abbreviated new drug application, the term "same as" means identical in active ingredient(s), dosage form, strength, route of administration, and conditions of use, except that conditions of use for which approval cannot be granted because of exclusivity or an existing patent may be omitted. If a listed drug has been voluntarily withdrawn from or not offered for sale by its manufacturer, a person who wishes to submit an abbreviated new drug application for the drug shall comply with § 314.122.

(2) [Reserved]

(3) Drug products that have been declared suitable for an abbreviated new drug application submission by FDA through the petition procedures set forth under § 10.30 of this chapter and § 314.93.

(b) FDA will publish in the list listed drugs for which abbreviated applications may be submitted. The list is available from the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402, 202-783-3238.

[57 FR 17983, Apr. 28, 1992, as amended at 64 FR 401, Jan. 5, 1999]

§ 314.93 Petition to request a change from a listed drug.

(a) The only changes from a listed drug for which the agency will accept a petition under this section are those changes described in paragraph (b) of this section. Petitions to submit ANDAs for other changes from a listed drug will not be approved.

(b) A person who wants to submit an ANDA for a drug product which is not identical to a listed drug in route of administration, dosage form, and strength, or in which one active ingredient is substituted for one of the active ingredients in a listed combination drug, must first obtain permission from FDA to submit such an ANDA.

(c) To obtain permission to submit an ANDA for a change described in paragraph (b) of this section, a person must submit and obtain approval of a petition requesting the change. A person seeking permission to request such a change from a reference listed drug shall submit a petition in accordance with § 10.20 of this chapter and in the format specified in § 10.30 of this chapter. The petition shall contain the information specified in § 10.30 of this chapter and any additional information required by this section. If any provision of § 10.20 or § 10.30 of this chapter is inconsistent with any provision of this section, the provisions of this section apply.

(d) The petitioner shall identify a listed drug and include a copy of the proposed labeling for the drug product that is the subject of the petition and a copy of the approved labeling for the listed drug. The petitioner may, under limited circumstances, identify more than one listed drug, for example, when the proposed drug product is a combination product that differs from the combination reference listed drug with regard to an active ingredient, and the different active ingredient is an active ingredient of a listed drug. The petitioner shall also include information to show that:

(1) The active ingredients of the proposed drug product are of the same pharmacological or therapeutic class as those of the reference listed drug.

(2) The drug product can be expected to have the same therapeutic effect as the reference listed drug when administered to patients for each condition of use in the reference listed drug's labeling for which the applicant seeks approval.

(3) If the proposed drug product is a combination product with one different active ingredient, including a different ester or salt, from the reference listed drug, that the different active ingredient has previously been approved in a listed drug or is a drug that does not meet the definition of "new drug" in section 201(p) of the Federal Food, Drug, and Cosmetic Act.

(e) No later than 90 days after the date a petition that is permitted under paragraph (a) of this section is submitted, FDA will approve or disapprove the petition.

(1) FDA will approve a petition properly submited under this section unless it finds that:

(i) Investigations must be conducted to show the safety and effectiveness of the drug product or of any of its active ingredients, its route of administration, dosage form, or strength which differs from the reference listed drug; or

(ii) For a petition that seeks to change an active ingredient, the drug product that is the subject of the petition is not a combination drug; or

(iii) For a combination drug product that is the subject of the petition and has an active ingredient different from the reference listed drug:

(A) The drug product may not be adequately evaluated for approval as safe and effective on the basis of the information required to be submitted under § 314.94; or

(B) The petition does not contain information to show that the different active ingredient of the drug product is of the same pharmacological or therapeutic class as the ingredient of the reference listed drug that is to be changed and that the drug product can be expected to have the same therapeutic effect as the reference listed drug when administered to patients for each condition of use in the listed drug's labeling for which the applicant seeks approval; or

(C) The different active ingredient is not an active ingredient in a listed drug or a drug that meets the requirements of section 201(p) of the Federal Food, Drug, and Cosmetic Act; or

(D) The remaining active ingredients are not identical to those of the listed combination drug; or

(iv) Any of the proposed changes from the listed drug would jeopardize the safe or effective use of the product so as to necessitate significant labeling changes to address the newly introduced safety or effectiveness problem; or

(v) FDA has determined that the reference listed drug has been withdrawn from sale for safety or effectiveness reasons under § 314.161, or the reference listed drug has been voluntarily withdrawn from sale and the agency has not determined whether the withdrawal is for safety or effectiveness reasons; or

(vi) A drug product is approved in an NDA for the change described in the petition.

(2) For purposes of this paragraph, "investigations must be conducted" means that information derived from animal or clinical studies is necessary to show that the drug product is safe or effective. Such information may be contained in published or unpublished reports.

(3) If FDA approves a petition submitted under this section, the agency's response may describe what additional information, if any, will be required to support an ANDA for the drug product. FDA may, at any time during the course of its review of an ANDA, request additional information required to evaluate the change approved under the petition.

(f)(1) FDA may withdraw approval of a petition if the agency receives any information demonstrating that the petition no longer satisfies the conditions under paragraph (e) of this section.

(2) If, after approval of a petition and before approval of an ANDA submitted pursuant to the approved petition, a drug product is approved in an NDA for the change described in the petition, the petition and the listed drug identified in the petition can no longer be the basis for ANDA submission, irrespective of whether FDA has withdrawn approval of the petition. A person seeking approval for such drug product must submit a new ANDA that identifies the pharmaceutically equivalent reference listed drug as the basis for ANDA submission and comply with applicable regulatory requirements.

[57 FR 17983, Apr. 28, 1992, as amended at 81 FR 69649, Oct. 6, 2016]

§ 314.94 Content and format of an ANDA.

ANDAs are required to be submitted in the form and contain the information required under this section. Three copies of the ANDA are required, an archival copy, a review copy, and a field copy. FDA will maintain guidance documents on the format and content of ANDAs to assist applicants in their preparation.

(a) *ANDAs*. Except as provided in paragraph (b) of this section, the applicant must submit a complete archival copy of the abbreviated new drug application that includes the following:

(1) *Application form.* The applicant must submit a completed and signed application form that contains the information described under § 314.50(a)(1), (a)(3), (a)(4), and (a)(5). The applicant must state whether the submission is an ANDA under this section or a supplement to an ANDA under § 314.97.

(2) *Table of contents.* The archival copy of the ANDA is required to contain a table of contents that shows the volume number and page number of the contents of the submission.

(3) *Basis for ANDA submission.* An ANDA must refer to a listed drug. Ordinarily, that listed drug will be the drug product selected by the Agency as the reference standard for conducting bioequivalence testing. The ANDA must contain:

(i) The name of the reference listed drug, including its dosage form and strength. For an ANDA based on an approved petition under § 10.30 of this chapter and § 314.93, the reference listed drug must be the same as the listed drug referenced in the approved petition.

(ii) A statement as to whether, according to the information published in the list, the reference listed drug is entitled to a period of marketing exclusivity under section 505(j)(5)(F) of the Federal Food, Drug, and Cosmetic Act.

(iii) For an ANDA based on an approved petition under § 10.30 of this chapter and § 314.93, a reference to the FDA-assigned docket number for the petition and a copy of FDA's correspondence approving the petition.

(4) *Conditions of use.* (i) A statement that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the drug product have been previously approved for the reference listed drug.

(ii) A reference to the applicant's annotated proposed labeling and to the currently approved labeling for the reference listed drug provided under paragraph (a)(8) of this section.

(5) *Active ingredients.* (i) For a single-active-ingredient drug product, information to show that the active ingredient is the same as that of the reference single-active-ingredient listed drug, as follows:

(A) A statement that the active ingredient of the proposed drug product is the same as that of the reference listed drug.

(B) A reference to the applicant's annotated proposed labeling and to the currently approved labeling for the reference listed drug provided under paragraph (a)(8) of this section.

(ii) For a combination drug product, information to show that the active ingredients are the same as those of the reference listed drug except for any different active ingredient that has been the subject of an approved petition, as follows:

(A) A statement that the active ingredients of the proposed drug product are the same as those of the reference listed drug, or if one of the active ingredients differs from one of the active ingredients of the reference listed drug and the ANDA is submitted under the approval of a petition under § 314.93 to vary such active ingredient, information to show that the other active ingredients of the drug product are the same as the other active ingredients of the reference listed drug, information to show that the different active ingredient is an active ingredient of another listed drug or of a drug

that does not meet the definition of "new drug" in section 201(p) of the Federal Food, Drug, and Cosmetic Act, and such other information about the different active ingredient that FDA may require.

(B) A reference to the applicant's annotated proposed labeling and to the currently approved labeling for the reference listed drug provided under paragraph (a)(8) of this section.

(6) *Route of administration, dosage form, and strength.* (i) Information to show that the route of administration, dosage form, and strength of the drug product are the same as those of the reference listed drug except for any differences that have been the subject of an approved petition, as follows:

(A) A statement that the route of administration, dosage form, and strength of the proposed drug product are the same as those of the reference listed drug.

(B) A reference to the applicant's annotated proposed labeling and to the currently approved labeling for the reference listed drug provided under paragraph (a)(8) of this section.

(ii) If the route of administration, dosage form, or strength of the drug product differs from the reference listed drug and the ANDA is submitted under an approved petition under § 314.93, such information about the different route of administration, dosage form, or strength that FDA may require.

(7) *Bioequivalence.* (i) Information that shows that the drug product is bioequivalent to the reference listed drug upon which the applicant relies. A complete study report must be submitted for the bioequivalence study upon which the applicant relies for approval. For all other bioequivalence studies conducted on the same drug product formulation as defined in § 314.3(b), the applicant must submit either a complete or summary report. If a summary report of a bioequivalence study is submitted and FDA determines that there may be bioequivalence issues or concerns with the product, FDA may require that the applicant submit a complete report of the bioequivalence study to FDA; or

(ii) If the ANDA is submitted pursuant to a petition approved under § 314.93, the results of any bioavailability or bioequivalence testing required by the Agency, or any other information required by the Agency to show that the active ingredients of the proposed drug product are of the same pharmacological or therapeutic class as those in the reference listed drug and that the proposed drug product can be expected to have the same therapeutic effect as the reference listed drug. If the proposed drug product contains a different active ingredient than the reference listed drug, FDA will consider the proposed drug product to have the same therapeutic effect as the reference listed drug if the applicant provides information demonstrating that:

(A) There is an adequate scientific basis for determining that substitution of the specific proposed dose of the different active ingredient for the dose of the member of the same pharmacological or therapeutic class in the reference listed drug will yield a resulting drug product whose safety and effectiveness have not been adversely affected.

(B) The unchanged active ingredients in the proposed drug product are bioequivalent to those in the reference listed drug.

(C) The different active ingredient in the proposed drug product is bioequivalent to an approved dosage form containing that ingredient and approved for the same indication as the proposed drug product or is bioequivalent to a drug product offered for that indication which does not meet the definition of "new drug" under section 201(p) of the Federal Food, Drug, and Cosmetic Act.

(iii) For each in vivo or in vitro bioequivalence study contained in the ANDA:

(A) A description of the analytical and statistical methods used in each study; and

(B) With respect to each study involving human subjects, a statement that the study either was conducted in compliance with the institutional review board regulations in part 56 of this chapter, or was not subject to the regulations under § 56.104 or § 56.105 of this chapter, and that it was conducted in compliance with the informed consent regulations in part 50 of this chapter.

(8) *Labeling*—(i) *Listed drug labeling.* A copy of the currently approved labeling (including, if applicable, any Medication Guide required under part 208 of this chapter) for the listed drug referred to in the ANDA, if the ANDA relies on a reference listed drug.

(ii) *Copies of proposed labeling.* Copies of the label and all labeling for the drug product including, if applicable, any Medication Guide required under part 208 of this chapter (4 copies of draft labeling or 12 copies of final printed labeling).

(iii) *Statement on proposed labeling.* A statement that the applicant's proposed labeling including, if applicable, any Medication Guide required under part 208 of this chapter is the same as the labeling of the reference listed drug except for differences annotated and explained under paragraph (a)(8)(iv) of this section.

(iv) *Comparison of approved and proposed labeling.* A side-by-side comparison of the applicant's proposed labeling including, if applicable, any Medication Guide required under part 208 of this chapter with the approved labeling for the reference listed drug with all differences annotated and explained. Labeling (including the container label, package insert, and, if applicable, Medication Guide) proposed for the drug product must be the same as the labeling approved for the reference listed drug, except for changes required because of differences approved under a petition filed under § 314.93 or because the drug product and the reference listed drug are produced or distributed by different manufacturers. Such differences between the applicant's proposed labeling and labeling approved for the reference listed drug may include differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(5)(F) of the Federal Food, Drug, and Cosmetic Act.

(9) *Chemistry, manufacturing, and controls.* (i) The information required under § 314.50(d)(1), except that the information required under § 314.50(d)(1)(ii)(c) must contain the proposed or actual master production record, including a description of the equipment, to be used for the manufacture of a commercial lot of the drug product.

(ii) *Inactive ingredients.* Unless otherwise stated in paragraphs (a)(9)(iii) through (a)(9)(v) of this section, an applicant must identify and characterize the inactive ingredients in the proposed drug product and provide information demonstrating that such inactive ingredients do not affect the safety or efficacy of the proposed drug product.

(iii) *Inactive ingredient changes permitted in drug products intended for parenteral use*. Generally, a drug product intended for parenteral use must contain the same inactive ingredients and in the same concentration as the reference listed drug identified by the applicant under paragraph (a)(3) of this section. However, an applicant may seek approval of a drug product that differs from the reference listed drug in preservative, buffer, or antioxidant provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.

(iv) *Inactive ingredient changes permitted in drug products intended for ophthalmic or otic use.* Generally, a drug product intended for ophthalmic or otic use must contain the same inactive ingredients and in the same concentration as the reference listed drug identified by the applicant under paragraph (a)(3) of this section. However, an applicant may seek approval of a drug product that differs from the reference listed drug in preservative, buffer, substance to adjust tonicity, or thickening agent provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product, except that, in a product intended for ophthalmic use, an applicant may not change a buffer or substance to adjust tonicity for the purpose of claiming a therapeutic advantage over or difference from the listed drug, e.g., by using a balanced salt solution as a diluent as opposed to an

isotonic saline solution, or by making a significant change in the pH or other change that may raise questions of irritability.

(v) *Inactive ingredient changes permitted in drug products intended for topical use.* Generally, a drug product intended for topical use, solutions for aerosolization or nebulization, and nasal solutions shall contain the same inactive ingredients as the reference listed drug identified by the applicant under paragraph (a)(3) of this section. However, an ANDA may include different inactive ingredients provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.

(10) *Samples.* The information required under § 314.50(e)(1) and (e)(2)(i). Samples need not be submitted until requested by FDA.

(11) *Other.* The information required under § 314.50(g).

(12) *Patent certification*—(i) *Patents claiming drug substance, drug product, or method of use.* (A) An appropriate patent certification or statement with respect to each patent issued by the U.S. Patent and Trademark Office that, in the opinion of the applicant and to the best of its knowledge, claims the reference listed drug or that claims a use of such listed drug for which the applicant is seeking approval under section 505(j) of the Federal Food, Drug, and Cosmetic Act and for which information is required to be filed under section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act and § 314.53. For each such patent, the applicant must provide the patent number and certify, in its opinion and to the best of its knowledge, one of the following circumstances:

(1) That the patent information has not been submitted to FDA. The applicant must entitle such a certification "Paragraph I Certification";

(2) That the patent has expired. The applicant must entitle such a certification "Paragraph II Certification";

(3) The date on which the patent will expire. The applicant must entitle such a certification "Paragraph III Certification"; or

(4)(i) That the patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the ANDA is submitted. The applicant must entitle such a certification "Paragraph IV Certification". This certification must be submitted in the following form:

> I, *(name of applicant),* certify that Patent No. _____ *(is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of) (name of proposed drug product)* for which this ANDA is submitted.

(ii) The certification must be accompanied by a statement that the applicant will comply with the requirements under § 314.95(a) with respect to providing a notice to each owner of the patent or its representative and to the NDA holder (or, if the NDA holder does not reside or maintain a place of business within the United States, its attorney, agent, or other authorized official) for the listed drug, with the requirements under § 314.95(b) with respect to sending the notice, and with the requirements under § 314.95(c) with respect to the content of the notice.

(B) If the ANDA refers to a listed drug that is itself a licensed generic product of a patented drug first approved under section 505(b) of the Federal Food, Drug, and Cosmetic Act, an appropriate patent certification or statement under paragraph (a)(12)(i) and/or (iii) of this section with respect to each patent that claims the first-approved patented drug or that claims a use for such drug.

(ii) *No relevant patents.* If, in the opinion of the applicant and to the best of its knowledge, there are no patents described in paragraph (a)(12)(i) of this section, a certification in the following form:

> In the opinion and to the best knowledge of (name of applicant), there are no patents that claim the listed drug referred to in this ANDA or that claim a use of the listed drug.

(iii) *Method-of-use patent.* (A) If patent information is submitted under section 505(b) or (c) of the Federal Food, Drug, and Cosmetic Act and §314.53 for a patent claiming a method of using the listed drug, and the labeling for the drug product for which the applicant is seeking approval does not include an indication or other condition of use that is covered by the method-of-use patent, a statement explaining that the method-of-use patent does not claim a proposed indication or other condition of use.

(B) If the labeling of the drug product for which the applicant is seeking approval includes an indication or other condition of use that, according to the patent information submitted under section 505(b) or (c) of the Federal Food, Drug, and Cosmetic Act and §314.53 or in the opinion of the applicant, is claimed by a method-of-use patent, an applicable certification under paragraph (a)(12)(i) of this section.

(iv) [Reserved]

(v) *Licensing agreements.* If the ANDA is for a drug or method of using a drug claimed by a patent and the applicant has a licensing agreement with the patent owner, the applicant must submit a paragraph IV certification as to that patent and a statement that the applicant has been granted a patent license. If the patent owner consents to approval of the ANDA (if otherwise eligible for approval) as of a specific date, the ANDA must contain a written statement from the patent owner that it has a licensing agreement with the applicant and that it consents to approval of the ANDA as of a specific date.

(vi) *Untimely filing of patent information.* (A) If a patent on the listed drug is issued and the holder of the approved NDA for the listed drug does not file with FDA the required information on the patent within 30 days of issuance of the patent, an applicant who submitted an ANDA for that drug that contained an appropriate patent certification or statement before the submission of the patent information is not required to submit a patent certification or statement to address the patent or patent information that is late-listed with respect to the pending ANDA. Except as provided in §314.53(f)(1), an NDA holder's amendment to the description of the approved method(s) of use claimed by the patent will be considered untimely filing of patent information unless:

(1) The amendment to the description of the approved method(s) of use claimed by the patent is submitted within 30 days of patent issuance;

(2) The amendment to the description of the approved method(s) of use claimed by the patent is submitted within 30 days of approval of a corresponding change to product labeling; or

(3) The amendment to the description of the approved method(s) of use claimed by the patent is submitted within 30 days of a decision by the U.S. Patent and Trademark Office or by a Federal district court, the Court of Appeals for the Federal Circuit, or the U.S. Supreme Court that is specific to the patent and alters the construction of a method-of-use claim(s) of the patent, and the amendment contains a copy of the decision.

(B) An applicant whose ANDA is submitted after the NDA holder's untimely filing of patent information, or whose pending ANDA was previously submitted but did not contain an appropriate patent certification or statement at the time of the patent submission, must submit a certification under paragraph (a)(12)(i) of this section and/or a statement under paragraph (a)(12)(iii) of this section as to that patent.

(vii) *Disputed patent information.* If an applicant disputes the accuracy or relevance of patent information submitted to FDA, the applicant may seek a confirmation of the correctness of the patent information in accordance with the procedures under §314.53(f). Unless the patent information is withdrawn, the applicant must submit an appropriate certification or statement for each listed patent.

(viii) *Amended certifications.* A patent certification or statement submitted under paragraphs (a)(12)(i) through (iii) of this section may be amended at any time before the approval of the ANDA. If an applicant with a pending ANDA voluntarily makes a patent certification for an untimely filed patent, the applicant may withdraw the patent certification for the untimely filed patent. An applicant must submit an amended certification as an amendment to a pending ANDA. Once an amendment is submitted to change a certification, the ANDA will no longer be considered to contain the prior certification.

(A) *After finding of infringement.* An applicant who has submitted a paragraph IV certification and is sued for patent infringement must submit an amendment to change its certification if a court enters a final decision from which no appeal has been or can be taken, or signs and enters a settlement order or consent decree in the action that includes a finding that the patent is infringed, unless the final decision, settlement order, or consent decree also finds the patent to be invalid. In its amendment, the applicant must certify under paragraph (a)(12)(i)(A)(3) of this section that the patent will expire on a specific date or, with respect to a patent claiming a method of use, the applicant may instead provide a statement under paragraph (a)(12)(iii) of this section if the applicant amends its ANDA such that the applicant is no longer seeking approval for a method of use claimed by the patent. Once an amendment for the change has been submitted, the ANDA will no longer be considered to contain a paragraph IV certification to the patent. If a final judgment finds the patent to be invalid and infringed, an amended certification is not required.

(B) *After request to remove a patent or patent information from the list.* If the list reflects that an NDA holder has requested that a patent or patent information be removed from the list and no ANDA applicant is eligible for 180-day exclusivity based on a paragraph IV certification to that patent, the patent or patent information will be removed and any applicant with a pending ANDA (including a tentatively approved ANDA) who has made a certification with respect to such patent must submit an amendment to withdraw its certification. In the amendment, the applicant must state the reason for withdrawing the certification or statement (that the patent has been removed from the list). If the list reflects that an NDA holder has requested that a patent or patent information be removed from the list and one or more first applicants are eligible for 180-day exclusivity based on a paragraph IV certification to that patent, the patent will remain listed until any 180-day exclusivity based on that patent has expired or has been extinguished. After any applicable 180-day exclusivity has expired or has been extinguished, the patent or patent information will be removed and any applicant with a pending ANDA (including a tentatively approved ANDA) who has made a certification with respect to such patent must submit an amendment to withdraw its certification. Once an amendment to withdraw the certification has been submitted, the ANDA will no longer be considered to contain a paragraph IV certification to the patent. If removal of a patent from the list results in there being no patents listed for the listed drug identified in the ANDA, the applicant must submit an amended certification reflecting that there are no relevant patents.

(C) *Other amendments.* (1) Except as provided in paragraphs (a)(12)(vi) and (a)(12)(viii)(C)(2) of this section:

(i) An applicant must amend a submitted certification or statement if, at any time before the date of approval of the ANDA, the applicant learns that the submitted certification or statement is no longer accurate; and

(ii) An applicant must submit an appropriate patent certification or statement under paragraph (a)(12)(i) and/or (iii) of this section if, after submission of the ANDA, a new patent is issued by the U.S. Patent and Trademark Office that, in the opinion of the applicant and to the best of its knowledge, claims the reference listed drug or that claims an approved use for such reference listed drug and for which information is required to be filed under section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act and § 314.53. For a paragraph IV certification, the certification must not be submitted earlier than the first working day after the day the patent is published in the list.

(2) An applicant is not required to submit a supplement to change a submitted certification when information on a patent on the listed drug is submitted after the approval of the ANDA.

(13) *Financial certification or disclosure statement.* An ANDA must contain a financial certification or disclosure statement as required by part 54 of this chapter.

(b) *Drug products subject to the Drug Efficacy Study Implementation (DESI) review.* If the ANDA is for a duplicate of a drug product that is subject to FDA's DESI review (a review of drug products approved as safe between 1938 and 1962) or other DESI-like review and the drug product evaluated in the review is a listed drug, the applicant must comply with the provisions of paragraph (a) of this section.

(c) [Reserved]

(d) *Format of an ANDA.* (1) The applicant must submit a complete archival copy of the ANDA as required under paragraphs (a) and (c) of this section. FDA will maintain the archival copy during the review of the ANDA to permit individual reviewers to refer to information that is not contained in their particular technical sections of the ANDA, to give other Agency personnel access to the ANDA for official business, and to maintain in one place a complete copy of the ANDA.

(i) *Format of submission.* An applicant may submit portions of the archival copy of the ANDA in any form that the applicant and FDA agree is acceptable, except as provided in paragraph (d)(1)(ii) of this section.

(ii) *Labeling*. The content of labeling required under § 201.100(d)(3) of this chapter (commonly referred to as the package insert or professional labeling), including all text, tables, and figures, must be submitted to the agency in electronic format as described in paragraph (d)(1)(iii) of this section. This requirement applies to the content of labeling for the proposed drug product only and is in addition to the requirements of paragraph (a)(8)(ii) of this section that copies of the formatted label and all proposed labeling be submitted. Submissions under this paragraph must be made in accordance with part 11 of this chapter, except for the requirements of § 11.10(a), (c) through (h), and (k), and the corresponding requirements of § 11.30.

(iii) *Electronic format submissions.* Electronic format submissions must be in a form that FDA can process, review, and archive. FDA will periodically issue guidance on how to provide the electronic submission (e.g., method of transmission, media, file formats, preparation and organization of files).

(2) For ANDAs, the applicant must submit a review copy of the ANDA that contains two separate sections. One section must contain the information described under paragraphs (a)(2) through (6) and (8) and (9) of this section and section 505(j)(2)(A)(vii) of the Federal Food, Drug, and Cosmetic Act and a copy of the analytical procedures and descriptive information needed by FDA's laboratories to perform tests on samples of the proposed drug product and to validate the applicant's analytical procedures. The other section must contain the information described under paragraphs (a)(3), (7), and (8) of this section. Each of the sections in the review copy is required to contain a copy of the application form described under paragraph (a) of this section.

(3) [Reserved]

(4) The applicant may obtain from FDA sufficient folders to bind the archival, the review, and the field copies of the ANDA.

(5) The applicant must submit a field copy of the ANDA that contains the technical section described in paragraph (a)(9) of this section, a copy of the application form required under paragraph (a)(1) of this section, and a certification that the field copy is a true copy of the technical section described in paragraph (a)(9) of this section contained in the archival and review copies of the ANDA.

[57 FR 17983, Apr. 28, 1992; 57 FR 29353, July 1, 1992, as amended at 58 FR 47352, Sept. 8, 1993; 59 FR 50364, Oct. 3, 1994; 63 FR 5252, Feb. 2, 1998; 63 FR 66399, Dec. 1, 1998; 64 FR 401, Jan. 5, 1999; 65 FR

56479, Sept. 19, 2000; 67 FR 77672, Dec. 19, 2002; 68 FR 69019, Dec. 11, 2003; 69 FR 18766, Apr. 8, 2004; 74 FR 2861, Jan. 16, 2009; 76 FR 13880, Mar. 15, 2011; 81 FR 69649, Oct. 6, 2016]

§ 314.95 Notice of certification of invalidity, unenforceability, or noninfringement of a patent.

(a) *Notice of certification.* For each patent that claims the listed drug or that claims a use for such listed drug for which the applicant is seeking approval and for which the applicant submits a paragraph IV certification, the applicant must send notice of such certification by registered or certified mail, return receipt requested, or by a designated delivery service, as defined in paragraph (g) of this section to each of the following persons:

(1) Each owner of the patent that is the subject of the certification or the representative designated by the owner to receive the notice. The name and address of the patent owner or its representative may be obtained from the U.S. Patent and Trademark Office; and

(2) The holder of the approved NDA under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the listed drug that is claimed by the patent and for which the applicant is seeking approval, or, if the NDA holder does not reside or maintain a place of business within the United States, the NDA holder's attorney, agent, or other authorized official. The name and address of the NDA holder or its attorney, agent, or authorized official may be obtained by sending a written or electronic communication to the Orange Book Staff, Office of Generic Drugs, 7620 Standish Pl., Rockville, MD 20855 or to the Orange Book Staff at the email address listed on the Agency's Web site at *http://www.fda.gov.*

(3) This paragraph (a) does not apply to a method-of-use patent that does not claim a use for which the applicant is seeking approval.

(4) An applicant may send notice by an alternative method only if FDA has agreed in advance that the method will produce an acceptable form of documentation.

(b) *Sending the notice.* (1) Except as provided under paragraph (d) of this section, the applicant must send the notice required by paragraph (a) of this section on or after the date it receives a paragraph IV acknowledgment letter from FDA, but not later than 20 days after the date of the postmark on the paragraph IV acknowledgment letter. The 20-day clock described in this paragraph (b) begins on the day after the date of the postmark on the paragraph IV acknowledgment letter. When the 20th day falls on Saturday, Sunday, or a Federal holiday, the 20th day will be the next day that is not a Saturday, Sunday, or Federal holiday.

(2) Any notice required by paragraph (a) of this section is invalid if it is sent before the applicant's receipt of a paragraph IV acknowledgment letter, or before the first working day after the day the patent is published in the list. The applicant will not have complied with this paragraph (b) until it sends valid notice.

(3) The applicant must submit to FDA an amendment to its ANDA that includes a statement certifying that the notice has been provided to each person identified under paragraph (a) of this section and that the notice met the content requirements under paragraph (c) of this section. A copy of the notice itself need not be submitted to the Agency.

(c) *Contents of a notice.* In the notice, the applicant must cite section 505(j)(2)(B)(iv) of the Federal Food, Drug, and Cosmetic Act and the notice must include, but is not limited to, the following information:

(1) A statement that FDA has received an ANDA submitted by the applicant containing any required bioavailability or bioequivalence data or information.

(2) The ANDA number.

(3) A statement that the applicant has received the paragraph IV acknowledgment letter for the ANDA.

(4) The established name, if any, as defined in section 502(e)(3) of the Federal Food, Drug, and Cosmetic Act, of the proposed drug product.

(5) The active ingredient, strength, and dosage form of the proposed drug product.

(6) The patent number and expiration date of each listed patent for the reference listed drug alleged to be invalid, unenforceable, or not infringed.

(7) A detailed statement of the factual and legal basis of the applicant's opinion that the patent is not valid, unenforceable, or will not be infringed. The applicant must include in the detailed statement:

(i) For each claim of a patent alleged not to be infringed, a full and detailed explanation of why the claim is not infringed.

(ii) For each claim of a patent alleged to be invalid or unenforceable, a full and detailed explanation of the grounds supporting the allegation.

(8) If the applicant alleges that the patent will not be infringed and the applicant seeks to preserve the option to later file a civil action for declaratory judgment in accordance with section 505(j)(5)(C) of the Federal Food, Drug, and Cosmetic Act, then the notice must be accompanied by an offer of confidential access to the ANDA for the sole and limited purpose of evaluating possible infringement of the patent that is the subject of the paragraph IV certification.

(9) If the applicant does not reside or have a place of business in the United States, the name and address of an agent in the United States authorized to accept service of process for the applicant.

(d) *Amendment or supplement to an ANDA.* (1) If, after receipt of a paragraph IV acknowledgment letter or acknowledgment letter, an applicant submits an amendment or supplement to its ANDA that includes a paragraph IV certification, the applicant must send the notice required by paragraph (a) of this section at the same time that the amendment or supplement to the ANDA is submitted to FDA, regardless of whether the applicant has already given notice with respect to another such certification contained in the ANDA or in an amendment or supplement to the ANDA.

(2) If, before receipt of a paragraph IV acknowledgment letter, an applicant submits an amendment to its ANDA that includes a paragraph IV certification, the applicant must send the notice required by paragraph (a) of this section in accordance with the procedures in paragraph (b) of this section. If an ANDA applicant's notice of its paragraph IV certification is timely provided in accordance with paragraph (b) of this section and the applicant has not submitted a previous paragraph IV certification, FDA will base its determination of whether the applicant is a first applicant on the date of submission of the amendment containing the paragraph IV certification.

(3) An applicant that submits an amendment or supplement to seek approval of a different strength must provide notice of any paragraph IV certification in accordance with paragraph (d)(1) or (2) of this section, as applicable.

(e) *Documentation of timely sending and receipt of notice.* The applicant must amend its ANDA to provide documentation of the date of receipt of the notice required under paragraph (a) of this section by each person provided the notice. The amendment must be submitted to FDA within 30 days after the last date on which notice was received by a person described in paragraph (a) of this section. The applicant's amendment also must include documentation that its notice was sent on a date that complies with the timeframe required by paragraph (b) or (d) of this section, as applicable, and a dated printout of the entry for the reference listed drug in FDA's "Approved Drug Products With Therapeutic Equivalence Evaluations" (the list) that includes the patent that is the subject of the paragraph IV certification. FDA will accept, as adequate documentation of the date the notice was sent, a copy of the registered mail receipt, certified mail receipt, or receipt from a designated delivery

service as defined in paragraph (g) of this section. FDA will accept as adequate documentation of the date of receipt a return receipt, signature proof of delivery by a designated delivery service, or a letter acknowledging receipt by the person provided the notice. An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance. A copy of the notice itself need not be submitted to the Agency.

(f) *Forty-five day period after receipt of notice.* If the requirements of this section are met, FDA will presume the notice to be complete and sufficient, and it will count the day following the date of receipt of the notice by the patent owner or its representative and by the approved NDA holder or its attorney, agent, or other authorized official as the first day of the 45-day period provided for in section 505(j)(5)(B)(iii) of the Federal Food, Drug, and Cosmetic Act. FDA may, if the applicant provides a written statement to FDA that a later date should be used, count from such later date.

(g) *Designated delivery services.* (1) For purposes of this section, the term "designated delivery service" means any delivery service provided by a trade or business that the Agency determines:

(i) Is available to the general public throughout the United States;

(ii) Records electronically to its database, kept in the regular course of its business, or marks on the cover in which any item referred to in this section is to be delivered, the date on which such item was given to such trade or business for delivery; and

(iii) Provides overnight or 2-day delivery service throughout the United States.

(2) FDA may periodically issue guidance regarding designated delivery services.

[81 FR 69651, Oct. 6, 2016]

§ 314.96 Amendments to an unapproved ANDA.

(a) *ANDA.* (1) An applicant may amend an ANDA that is submitted under § 314.94, but not yet approved, to revise existing information or provide additional information. Amendments containing bioequivalence studies must contain reports of all bioequivalence studies conducted by the applicant on the same drug product formulation, unless the information has previously been submitted to FDA in the ANDA. A complete study report must be submitted for any bioequivalence study upon which the applicant relies for approval. For all other bioequivalence studies conducted on the same drug product formulation as defined in § 314.3 of this chapter, the applicant must submit either a complete or summary report. If a summary report of a bioequivalence study is submitted and FDA determines that there may be bioequivalence issues or concerns with the product, FDA may require that the applicant submit a complete report of the bioequivalence study to FDA.

(2) Submission of an amendment containing significant data or information before the end of the initial review cycle constitutes an agreement between FDA and the applicant to extend the initial review cycle only for the time necessary to review the significant data or information and for no more than 180 days.

(b) *Field copy.* The applicant must submit a field copy of each amendment under § 314.94(a)(9). The applicant, other than a foreign applicant, must include in its submission of each such amendment to FDA a statement certifying that a field copy of the amendment has been sent to the applicant's home FDA district office.

(c) *Different listed drug.* An applicant may not amend an ANDA to seek approval of a drug referring to a listed drug that is different from the reference listed drug identified in the ANDA. This paragraph (c) applies if, at any time before the approval of the ANDA, a different listed drug is approved that is the pharmaceutical equivalent to the product in the ANDA and is designated as a reference listed drug. This paragraph (c) also applies if changes are proposed in an amendment to the ANDA such that the proposed product is a pharmaceutical equivalent to a different listed drug than the reference listed drug identified in the ANDA. A change of the reference listed drug must be submitted in

a new ANDA. However, notwithstanding the limitation described in this paragraph (c), an applicant may amend the ANDA to seek approval of a different strength.

(d)(1) *Patent certification requirements.* An amendment to an ANDA is required to contain an appropriate patent certification or statement described in § 314.94(a)(12) or a recertification for a previously submitted paragraph IV certification if approval is sought for any of the following types of amendments:

(i) To add a new indication or other condition of use;

(ii) To add a new strength;

(iii) To make other than minor changes in product formulation; or

(iv) To change the physical form or crystalline structure of the active ingredient.

(2) If the amendment to the ANDA does not contain a patent certification or statement, the applicant must verify that the proposed change described in the amendment is not one of the types of amendments described in paragraph (d)(1) of this section.

[57 FR 17983, Apr. 28, 1992, as amended at 58 FR 47352, Sept. 8, 1993; 64 FR 401, Jan. 5, 1999; 73 FR 39609, July 10, 2008; 74 FR 2861, Jan. 16, 2009; 81 FR 69652, Oct. 6, 2016]

§ 314.97 Supplements and other changes to an approved ANDA.

(a) *General requirements.* The applicant must comply with the requirements of §§ 314.70 and 314.71 regarding the submission of supplemental ANDAs and other changes to an approved ANDA.

(b) *Different listed drug.* An applicant may not supplement an ANDA to seek approval of a drug referring to a listed drug that is different from the current reference listed drug identified in the ANDA. This paragraph (b) applies if changes are proposed in a supplement to the ANDA such that the proposed product is a pharmaceutical equivalent to a different listed drug than the reference listed drug identified in the ANDA. A change of reference listed drug must be submitted in a new ANDA. However, notwithstanding the limitation described in this paragraph (b), an applicant may supplement the ANDA to seek approval of a different strength.

[81 FR 69653, Oct. 6, 2016]

§ 314.98 Postmarketing reports.

(a) Each applicant having an approved abbreviated new drug application under § 314.94 that is effective must comply with the requirements of § 314.80 regarding the reporting and recordkeeping of adverse drug experiences.

(b) Each applicant must make the reports required under § 314.81 and section 505(k) of the Federal Food, Drug, and Cosmetic Act for each of its approved abbreviated applications.

[79 FR 33089, June 10, 2014]

§ 314.99 Other responsibilities of an applicant of an ANDA.

(a) An applicant must comply with the requirements of § 314.65 regarding withdrawal by the applicant of an unapproved ANDA and § 314.72 regarding a change in ownership of an ANDA.

(b) An applicant may ask FDA to waive under this section any requirement that applies to the applicant under §§ 314.92 through 314.99. The applicant must comply with the requirements for a waiver under § 314.90. If FDA grants the applicant's waiver request with respect to a requirement under §§ 314.92 through 314.99, the waived requirement will not constitute a basis for refusal to approve an ANDA under § 314.127.

81 FR 69653, Oct. 6, 2016]

Subpart D—FDA Action on Applications and Abbreviated Applications

Source: 50 FR 7493, Feb. 22, 1985, unless otherwise noted. Redesignated at 57 FR 17983, Apr. 28, 1992.

(a) Except as provided in paragraph (c) of this section, within 180 days of receipt of an application for a new drug under section 505(b) of the act or an abbreviated application for a new drug under section 505(j) of the act, FDA will review it and send the applicant either an approval letter under § 314.105 or a complete response letter under § 314.110. This 180-day period is called the "initial review cycle."

(b) At any time before approval, an applicant may withdraw an application under § 314.65 or an abbreviated application under § 314.99 and later submit it again for consideration.

(c) The initial review cycle may be adjusted by mutual agreement between FDA and an applicant or as provided in §§ 314.60 and 314.96, as the result of a major amendment.

[73 FR 39609, July 10, 2008]

§ 314.101 Filing an NDA and receiving an ANDA.

(a) *Filing an NDA.* (1) Within 60 days after FDA receives an NDA, the Agency will determine whether the NDA may be filed. The filing of an NDA means that FDA has made a threshold determination that the NDA is sufficiently complete to permit a substantive review.

(2) If FDA finds that none of the reasons in paragraphs (d) and (e) of this section for refusing to file the NDA apply, the Agency will file the NDA and notify the applicant in writing. In the case of a 505(b)(2) application that contains a paragraph IV certification, the applicant will be notified via a paragraph IV acknowledgment letter. The date of filing will be the date 60 days after the date FDA received the NDA. The date of filing begins the 180-day period described in section 505(c) of the Federal Food, Drug, and Cosmetic Act. This 180-day period is called the "filing clock."

(3) If FDA refuses to file the NDA, the Agency will notify the applicant in writing and state the reason under paragraph (d) or (e) of this section for the refusal. If FDA refuses to file the NDA under paragraph (d) of this section, the applicant may request in writing within 30 days of the date of the Agency's notification an informal conference with the Agency about whether the Agency should file the NDA. If, following the informal conference, the applicant requests that FDA file the NDA (with or without amendments to correct the deficiencies), the Agency will file the NDA over protest under paragraph (a)(2) of this section, notify the applicant in writing, and review it as filed. If the NDA is filed over protest, the date of filing will be the date 60 days after the date the applicant requested the informal conference. The applicant need not resubmit a copy of an NDA that is filed over protest. If FDA refuses to file the NDA under paragraph (e) of this section, the applicant may amend the NDA and resubmit it, and the Agency will make a determination under this section whether it may be filed.

(b)(1) *Receiving an ANDA.* An ANDA will be evaluated after it is submitted to determine whether the ANDA may be received. Receipt of an ANDA means that FDA has made a threshold determination that the abbreviated application is substantially complete.

(2) If FDA finds that none of the reasons in paragraphs (d) and (e) of this section for considering the ANDA not to have been received applies, the ANDA is substantially complete and the Agency will receive the ANDA and notify the applicant in writing. If FDA determines, upon evaluation, that an ANDA was substantially complete as of the date it was submitted to FDA, FDA will consider the ANDA to have been received as of the date of submission. In the case of an ANDA that contains a paragraph IV certification, the applicant will be notified via a paragraph IV acknowledgment letter.

(3) If FDA considers the ANDA not to have been received under paragraph (d) or (e) of this section, FDA will notify the applicant of the refuse-to-receive decision. The applicant may then:

(i) Withdraw the ANDA under § 314.99; or

(ii) Correct the deficiencies and resubmit the ANDA; or

(iii) Take no action, in which case FDA may consider the ANDA withdrawn after 1 year.

(c) [Reserved]

(d) *NDA or ANDA deficiencies.* FDA may refuse to file an NDA or may not consider an ANDA to be received if any of the following applies:

(1) The NDA or ANDA does not contain a completed application form.

(2) The NDA or ANDA is not submitted in the form required under § 314.50 or § 314.94.

(3) The NDA or ANDA is incomplete because it does not on its face contain information required under section 505(b) or section 505(j) of the Federal Food, Drug, and Cosmetic Act and § 314.50 or § 314.94. In determining whether an ANDA is incomplete on its face, FDA will consider the nature (e.g., major or minor) of the deficiencies, including the number of deficiencies in the ANDA.

(4) The applicant fails to submit a complete environmental assessment, which addresses each of the items specified in the applicable format under § 25.40 of this chapter or fails to provide sufficient information to establish that the requested action is subject to categorical exclusion under § 25.30 or § 25.31 of this chapter.

(5) The NDA or ANDA does not contain an accurate and complete English translation of each part of the NDA or ANDA that is not in English.

(6) The NDA or ANDA does not contain a statement for each nonclinical laboratory study that the study was conducted in compliance with the requirements set forth in part 58 of this chapter, or, for each study not conducted in compliance with part 58 of this chapter, a brief statement of the reason for the noncompliance.

(7) The NDA or ANDA does not contain a statement for each clinical study that the study was conducted in compliance with the institutional review board regulations in part 56 of this chapter, or was not subject to those regulations, and that it was conducted in compliance with the informed consent regulations in part 50 of this chapter, or, if the study was subject to but was not conducted in compliance with those regulations, the NDA or ANDA does not contain a brief statement of the reason for the noncompliance.

(8) The drug product that is the subject of the submission is already covered by an approved NDA or ANDA and the applicant of the submission:

(i) Has an approved NDA or ANDA for the same drug product; or

(ii) Is merely a distributor and/or repackager of the already approved drug product.

(9) The NDA is submitted as a 505(b)(2) application for a drug that is a duplicate of a listed drug and is eligible for approval under section 505(j) of the Federal Food, Drug, and Cosmetic Act.

(e) *Regulatory deficiencies.* The Agency will refuse to file an NDA or will consider an ANDA not to have been received if any of the following applies:

(1) The drug product is subject to licensing by FDA under the Public Health Service Act (42 U.S.C. 201 et seq.) and subchapter F of this chapter.

(2) Submission of a 505(b)(2) application or an ANDA is not permitted under section 505(c)(3)(E)(ii), 505(j)(5)(F)(ii), 505A(b)(1)(A)(i)(I), 505A(c)(1)(A)(i)(I), or 505E(a) of the Federal Food, Drug, and Cosmetic Act.

(f) Outcome of FDA review. (1) Within 180 days after the date of filing, plus the period of time the review period was extended (if any), FDA will either:

(i) Approve the NDA; or

(ii) Issue a notice of opportunity for a hearing if the applicant asked FDA to provide it an opportunity for a hearing on an NDA in response to a complete response letter.

(2) Within 180 days after the date of receipt, plus the period of time the review clock was extended (if any), FDA will either approve or disapprove the ANDA. If FDA disapproves the ANDA, FDA will issue a notice of opportunity for hearing if the applicant asked FDA to provide it an opportunity for a hearing on an ANDA in response to a complete response letter.

(3) This paragraph (f) does not apply to NDAs or ANDAs that have been withdrawn from FDA review by the applicant.

[81 FR 69653, Oct. 6, 2016]

§ 314.102 Communications between FDA and applicants.

(a) *General principles.* During the course of reviewing an application or an abbreviated application, FDA shall communicate with applicants about scientific, medical, and procedural issues that arise during the review process. Such communication may take the form of telephone conversations, letters, or meetings, whichever is most appropriate to discuss the particular issue at hand. Communications shall be appropriately documented in the application in accordance with § 10.65 of this chapter. Further details on the procedures for communication between FDA and applicants are contained in a staff manual guide that is publicly available.

(b) *Notification of easily correctable deficiencies.* FDA reviewers shall make every reasonable effort to communicate promptly to applicants easily correctable deficiencies found in an application or an abbreviated application when those deficiencies are discovered, particularly deficiencies concerning chemistry, manufacturing, and controls issues. The agency will also inform applicants promptly of its need for more data or information or for technical changes in the application or the abbreviated application needed to facilitate the agency's review. This early communication is intended to permit applicants to correct such readily identified deficiencies relatively early in the review process and to submit an amendment before the review period has elapsed. Such early communication would not ordinarily apply to major scientific issues, which require consideration of the entire pending application or abbreviated application by agency managers as well as reviewing staff. Instead, major scientific issues will ordinarily be addressed in a complete response letter.

(c) *Ninety-day conference.* Approximately 90 days after the agency receives the application, FDA will provide applicants with an opportunity to meet with agency reviewing officials. The purpose of the meeting will be to inform applicants of the general progress and status of their applications, and to advise applicants of deficiencies that have been identified by that time and that have not already been communicated. This meeting will be available on applications for all new chemical entities and major new indications of marketed drugs. Such meetings will be held at the applicant's option, and may be held by telephone if mutually agreed upon. Such meetings would not ordinarily be held on abbreviated applications because they are not submitted for new chemical entities or new indications.

(d) *End-of-review conference.* At the conclusion of FDA's review of an NDA as designated by the issuance of a complete response letter, FDA will provide the applicant with an opportunity to meet with agency reviewing officials. The purpose of the meeting will be to discuss what further steps need to be taken by the applicant before the application can be approved. Requests for such meetings must be directed to the director of the division responsible for reviewing the application.

(e) *Other meetings.* Other meetings between FDA and applicants may be held, with advance notice, to discuss scientific, medical, and other issues that arise during the review process. Requests for meetings shall be directed to the director of the division responsible for reviewing the application or abbreviated application. FDA will make every attempt to grant requests for meetings that involve

important issues and that can be scheduled at mutually convenient times. However, "drop-in" visits (i.e., an unannounced and unscheduled visit by a company representative) are discouraged except for urgent matters, such as to discuss an important new safety issue.

[57 FR 17988, Apr. 28, 1992; 57 FR 29353, July 1, 1992, as amended at 73 FR 39609, July 10, 2008]

§ 314.103 Dispute resolution.

(a) *General.* FDA is committed to resolving differences between applicants and FDA reviewing divisions with respect to technical requirements for applications or abbreviated applications as quickly and amicably as possible through the cooperative exchange of information and views.

(b) *Administrative and procedural issues.* When administrative or procedural disputes arise, the applicant should first attempt to resolve the matter with the division responsible for reviewing the application or abbreviated application, beginning with the consumer safety officer assigned to the application or abbreviated application. If resolution is not achieved, the applicant may raise the matter with the person designated as ombudsman, whose function shall be to investigate what has happened and to facilitate a timely and equitable resolution. Appropriate issues to raise with the ombudsman include resolving difficulties in scheduling meetings, obtaining timely replies to inquiries, and obtaining timely completion of pending reviews. Further details on this procedure are contained in a staff manual guide that is publicly available under FDA's public information regulations in part 20.

(c) *Scientific and medical disputes.* (1) Because major scientific issues are ordinarily communicated to applicants in a complete response letter pursuant to § 314.110, the "end-of-review conference" described in § 314.102(d) will provide a timely forum for discussing and resolving, if possible, scientific and medical issues on which the applicant disagrees with the agency. In addition, the "ninety-day conference" described in § 314.102(c) will provide a timely forum for discussing and resolving, if possible, issues identified by that date.

(2) When scientific or medical disputes arise at other times during the review process, applicants should discuss the matter directly with the responsible reviewing officials. If necessary, applicants may request a meeting with the appropriate reviewing officials and management representatives in order to seek a resolution. Ordinarily, such meetings would be held first with the Division Director, then with the Office Director, and finally with the Center Director if the matter is still unresolved. Requests for such meetings shall be directed to the director of the division responsible for reviewing the application or abrreviated application. FDA will make every attempt to grant requests for meetings that involve important issues and that can be scheduled at mutually convenient times.

(3) In requesting a meeting designed to resolve a scientific or medical dispute, applicants may suggest that FDA seek the advice of outside experts, in which case FDA may, in its discretion, invite to the meeting one or more of its advisory committee members or other consultants, as designated by the agency. Applicants may also bring their own consultants. For major scientific and medical policy issues not resolved by informal meetings, FDA may refer the matter to one of its standing advisory committees for its consideration and recommendations.

[50 FR 7493, Feb. 22, 1985; 50 FR 14212, Apr. 11, 1985, as amended at 57 FR 17989, Apr. 28, 1992; 73 FR 39609, July 10, 2008]

§ 314.104 Drugs with potential for abuse.

The Food and Drug Administration will inform the Drug Enforcement Administration under section 201(f) of the Controlled Substances Act (21 U.S.C. 801) when an application or abbreviated application is submitted for a drug that appears to have an abuse potential.

[57 FR 17989, Apr. 28, 1992]

§ 314.105 Approval of an NDA and an ANDA.

(a) FDA will approve an NDA and send the applicant an approval letter if none of the reasons in § 314.125 for refusing to approve the NDA applies. FDA will issue a tentative approval letter if an NDA otherwise meets the requirements for approval under the Federal Food, Drug, and Cosmetic Act, but cannot be approved because there is a 7-year period of orphan exclusivity for the listed drug under section 527 of the Federal Food, Drug, and Cosmetic Act and § 316.31 of this chapter, or if a 505(b)(2) application otherwise meets the requirements for approval under the Federal Food, Drug, and Cosmetic Act, but cannot be approved until the conditions in § 314.107(b)(3) are met; because there is a period of exclusivity for the listed drug under § 314.108; because there is a period of pediatric exclusivity for the listed drug under section 505A of the Federal Food, Drug, and Cosmetic Act; or because there is a period of exclusivity for the listed drug under section 505E of the Federal Food, Drug, and Cosmetic Act. A drug product that is granted tentative approval is not an approved drug and will not be approved until FDA issues an approval after any necessary additional review of the NDA. FDA's tentative approval of a drug product is based on information available to FDA at the time of the tentative approval letter (i.e., information in the 505(b)(2) application and the status of current good manufacturing practices of the facilities used in the manufacturing and testing of the drug product) and is therefore subject to change on the basis of new information that may come to FDA's attention. A new drug product may not be marketed until the date of approval.

(b) FDA will approve an NDA and issue the applicant an approval letter on the basis of draft labeling if the only deficiencies in the NDA concern editorial or similar minor deficiencies in the draft labeling. Such approval will be conditioned upon the applicant incorporating the specified labeling changes exactly as directed, and upon the applicant submitting to FDA a copy of the final printed labeling prior to marketing.

(c) FDA will approve an NDA after it determines that the drug meets the statutory standards for safety and effectiveness, manufacturing and controls, and labeling, and an ANDA after it determines that the drug meets the statutory standards for manufacturing and controls, labeling, and, where applicable, bioequivalence. While the statutory standards apply to all drugs, the many kinds of drugs that are subject to the statutory standards and the wide range of uses for those drugs demand flexibility in applying the standards. Thus FDA is required to exercise its scientific judgment to determine the kind and quantity of data and information an applicant is required to provide for a particular drug to meet the statutory standards. FDA makes its views on drug products and classes of drugs available through guidance documents, recommendations, and other statements of policy.

(d) FDA will approve an ANDA and send the applicant an approval letter if none of the reasons in § 314.127 for refusing to approve the ANDA applies. FDA will issue a tentative approval letter if an ANDA otherwise meets the requirements for approval under the Federal Food, Drug, and Cosmetic Act, but cannot be approved because there is a 7-year period of orphan exclusivity for the listed drug under section 527 of the Federal Food, Drug, and Cosmetic Act and § 316.31 of this chapter, or cannot be approved until the conditions in § 314.107(b)(3) or (c) are met; because there is a period of exclusivity for the listed drug under § 314.108; because there is a period of pediatric exclusivity for the listed drug under section 505A of the Federal Food, Drug, and Cosmetic Act; or because there is a period of exclusivity for the listed drug under section 505E of the Federal Food, Drug, and Cosmetic Act. A drug product that is granted tentative approval is not an approved drug and will not be approved until FDA issues an approval after any necessary additional review of the ANDA. FDA's tentative approval of a drug product is based on information available to FDA at the time of the tentative approval letter (i.e., information in the ANDA and the status of current good manufacturing practices of the facilities used in the manufacturing and testing of the drug product) and is therefore subject to change on the basis of new information that may come to FDA's attention. A new drug product may not be marketed until the date of approval.

[81 FR 69654, Oct. 6, 2016]

§ 314.106 Foreign data.

(a) *General*. The acceptance of foreign data in an application generally is governed by § 312.120 of this chapter.

(b) *As sole basis for marketing approval.* An application based solely on foreign clinical data meeting U.S. criteria for marketing approval may be approved if: (1) The foreign data are applicable to the U.S. population and U.S. medical practice; (2) the studies have been performed by clinical investigators of recognized competence; and (3) the data may be considered valid without the need for an on-site inspection by FDA or, if FDA considers such an inspection to be necessary, FDA is able to validate the data through an on-site inspection or other appropriate means. Failure of an application to meet any of these criteria will result in the application not being approvable based on the foreign data alone. FDA will apply this policy in a flexible manner according to the nature of the drug and the data being considered.

(c) *Consultation between FDA and applicants.* Applicants are encouraged to meet with agency officials in a "presubmission" meeting when approval based solely on foreign data will be sought.

[50 FR 7493, Feb. 22, 1985, as amended at 55 FR 11580, Mar. 29, 1990]

§ 314.107 Date of approval of a 505(b)(2) application or ANDA.

(a) *General*. A drug product may be introduced or delivered for introduction into interstate commerce when the 505(b)(2) application or ANDA for the drug product is approved. A 505(b)(2) application or ANDA for a drug product is approved on the date FDA issues an approval letter under § 314.105 for the 505(b)(2) application or ANDA.

(b) *Effect of patent(s) on the listed drug.* As described in paragraphs (b)(1) and (2) of this section, the status of patents listed for the listed drug(s) relied upon or reference listed drug, as applicable, must be considered in determining the first possible date on which a 505(b)(2) application or ANDA can be approved. The criteria in paragraphs (b)(1) and (2) of this section will be used to determine, for each relevant patent, the date that patent will no longer prevent approval. The first possible date on which the 505(b)(2) application or ANDA can be approved will be calculated for each patent, and the 505(b)(2) application or ANDA may be approved on the last applicable date.

(1) *Timing of approval based on patent certification or statement.* If none of the reasons in § 314.125 or § 314.127, as applicable, for refusing to approve the 505(b)(2) application or ANDA applies, and none of the reasons in paragraph (d) of this section for delaying approval applies, the 505(b)(2) application or ANDA may be approved as follows:

(i) Immediately, if the applicant certifies under § 314.50(i) or § 314.94(a)(12) that:

(A) The applicant is aware of a relevant patent but the patent information required under section 505(b) or (c) of the Federal Food, Drug, and Cosmetic Act has not been submitted to FDA; or

(B) The relevant patent has expired; or

(C) The relevant patent is invalid, unenforceable, or will not be infringed, except as provided in paragraphs (b)(3) and (c) of this section, and the 45-day period provided for in section 505(c)(3)(C) and (j)(5)(B)(iii) of the Federal Food, Drug, and Cosmetic Act has expired; or

(D) There are no relevant patents.

(ii) Immediately, if the applicant submits an appropriate statement under § 314.50(i) or § 314.94(a)(12) explaining that a method-of-use patent does not claim an indication or other condition of use for which the applicant is seeking approval, except that if the applicant also submits a paragraph IV certification to the patent, then the 505(b)(2) application or ANDA may be approved as provided in paragraph (b)(1)(i)(C) of this section.

(iii) On the date specified, if the applicant certifies under § 314.50(i) or § 314.94(a)(12) that the relevant patent will expire on a specified date.

(2) *Patent information filed after submission of 505(b)(2) application or ANDA.* If the holder of the approved NDA for the listed drug submits patent information required under §314.53 after the date on which the 505(b)(2) application or ANDA was submitted to FDA, the 505(b)(2) applicant or ANDA applicant must comply with the requirements of §314.50(i)(4) and (6) and §314.94(a)(12)(vi) and (viii) regarding submission of an appropriate patent certification or statement. If the applicant submits an amendment certifying under §314.50(i)(1)(i)(A)(4) or §314.94(a)(12)(i)(A)(4) that the relevant patent is invalid, unenforceable, or will not be infringed, and complies with the requirements of §314.52 or §314.95, the 505(b)(2) application or ANDA may be approved immediately upon submission of documentation of receipt of notice of paragraph IV certification under §314.52(e) or §314.95(e). The 45-day period provided for in section 505(c)(3)(C) and (j)(5)(B)(iii) of the Federal Food, Drug, and Cosmetic Act does not apply in these circumstances.

(3) *Disposition of patent litigation*—(i) *Approval upon expiration of 30-month period or 71/2 years from date of listed drug approval.* (A) Except as provided in paragraphs (b)(3)(ii) through (viii) of this section, if, with respect to patents for which required information was submitted under §314.53 before the date on which the 505(b)(2) application or ANDA was submitted to FDA (excluding an amendment or supplement to the 505(b)(2) application or ANDA), the applicant certifies under §314.50(i) or §314.94(a)(12) that the relevant patent is invalid, unenforceable, or will not be infringed, and the patent owner or its representative or the exclusive patent licensee brings suit for patent infringement within 45 days of receipt of the notice of certification from the applicant under §314.52 or §314.95, the 505(b)(2) application or ANDA may be approved 30 months after the later of the date of the receipt of the notice of certification by any owner of the listed patent or by the NDA holder (or its representative(s)) unless the court has extended or reduced the period because of a failure of either the plaintiff or defendant to cooperate reasonably in expediting the action; or

(B) If the patented drug product qualifies for 5 years of exclusive marketing under §314.108(b)(2) and the patent owner or its representative or the exclusive patent licensee brings suit for patent infringement during the 1-year period beginning 4 years after the date of approval of the patented drug and within 45 days of receipt of the notice of certification from the applicant under §314.52 or §314.95, the 505(b)(2) application or ANDA may be approved at the expiration of the 71/2 years from the date of approval of the NDA for the patented drug product.

(ii) *Federal district court decision of invalidity, unenforceability, or non-infringement.* If before the expiration of the 30-month period, or 71/2 years where applicable, the district court decides that the patent is invalid, unenforceable, or not infringed (including any substantive determination that there is no cause of action for patent infringement or invalidity), the 505(b)(2) application or ANDA may be approved on:

(A) The date on which the court enters judgment reflecting the decision; or

(B) The date of a settlement order or consent decree signed and entered by the court stating that the patent that is the subject of the certification is invalid, unenforceable, or not infringed.

(iii) Appeal of Federal district court judgment of infringement. If before the expiration of the 30-month period, or 71/2 years where applicable, the district court decides that the patent has been infringed, and if the judgment of the district court is appealed, the 505(b)(2) application or ANDA may be approved on:

(A) The date on which the mandate is issued by the court of appeals entering judgment that the patent is invalid, unenforceable, or not infringed (including any substantive determination that there is no cause of action for patent infringement or invalidity); or

(B) The date of a settlement order or consent decree signed and entered by the court of appeals stating that the patent that is the subject of the certification is invalid, unenforceable, or not infringed.

(iv) *Affirmation or non-appeal of Federal district court judgment of infringement.* If before the expiration of the 30-month period, or 71/2 years where applicable, the district court decides that the patent has been infringed, and if the judgment of the district court is not appealed or is affirmed, the 505(b)(2) application or ANDA may be approved no earlier than the date specified by the district court in an order under 35 U.S.C. 271(e)(4)(A).

(v) *Grant of preliminary injunction by Federal district court.* If before the expiration of the 30-month period, or 71/2 years where applicable, the district court grants a preliminary injunction prohibiting the applicant from engaging in the commercial manufacture or sale of the drug product until the court decides the issues of patent validity and infringement, and if the court later decides that:

(A) The patent is invalid, unenforceable, or not infringed, the 505(b)(2) application or ANDA may be approved as provided in paragraph (b)(3)(ii) of this section; or

(B) The patent is infringed, the 505(b)(2) application or ANDA may be approved as provided in paragraph (b)(3)(iii) or (iv) of this section, whichever is applicable.

(vi) *Written consent to approval by patent owner or exclusive patent licensee.* If before the expiration of the 30-month period, or 71/2 years where applicable, the patent owner or the exclusive patent licensee (or their representatives) agrees in writing that the 505(b)(2) application or ANDA may be approved any time on or after the date of the consent, approval may be granted on or after that date.

(vii) *Court order terminating 30-month or 71/2-year period.* If before the expiration of the 30-month period, or 71/2 years where applicable, the court enters an order requiring the 30-month or 71/2-year period to be terminated, the 505(b)(2) application or ANDA may be approved in accordance with the court's order.

(viii) *Court order of dismissal without a finding of infringement.* If before the expiration of the 30-month period, or 71/2 years where applicable, the court(s) enter(s) an order of dismissal, with or without prejudice, without a finding of infringement in each pending suit for patent infringement brought within 45 days of receipt of the notice of paragraph IV certification sent by the 505(b)(2) or ANDA applicant, the 505(b)(2) application or ANDA may be approved on or after the date of the order.

(4) *Tentative approval.* FDA will issue a tentative approval letter when tentative approval is appropriate in accordance with this section. In order for a 505(b)(2) application or ANDA to be approved under paragraph (b)(3) of this section, the applicant must receive an approval letter from the Agency. Tentative approval of an NDA or ANDA does not constitute "approval" of an NDA or ANDA and cannot, absent an approval letter from the Agency, result in an approval under paragraph (b)(3) of this section.

(c) *Timing of approval of subsequent ANDA.* (1) If an ANDA contains a paragraph IV certification for a relevant patent and the ANDA is not that of a first applicant, the ANDA is regarded as the ANDA of a subsequent applicant. The ANDA of a subsequent applicant will not be approved during the period when any first applicant is eligible for 180-day exclusivity or during the 180-day exclusivity period of a first applicant. Any applicable 180-day exclusivity period cannot extend beyond the expiration of the patent upon which the 180-day exclusivity period was based.

(2) A first applicant must submit correspondence to its ANDA notifying FDA within 30 days of the date of its first commercial marketing of its drug product or the reference listed drug. If an applicant does not notify FDA, as required in this paragraph (c)(2), of this date, the date of first commercial marketing will be deemed to be the date of the drug product's approval.

(3) If FDA concludes that a first applicant is not actively pursuing approval of its ANDA, FDA may immediately approve an ANDA(s) of a subsequent applicant(s) if the ANDA(s) is otherwise eligible for approval.

(d) *Delay due to exclusivity.* The Agency will also delay the approval of a 505(b)(2) application or ANDA if delay is required by the exclusivity provisions in §314.108; section 527 of the Federal Food, Drug, and Cosmetic Act and §316.31 of this chapter; section 505A of the Federal Food, Drug, and Cosmetic Act; or section 505E of the Federal Food, Drug, and Cosmetic Act. When the approval of a 505(b)(2) application or ANDA is delayed under this section and §314.108; section 527 of the Federal Food, Drug, and Cosmetic Act and §316.31 of this chapter; section 505A of the Federal Food, Drug, and Cosmetic Act; or section 505E of the Federal Food, Drug, and Cosmetic Act, the 505(b)(2) application or ANDA will be approved on the latest of the days specified under this section and §314.108; section 527 of the Federal Food, Drug, and Cosmetic Act and §316.31 of this chapter; section 505A of the Federal Food, Drug, and Cosmetic Act; or section 505E of the Federal Food, Drug, and Cosmetic Act, as applicable.

(e) *Notification of court actions or written consent to approval.* (1) The applicant must submit the following information to FDA, as applicable:

(i) A copy of any judgment by the court (district court or mandate of the court of appeals) or settlement order or consent decree signed and entered by the court (district court or court of appeals) finding a patent described in paragraph (b)(3) of this section invalid, unenforceable, or not infringed, or finding the patent valid and infringed;

(ii) Written notification of whether or not any action by the court described in paragraph (e)(1)(i) of this section has been appealed within the time permitted for an appeal;

(iii) A copy of any order entered by the court terminating the 30-month or 71/2-year period as described in paragraph (b)(3)(i), (ii), (vii), or (viii) of this section;

(iv) A copy of any written consent to approval by the patent owner or exclusive patent licensee described in paragraph (b)(3)(vi) of this section;

(v) A copy of any preliminary injunction described in paragraph (b)(3)(v) of this section, and a copy of any subsequent court order lifting the injunction; and

(vi) A copy of any court order pursuant to 35 U.S.C. 271(e)(4)(A) ordering that a 505(b)(2) application or ANDA may be approved no earlier than the date specified (irrespective of whether the injunction relates to a patent described in paragraph (b)(3) of this section).

(2) All information required by paragraph (e)(1) of this section must be sent to the applicant's NDA or ANDA, as appropriate, within 14 days of the date of entry by the court, the date of appeal or expiration of the time for appeal, or the date of written consent to approval, as applicable.

(f) *Forty-five day period after receipt of notice of paragraph IV certification*—(1) *Computation of 45-day time clock.* The 45-day clock described in paragraph (b)(3) of this section as to each recipient required to receive notice of paragraph IV certification under §314.52 or §314.95 begins on the day after the date of receipt of the applicant's notice of paragraph IV certification by the recipient. When the 45th day falls on Saturday, Sunday, or a Federal holiday, the 45th day will be the next day that is not a Saturday, Sunday, or a Federal holiday.

(2) *Notification of filing of legal action.* (i) The 505(b)(2) or ANDA applicant must notify FDA in writing within 14 days of the filing of any legal action filed within 45 days of receipt of the notice of paragraph IV certification by any recipient. A 505(b)(2) applicant must send the notification to its NDA. An ANDA applicant must send the notification to its ANDA. The notification to FDA of the legal action must include:

(A) The 505(b)(2) application or ANDA number.

(B) The name of the 505(b)(2) or ANDA applicant.

(C) The established name of the drug product or, if no established name exists, the name(s) of the active ingredient(s), the drug product's strength, and dosage form.

(D) A statement that an action for patent infringement, identified by court, case number, and the patent number(s) of the patent(s) at issue in the action, has been filed in an appropriate court on a specified date.

(ii) A patent owner or NDA holder (or its representative(s)) may also notify FDA of the filing of any legal action for patent infringement. The notice should contain the information and be sent to the offices or divisions described in paragraph (f)(2)(i) of this section.

(iii) If the 505(b)(2) or ANDA applicant, the patent owner(s), the NDA holder, or its representative(s) does not notify FDA in writing before the expiration of the 45-day time period or the completion of the Agency's review of the 505(b)(2) application or ANDA, whichever occurs later, that a legal action for patent infringement was filed within 45 days of receipt of the notice of paragraph IV certification, the 505(b)(2) application or ANDA may be approved upon expiration of the 45-day period (if the 505(b)(2) or ANDA applicant confirms that a legal action for patent infringement has not been filed) or upon completion of the Agency's review of the 505(b)(2) application or ANDA, whichever is later.

(3) Waiver. If the patent owner or NDA holder who is an exclusive patent licensee (or its representative(s)) waives its opportunity to file a legal action for patent infringement within 45 days of a receipt of the notice of certification and the patent owner or NDA holder who is an exclusive patent licensee (or its representative(s)) submits to FDA a valid waiver before the 45 days elapse, the 505(b)(2) application or ANDA may be approved upon completion of the Agency's review of the NDA or ANDA. FDA will only accept a waiver in the following form:

> (Name of patent owner or NDA holder who is an exclusive patent licensee or its representative(s)) has received notice from *(name of applicant) under (section 505(b)(3) or 505(j)(2)(B) of the Federal Food, Drug, and Cosmetic Act)* and does not intend to file an action for patent infringement against *(name of applicant)* concerning the drug *(name of drug)* before *(date on which 45 days elapse). (Name of patent owner or NDA holder who is an exclusive patent licensee)* waives the opportunity provided by *(section 505(c)(3)(C) or 505(j)(5)(B)(iii) of the Federal Food, Drug, and Cosmetic Act)* and does not object to FDA's approval of *(name of applicant)'s (505(b)(2) application or ANDA)* for *(name of drug)* with an approval date on or after the date of this submission.

(g) Conversion of approval to tentative approval. If FDA issues an approval letter in error or a court enters an order requiring, in the case of an already approved 505(b)(2) application or ANDA, that the date of approval be delayed, FDA will convert the approval to a tentative approval if appropriate.

[81 FR 69655, Oct. 6, 2016]

§ 314.108 New drug product exclusivity.

(a) *Definitions*. The definitions in § 314.3 and the following definitions of terms apply to this section:

Approved under section 505(b) means an NDA submitted under section 505(b) and approved on or after October 10, 1962, or an application that was "deemed approved" under section 107(c)(2) of Public Law 87-781.

Bioavailability study means a study to determine the bioavailability or the pharmacokinetics of a drug.

Clinical investigation means any experiment other than a bioavailability study in which a drug is administered or dispensed to, or used on, human subjects.

Conducted or sponsored by the applicant with regard to an investigation means that before or during the investigation, the applicant was named in Form FDA-1571 filed with FDA as the sponsor of the investigational new drug application under which the investigation was conducted, or the applicant or the applicant's predecessor in interest, provided substantial support for the investigation. To demonstrate "substantial support," an applicant must either provide a certified statement from a

certified public accountant that the applicant provided 50 percent or more of the cost of conducting the study or provide an explanation why FDA should consider the applicant to have conducted or sponsored the study if the applicant's financial contribution to the study is less than 50 percent or the applicant did not sponsor the investigational new drug. A predecessor in interest is an entity, e.g., a corporation, that the applicant has taken over, merged with, or purchased, or from which the applicant has purchased all rights to the drug. Purchase of nonexclusive rights to a clinical investigation after it is completed is not sufficient to satisfy this definition.

Essential to approval means, with regard to an investigation, that there are no other data available that could support approval of the NDA.

New chemical entity means a drug that contains no active moiety that has been approved by FDA in any other NDA submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act.

New clinical investigation means an investigation in humans the results of which have not been relied on by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population and do not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness or safety in a new patient population of a previously approved drug product. For purposes of this section, data from a clinical investigation previously submitted for use in the comprehensive evaluation of the safety of a drug product but not to support the effectiveness of the drug product would be considered new.

(b) Submission of and timing of approval of a 505(b)(2) application or ANDA. (1) [Reserved]

(2) If a drug product that contains a new chemical entity was approved after September 24, 1984, in an NDA submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, no person may submit a 505(b)(2) application or ANDA under section 505(j) of the Federal Food, Drug, and Cosmetic Act for a drug product that contains the same active moiety as in the new chemical entity for a period of 5 years from the date of approval of the first approved NDA, except that the 505(b)(2) application or ANDA may be submitted after 4 years if it contains a certification of patent invalidity or noninfringement described in § 314.50(i)(1)(i)(A)(4) or § 314.94(a)(12)(i)(A)(4).

(3) The approval of a 505(b)(2) application or ANDA described in paragraph (b)(2) of this section will occur as provided in § 314.107(b)(1) or (2), unless the owner of a patent that claims the drug, the patent owner's representative, or exclusive licensee brings suit for patent infringement against the applicant during the 1-year period beginning 48 months after the date of approval of the NDA for the new chemical entity and within 45 days after receipt of the notice described at § 314.52 or § 314.95, in which case, approval of the 505(b)(2) application or ANDA will occur as provided in § 314.107(b)(3).

(4) If an NDA:

(i) Was submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act;

(ii) Was approved after September 24, 1984;

(iii) Was for a drug product that contains an active moiety that has been previously approved in another NDA under section 505(b) of the Federal Food, Drug, and Cosmetic Act; and

(iv) Contained reports of new clinical investigations (other than bioavailability studies) conducted or sponsored by the applicant that were essential to approval of the application, for a period of 3 years after the date of approval of the application, the Agency will not approve a 505(b)(2) application or an ANDA for the conditions of approval of the NDA, or an ANDA submitted pursuant to an approved petition under section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act that relies on the information supporting the conditions of approval of an original NDA.

(5) If a supplemental NDA:

(i) Was approved after September 24, 1984; and

(ii) Contained reports of new clinical investigations (other than bioavailability studies) that were conducted or sponsored by the applicant that were essential to approval of the supplemental NDA, for a period of 3 years after the date of approval of the supplemental application, the Agency will not approve a 505(b)(2) application or an ANDA for a change, or an ANDA submitted pursuant to an approved petition under section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act that relies on the information supporting a change approved in the supplemental NDA.

[59 FR 50368, Oct. 3, 1994, as amended at 81 FR 69657, Oct. 6, 2016]

§ 314.110 Complete response letter to the applicant.

(a) *Complete response letter.* FDA will send the applicant a complete response letter if the agency determines that we will not approve the application or abbreviated application in its present form for one or more of the reasons given in § 314.125 or § 314.127, respectively.

(1) *Description of specific deficiencies.* A complete response letter will describe all of the specific deficiencies that the agency has identified in an application or abbreviated application, except as stated in paragraph (a)(3) of this section.

(2) *Complete review of data.* A complete response letter reflects FDA's complete review of the data submitted in an original application or abbreviated application (or, where appropriate, a resubmission) and any amendments that the agency has reviewed. The complete response letter will identify any amendments that the agency has not yet reviewed.

(3) *Inadequate data.* If FDA determines, after an application is filed or an abbreviated application is received, that the data submitted are inadequate to support approval, the agency might issue a complete response letter without first conducting required inspections and/or reviewing proposed product labeling.

(4) *Recommendation of actions for approval.* When possible, a complete response letter will recommend actions that the applicant might take to place the application or abbreviated application in condition for approval.

(b) *Applicant actions.* After receiving a complete response letter, the applicant must take one of following actions:

(1) *Resubmission*. Resubmit the application or abbreviated application, addressing all deficiencies identified in the complete response letter.

(i) A resubmission of an application or efficacy supplement that FDA classifies as a Class 1 resubmission constitutes an agreement by the applicant to start a new 2-month review cycle beginning on the date FDA receives the resubmission.

(ii) A resubmission of an application or efficacy supplement that FDA classifies as a Class 2 resubmission constitutes an agreement by the applicant to start a new 6-month review cycle beginning on the date FDA receives the resubmission.

(iii) A resubmission of an NDA supplement other than an efficacy supplement constitutes an agreement by the applicant to start a new review cycle the same length as the initial review cycle for the supplement (excluding any extension due to a major amendment of the initial supplement), beginning on the date FDA receives the resubmission.

(iv) A major resubmission of an abbreviated application constitutes an agreement by the applicant to start a new 6-month review cycle beginning on the date FDA receives the resubmission.

(v) A minor resubmission of an abbreviated application constitutes an agreement by the applicant to start a new review cycle beginning on the date FDA receives the resubmission.

(2) *Withdrawal*. Withdraw the application or abbreviated application. A decision to withdraw an application or abbreviated application is without prejudice to a subsequent submission.

(3) *Request opportunity for hearing.* Ask the agency to provide the applicant an opportunity for a hearing on the question of whether there are grounds for denying approval of the application or abbreviated application under section 505(d) or (j)(4) of the act, respectively. The applicant must submit the request to the Associate Director for Policy, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993. Within 60 days of the date of the request for an opportunity for a hearing, or within a different time period to which FDA and the applicant agree, the agency will either approve the application or abbreviated application under § 314.105, or refuse to approve the application under § 314.125 or abbreviated application under § 314.127 and give the applicant written notice of an opportunity for a hearing under § 314.200 and section 505(c)(1)(B) or (j)(5)(c) of the act on the question of whether there are grounds for denying approval of the application or abbreviated application under section 505(d) or (j)(4) of the act, respectively.

(c) *Failure to take action.* (1) An applicant agrees to extend the review period under section 505(c)(1) or (j)(5)(A) of the act until it takes any of the actions listed in paragraph (b) of this section. For an application or abbreviated application, FDA may consider an applicant's failure to take any of such actions within 1 year after issuance of a complete response letter to be a request by the applicant to withdraw the application, unless the applicant has requested an extension of time in which to resubmit the application. FDA will grant any reasonable request for such an extension. FDA may consider an applicant's failure to resubmit the application within the extended time period or to request an additional extension to be a request by the applicant to withdraw the application.

(2) If FDA considers an applicant's failure to take action in accordance with paragraph (c)(1) of this section to be a request to withdraw the application, the agency will notify the applicant in writing. The applicant will have 30 days from the date of the notification to explain why the application should not be withdrawn and to request an extension of time in which to resubmit the application. FDA will grant any reasonable request for an extension. If the applicant does not respond to the notification within 30 days, the application will be deemed to be withdrawn.

[73 FR 39609, July 10, 2008]

§ 314.120 [Reserved]

§ 314.122 Submitting an abbreviated application for, or a 505(j)(2)(C) petition that relies on, a listed drug that is no longer marketed.

(a) An abbreviated new drug application that refers to, or a petition under section 505(j)(2)(C) of the act and § 314.93 that relies on, a listed drug that has been voluntarily withdrawn from sale in the United States must be accompanied by a petition seeking a determination whether the listed drug was withdrawn for safety or effectiveness reasons. The petition must be submitted under §§ 10.25(a) and 10.30 of this chapter and must contain all evidence available to the petitioner concerning the reasons for the withdrawal from sale.

(b) When a petition described in paragraph (a) of this section is submitted, the agency will consider the evidence in the petition and any other evidence before the agency, and determine whether the listed drug is withdrawn from sale for safety or effectiveness reasons, in accordance with the procedures in § 314.161.

(c) An abbreviated new drug application described in paragraph (a) of this section will be disapproved, under § 314.127(a)(11), and a 505(j)(2)(C) petition described in paragraph (a) of this section will be disapproved, under § 314.93(e)(1)(iv), unless the agency determines that the withdrawal of the listed drug was not for safety or effectiveness reasons.

(d) Certain drug products approved for safety and effectiveness that were no longer marketed on September 24, 1984, are not included in the list. Any person who wishes to obtain marketing approval for such a drug product under an abbreviated new drug application must petition FDA for a

determination whether the drug product was withdrawn from the market for safety or effectiveness reasons and request that the list be amended to include the drug product. A person seeking such a determination shall use the petition procedures established in § 10.30 of this chapter. The petitioner shall include in the petition information to show that the drug product was approved for safety and effectiveness and all evidence available to the petitioner concerning the reason that marketing of the drug product ceased.

[57 FR 17990, Apr. 28, 1992; 57 FR 29353, July 1, 1992]

§ 314.125 Refusal to approve an NDA.

(a) The Food and Drug Administration will refuse to approve the NDA and for a new drug give the applicant written notice of an opportunity for a hearing under § 314.200 on the question of whether there are grounds for denying approval of the NDA under section 505(d) of the Federal Food, Drug, and Cosmetic Act, if:

(1) FDA sends the applicant a complete response letter under § 314.110;

(2) The applicant requests an opportunity for hearing for a new drug on the question of whether the NDA is approvable; and

(3) FDA finds that any of the reasons given in paragraph (b) of this section apply.

(b) FDA may refuse to approve an NDA for any of the following reasons, unless the requirement has been waived under § 314.90:

(1) The methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product are inadequate to preserve its identity, strength, quality, purity, stability, and bioavailability.

(2) The investigations required under section 505(b) of the Federal Food, Drug, and Cosmetic Act do not include adequate tests by all methods reasonably applicable to show whether or not the drug is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling.

(3) The results of the tests show that the drug is unsafe for use under the conditions prescribed, recommended, or suggested in its proposed labeling or the results do not show that the drug product is safe for use under those conditions.

(4) There is insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling.

(5) There is a lack of substantial evidence consisting of adequate and well-controlled investigations, as defined in § 314.126, that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling.

(6) The proposed labeling is false or misleading in any particular.

(7) The NDA contains an untrue statement of a material fact.

(8) The drug product's proposed labeling does not comply with the requirements for labels and labeling in part 201.

(9) The NDA does not contain bioavailability or bioequivalence data required under part 320 of this chapter.

(10) A reason given in a letter refusing to file the NDA under § 314.101(d), if the deficiency is not corrected.

(11) The drug will be manufactured in whole or in part in an establishment that is not registered and not exempt from registration under section 510 of the Federal Food, Drug, and Cosmetic Act and part 207.

(12) The applicant does not permit a properly authorized officer or employee of the Department of Health and Human Services an adequate opportunity to inspect the facilities, controls, and any records relevant to the NDA.

(13) The methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product do not comply with the current good manufacturing practice regulations in parts 210 and 211.

(14) The NDA does not contain an explanation of the omission of a report of any investigation of the drug product sponsored by the applicant, or an explanation of the omission of other information about the drug pertinent to an evaluation of the NDA that is received or otherwise obtained by the applicant from any source.

(15) A nonclinical laboratory study that is described in the NDA and that is essential to show that the drug is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling was not conducted in compliance with the good laboratory practice regulations in part 58 of this chapter and no reason for the noncompliance is provided or, if it is, the differences between the practices used in conducting the study and the good laboratory practice regulations do not support the validity of the study.

(16) Any clinical investigation involving human subjects described in the NDA, subject to the institutional review board regulations in part 56 of this chapter or informed consent regulations in part 50 of this chapter, was not conducted in compliance with those regulations such that the rights or safety of human subjects were not adequately protected.

(17) The applicant or contract research organization that conducted a bioavailability or bioequivalence study described in § 320.38 or § 320.63 of this chapter that is contained in the NDA refuses to permit an inspection of facilities or records relevant to the study by a properly authorized officer or employee of the Department of Health and Human Services or refuses to submit reserve samples of the drug products used in the study when requested by FDA.

(18) For a new drug, the NDA failed to contain the patent information required by section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act.

(19) The 505(b)(2) application failed to contain a patent certification or statement with respect to each listed patent for a drug product approved in an NDA that:

(i) Is pharmaceutically equivalent to the drug product for which the original 505(b)(2) application is submitted; and

(ii) Was approved before the original 505(b)(2) application was submitted.

(c) For drugs intended to treat life-threatening or severely-debilitating illnesses that are developed in accordance with §§ 312.80 through 312.88 of this chapter, the criteria contained in paragraphs (b) (3), (4), and (5) of this section shall be applied according to the considerations contained in § 312.84 of this chapter.

[50 FR 7493, Feb. 22, 1985, as amended at 53 FR 41524, Oct. 21, 1988; 57 FR 17991, Apr. 28, 1992; 58 FR 25926, Apr. 28, 1993; 64 FR 402, Jan. 5, 1999; 73 FR 39610, July 10, 2008; 74 FR 9766, Mar. 6, 2009; 81 FR 60221, Aug. 31, 2016; 81 FR 69658, Oct. 6, 2016]

§ 314.126 Adequate and well-controlled studies.

(a) The purpose of conducting clinical investigations of a drug is to distinguish the effect of a drug from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation. The characteristics described in paragraph (b) of this section have been developed over a period of years and are recognized by the scientific community as the essentials of an adequate and well-controlled clinical investigation. The Food and Drug Administration considers these characteristics in determining whether an investigation is adequate and well-controlled for

purposes of section 505 of the act. Reports of adequate and well-controlled investigations provide the primary basis for determining whether there is "substantial evidence" to support the claims of effectiveness for new drugs. Therefore, the study report should provide sufficient details of study design, conduct, and analysis to allow critical evaluation and a determination of whether the characteristics of an adequate and well-controlled study are present.

(b) An adequate and well-controlled study has the following characteristics:

(1) There is a clear statement of the objectives of the investigation and a summary of the proposed or actual methods of analysis in the protocol for the study and in the report of its results. In addition, the protocol should contain a description of the proposed methods of analysis, and the study report should contain a description of the methods of analysis ultimately used. If the protocol does not contain a description of the proposed methods of analysis, the study report should describe how the methods used were selected.

(2) The study uses a design that permits a valid comparison with a control to provide a quantitative assessment of drug effect. The protocol for the study and report of results should describe the study design precisely; for example, duration of treatment periods, whether treatments are parallel, sequential, or crossover, and whether the sample size is predetermined or based upon some interim analysis. Generally, the following types of control are recognized:

(i) *Placebo concurrent control.* The test drug is compared with an inactive preparation designed to resemble the test drug as far as possible. A placebo-controlled study may include additional treatment groups, such as an active treatment control or a dose-comparison control, and usually includes randomization and blinding of patients or investigators, or both.

(ii) *Dose-comparison concurrent control.* At least two doses of the drug are compared. A dose-comparison study may include additional treatment groups, such as placebo control or active control. Dose-comparison trials usually include randomization and blinding of patients or investigators, or both.

(iii) *No treatment concurrent control.* Where objective measurements of effectiveness are available and placebo effect is negligible, the test drug is compared with no treatment. No treatment concurrent control trials usually include randomization.

(iv) *Active treatment concurrent control.* The test drug is compared with known effective therapy; for example, where the condition treated is such that administration of placebo or no treatment would be contrary to the interest of the patient. An active treatment study may include additional treatment groups, however, such as a placebo control or a dose-comparison control. Active treatment trials usually include randomization and blinding of patients or investigators, or both. If the intent of the trial is to show similarity of the test and control drugs, the report of the study should assess the ability of the study to have detected a difference between treatments. Similarity of test drug and active control can mean either that both drugs were effective or that neither was effective. The analysis of the study should explain why the drugs should be considered effective in the study, for example, by reference to results in previous placebo-controlled studies of the active control drug.

(v) *Historical control.* The results of treatment with the test drug are compared with experience historically derived from the adequately documented natural history of the disease or condition, or from the results of active treatment, in comparable patients or populations. Because historical control populations usually cannot be as well assessed with respect to pertinent variables as can concurrent control populations, historical control designs are usually reserved for special circumstances. Examples include studies of diseases with high and predictable mortality (for example, certain malignancies) and studies in which the effect of the drug is self-evident (general anesthetics, drug metabolism).

(3) The method of selection of subjects provides adequate assurance that they have the disease or condition being studied, or evidence of susceptibility and exposure to the condition against which prophylaxis is directed.

(4) The method of assigning patients to treatment and control groups minimizes bias and is intended to assure comparability of the groups with respect to pertinent variables such as age, sex, severity of disease, duration of disease, and use of drugs or therapy other than the test drug. The protocol for the study and the report of its results should describe how subjects were assigned to groups. Ordinarily, in a concurrently controlled study, assignment is by randomization, with or without stratification.

(5) Adequate measures are taken to minimize bias on the part of the subjects, observers, and analysts of the data. The protocol and report of the study should describe the procedures used to accomplish this, such as blinding.

(6) The methods of assessment of subjects' response are well-defined and reliable. The protocol for the study and the report of results should explain the variables measured, the methods of observation, and criteria used to assess response.

(7) There is an analysis of the results of the study adequate to assess the effects of the drug. The report of the study should describe the results and the analytic methods used to evaluate them, including any appropriate statistical methods. The analysis should assess, among other things, the comparability of test and control groups with respect to pertinent variables, and the effects of any interim data analyses performed.

(c) The Director of the Center for Drug Evaluation and Research may, on the Director's own initiative or on the petition of an interested person, waive in whole or in part any of the criteria in paragraph (b) of this section with respect to a specific clinical investigation, either prior to the investigation or in the evaluation of a completed study. A petition for a waiver is required to set forth clearly and concisely the specific criteria from which waiver is sought, why the criteria are not reasonably applicable to the particular clinical investigation, what alternative procedures, if any, are to be, or have been employed, and what results have been obtained. The petition is also required to state why the clinical investigations so conducted will yield, or have yielded, substantial evidence of effectiveness, notwithstanding nonconformance with the criteria for which waiver is requested.

(d) For an investigation to be considered adequate for approval of a new drug, it is required that the test drug be standardized as to identity, strength, quality, purity, and dosage form to give significance to the results of the investigation.

(e) Uncontrolled studies or partially controlled studies are not acceptable as the sole basis for the approval of claims of effectiveness. Such studies carefully conducted and documented, may provide corroborative support of well-controlled studies regarding efficacy and may yield valuable data regarding safety of the test drug. Such studies will be considered on their merits in the light of the principles listed here, with the exception of the requirement for the comparison of the treated subjects with controls. Isolated case reports, random experience, and reports lacking the details which permit scientific evaluation will not be considered.

[50 FR 7493, Feb. 22, 1985, as amended at 50 FR 21238, May 23, 1985; 55 FR 11580, Mar. 29, 1990; 64 FR 402, Jan. 5, 1999; 67 FR 9586, Mar. 4, 2002]

§ 314.127 Refusal to approve an ANDA.

(a) FDA will refuse to approve an ANDA for a new drug under section 505(j) of the Federal Food, Drug, and Cosmetic Act for any of the following reasons, unless the requirement has been waived under § 314.99:

(1) The methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug product are inadequate to ensure and preserve its identity, strength, quality, and purity.

(2) Information submitted with the ANDA is insufficient to show that each of the proposed conditions of use has been previously approved for the listed drug referred to in the ANDA.

(3)(i) If the reference listed drug has only one active ingredient, information submitted with the ANDA is insufficient to show that the active ingredient is the same as that of the reference listed drug;

(ii) If the reference listed drug has more than one active ingredient, information submitted with the ANDA is insufficient to show that the active ingredients are the same as the active ingredients of the reference listed drug; or

(iii) If the reference listed drug has more than one active ingredient and if the ANDAis for a drug product that has an active ingredient different from the reference listed drug:

(A) Information submitted with the ANDA is insufficient to show:

(1) That the other active ingredients are the same as the active ingredients of the reference listed drug; or

(2) That the different active ingredient is an active ingredient of a listed drug or a drug that does not meet the requirements of section 201(p) of the Federal Food, Drug, and Cosmetic Act; or

(B) No petition to submit an ANDA for the drug product with the different active ingredient was approved under § 314.93.

(4)(i) If the ANDA is for a drug product whose route of administration, dosage form, or strength purports to be the same as that of the listed drug referred to in the ANDA, information submitted in the abbreviated new drug application is insufficient to show that the route of administration, dosage form, or strength is the same as that of the reference listed drug; or

(ii) If the ANDA is for a drug product whose route of administration, dosage form, or strength is different from that of the listed drug referred to in the application, no petition to submit an ANDA for the drug product with the different route of administration, dosage form, or strength was approved under § 314.93.

(5) If the ANDA was submitted under the approval of a petition under § 314.93, the ANDA did not contain the information required by FDA with respect to the active ingredient, route of administration, dosage form, or strength that is not the same as that of the reference listed drug.

(6)(i) Information submitted in the ANDA is insufficient to show that the drug product is bioequivalent to the listed drug referred to in the ANDA; or

(ii) If the ANDA was submitted under a petition approved under § 314.93, information submitted in the ANDA is insufficient to show that the active ingredients of the drug product are of the same pharmacological or therapeutic class as those of the reference listed drug and that the drug product can be expected to have the same therapeutic effect as the reference listed drug when administered to patients for each condition of use approved for the reference listed drug.

(7) Information submitted in the ANDA is insufficient to show that the labeling proposed for the drug is the same as the labeling approved for the listed drug referred to in the ANDA except for changes required because of differences approved in a petition under § 314.93 or because the drug product and the reference listed drug are produced or distributed by different manufacturers or because aspects of the listed drug's labeling are protected by patent, or by exclusivity, and such differences do not render the proposed drug product less safe or effective than the listed drug for all remaining, nonprotected conditions of use.

(8)(i) Information submitted in the ANDA or any other information available to FDA shows that:

(A) The inactive ingredients of the drug product are unsafe for use, as described in paragraph (a)(8)(ii) of this section, under the conditions prescribed, recommended, or suggested in the labeling proposed for the drug product; or

(B) The composition of the drug product is unsafe, as described in paragraph (a)(8)(ii) of this section, under the conditions prescribed, recommended, or suggested in the proposed labeling because of the type or quantity of inactive ingredients included or the manner in which the inactive ingredients are included.

(ii)(A) FDA will consider the inactive ingredients or composition of a drug product unsafe and refuse to approve an ANDA under paragraph (a)(8)(i) of this section if, on the basis of information available to the agency, there is a reasonable basis to conclude that one or more of the inactive ingredients of the proposed drug or its composition raises serious questions of safety or efficacy. From its experience with reviewing inactive ingredients, and from other information available to it, FDA may identify changes in inactive ingredients or composition that may adversely affect a drug product's safety or efficacy. The inactive ingredients or composition of a proposed drug product will be considered to raise serious questions of safety or efficacy if the product incorporates one or more of these changes. Examples of the changes that may raise serious questions of safety or efficacy include, but are not limited to, the following:

(1) A change in an inactive ingredient so that the product does not comply with an official compendium.

(2) A change in composition to include an inactive ingredient that has not been previously approved in a drug product for human use by the same route of administration.

(3) A change in the composition of a parenteral drug product to include an inactive ingredient that has not been previously approved in a parenteral drug product.

(4) A change in composition of a drug product for ophthalmic use to include an inactive ingredient that has not been previously approved in a drug for ophthalmic use.

(5) The use of a delivery or a modified release mechanism never before approved for the drug.

(6) A change in composition to include a significantly greater content of one or more inactive ingredients than previously used in the drug product.

(7) If the drug product is intended for topical administration, a change in the properties of the vehicle or base that might increase absorption of certain potentially toxic active ingredients thereby affecting the safety of the drug product, or a change in the lipophilic properties of a vehicle or base, e.g., a change from an oleaginous to a water soluble vehicle or base.

(B) FDA will consider an inactive ingredient in, or the composition of, a drug product intended for parenteral use to be unsafe and will refuse to approve the ANDA unless it contains the same inactive ingredients, other than preservatives, buffers, and antioxidants, in the same concentration as the listed drug, and, if it differs from the listed drug in a preservative, buffer, or antioxidant, the ANDA contains sufficient information to demonstrate that the difference does not affect the safety or efficacy of the drug product.

(C) FDA will consider an inactive ingredient in, or the composition of, a drug product intended for ophthalmic or otic use unsafe and will refuse to approve the ANDA unless it contains the same inactive ingredients, other than preservatives, buffers, substances to adjust tonicity, or thickening agents, in the same concentration as the listed drug, and if it differs from the listed drug in a preservative, buffer, substance to adjust tonicity, or thickening agent, the ANDA contains sufficient information to demonstrate that the difference does not affect the safety or efficacy of the drug product and the labeling does not claim any therapeutic advantage over or difference from the listed drug.

(9) Approval of the listed drug referred to in the ANDA has been withdrawn or suspended for grounds described in § 314.150(a) or FDA has published a notice of opportunity for hearing to withdraw approval of the reference listed drug under § 314.150(a).

(10) Approval of the listed drug referred to in the ANDA has been withdrawn under § 314.151 or FDA has proposed to withdraw approval of the reference listed drug under § 314.151(a).

(11) FDA has determined that the reference listed drug has been withdrawn from sale for safety or effectiveness reasons under § 314.161, or the reference listed drug has been voluntarily withdrawn from sale and the agency has not determined whether the withdrawal is for safety or effectiveness reasons, or approval of the reference listed drug has been suspended under § 314.153, or the agency has issued an initial decision proposing to suspend the reference listed drug under § 314.153(a)(1).

(12) The abbreviated new drug application does not meet any other requirement under section 505(j)(2)(A) of the Federal Food, Drug, and Cosmetic Act.

(13) The abbreviated new drug application contains an untrue statement of material fact.

(14) For an ANDA submitted pursuant to an approved petition under § 10.30 of this chapter and § 314.93, an NDA subsequently has been approved for the change described in the approved petition.

(b) FDA may refuse to approve an ANDA for a new drug if the applicant or contract research organization that conducted a bioavailability or bioequivalence study described in § 320.63 of this chapter that is contained in the ANDA refuses to permit an inspection of facilities or records relevant to the study by a properly authorized officer or employee of the Department of Health and Human Services or refuses to submit reserve samples of the drug products used in the study when requested by FDA.

[57 FR 17991, Apr. 28, 1992; 57 FR 29353, July 1, 1992, as amended at 58 FR 25927, Apr. 28, 1993; 67 FR 77672, Dec. 19, 2002; 81 FR 69658, Oct. 6, 2016]

§ 314.150 Withdrawal of approval of an application or abbreviated application.

(a) The Food and Drug Administration will notify the applicant, and, if appropriate, all other persons who manufacture or distribute identical, related, or similar drug products as defined in §§ 310.6 and 314.151(a) of this chapter and for a new drug afford an opportunity for a hearing on a proposal to withdraw approval of the application or abbreviated new drug application under section 505(e) of the act and under the procedure in § 314.200, if any of the following apply:

(1) The Secretary of Health and Human Services has suspended the approval of the application or abbreviated application for a new drug on a finding that there is an imminent hazard to the public health. FDA will promptly afford the applicant an expedited hearing following summary suspension on a finding of imminent hazard to health.

(2) FDA finds:

(i) That clinical or other experience, tests, or other scientific data show that the drug is unsafe for use under the conditions of use upon the basis of which the application or abbreviated application was approved; or

(ii) That new evidence of clinical experience, not contained in the application or not available to FDA until after the application or abbreviated application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when the application or abbreviated application was approved, evaluated together with the evidence available when the application or abbreviated application was approved, reveal that the drug is not shown to be safe for use under the conditions of use upon the basis of which the application or abbreviated application was approved; or

(iii) Upon the basis of new information before FDA with respect to the drug, evaluated together with the evidence available when the application or abbreviated application was approved, that there is a lack of substantial evidence from adequate and well-controlled investigations as defined in §314.126, that the drug will have the effect it is purported or represented to have under the conditions of use prescribed, recommended, or suggested in its labeling; or

(iv) That the application or abbreviated application contains any untrue statement of a material fact; or

(v) That the patent information prescribed by section 505(c) of the act was not submitted within 30 days after the receipt of written notice from FDA specifying the failure to submit such information; or

(b) FDA may notify the applicant, and, if appropriate, all other persons who manufacture or distribute identical, related, or similar drug products as defined in §310.6, and for a new drug afford an opportunity for a hearing on a proposal to withdraw approval of the application or abbreviated new drug application under section 505(e) of the act and under the procedure in §314.200, if the agency finds:

(1) That the applicant has failed to establish a system for maintaining required records, or has repeatedly or deliberately failed to maintain required records or to make required reports under section 505(k) or 507(g) of the act and §314.80, §314.81, or §314.98, or that the applicant has refused to permit access to, or copying or verification of, its records.

(2) That on the basis of new information before FDA, evaluated together with the evidence available when the application or abbreviated application was approved, the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are inadequate to ensure and preserve its identity, strength, quality, and purity and were not made adequate within a reasonable time after receipt of written notice from the agency.

(3) That on the basis of new information before FDA, evaluated together with the evidence available when the application or abbreviated application was approved, the labeling of the drug, based on a fair evaluation of all material facts, is false or misleading in any particular, and the labeling was not corrected by the applicant within a reasonable time after receipt of written notice from the agency.

(4) That the applicant has failed to comply with the notice requirements of section 510(j)(2) of the act.

(5) That the applicant has failed to submit bioavailability or bioequivalence data required under part 320 of this chapter.

(6) The application or abbreviated application does not contain an explanation of the omission of a report of any investigation of the drug product sponsored by the applicant, or an explanation of the omission of other information about the drug pertinent to an evaluation of the application or abbreviated application that is received or otherwise obtained by the applicant from any source.

(7) That any nonclinical laboratory study that is described in the application or abbreviated application and that is essential to show that the drug is safe for use under the conditions prescribed, recommended, or suggested in its labeling was not conducted in compliance with the good laboratory practice regulations in part 58 of this chapter and no reason for the noncompliance was provided or, if it was, the differences between the practices used in conducting the study and the good laboratory practice regulations do not support the validity of the study.

(8) Any clinical investigation involving human subjects described in the application or abbreviated application, subject to the institutional review board regulations in part 56 of this chapter or informed consent regulations in part 50 of this chapter, was not conducted in compliance with those regulations such that the rights or safety of human subjects were not adequately protected.

(9) That the applicant or contract research organization that conducted a bioavailability or bioequivalence study described in §320.38 or §320.63 of this chapter that is contained in the application or abbreviated application refuses to permit an inspection of facilities or records relevant to the study by a properly authorized officer or employee of the Department of Health and Human Services or refuses to submit reserve samples of the drug products used in the study when requested by FDA.

(10) That the labeling for the drug product that is the subject of the abbreviated new drug application is no longer consistent with that for the listed drug referred to in the abbreviated new drug application, except for differences approved in the abbreviated new drug application or those differences resulting from:

(i) A patent on the listed drug issued after approval of the abbreviated new drug application; or

(ii) Exclusivity accorded to the listed drug after approval of the abbreviated new drug application that do not render the drug product less safe or effective than the listed drug for any remaining, nonprotected condition(s) of use.

(c) FDA will withdraw approval of an application or abbreviated application if the applicant requests its withdrawal because the drug subject to the application or abbreviated application is no longer being marketed, provided none of the conditions listed in paragraphs (a) and (b) of this section applies to the drug. FDA will consider a written request for a withdrawal under this paragraph to be a waiver of an opportunity for hearing otherwise provided for in this section. Withdrawal of approval of an application or abbreviated application under this paragraph is without prejudice to refiling.

(d) FDA may notify an applicant that it believes a potential problem associated with a drug is sufficiently serious that the drug should be removed from the market and may ask the applicant to waive the opportunity for hearing otherwise provided for under this section, to permit FDA to withdraw approval of the application or abbreviated application for the product, and to remove voluntarily the product from the market. If the applicant agrees, the agency will not make a finding under paragraph (b) of this section, but will withdraw approval of the application or abbreviated application in a notice published in the Federal Register that contains a brief summary of the agency's and the applicant's views of the reasons for withdrawal.

[57 FR 17993, Apr. 28, 1992, as amended at 58 FR 25927, Apr. 28, 1993; 64 FR 402, Jan. 5, 1999]

§314.151 Withdrawal of approval of an abbreviated new drug application under section 505(j)(5) of the act.

(a) Approval of an abbreviated new drug application approved under §314.105(d) may be withdrawn when the agency withdraws approval, under §314.150(a) or under this section, of the approved drug referred to in the abbreviated new drug application. If the agency proposed to withdraw approval of a listed drug under §314.150(a), the holder of an approved application for the listed drug has a right to notice and opportunity for hearing. The published notice of opportunity for hearing will identify all drug products approved under §314.105(d) whose applications are subject to withdrawal under this section if the listed drug is withdrawn, and will propose to withdraw such drugs. Holders of approved applications for the identified drug products will be provided notice and an opportunity to respond to the proposed withdrawal of their applications as described in paragraphs (b) and (c) of this section.

(b)(1) The published notice of opportunity for hearing on the withdrawal of the listed drug will serve as notice to holders of identified abbreviated new drug applications of the grounds for the proposed withdrawal.

(2) Holders of applications for drug products identified in the notice of opportunity for hearing may submit written comments on the notice of opportunity for hearing issued on the proposed

withdrawal of the listed drug. If an abbreviated new drug application holder submits comments on the notice of opportunity for hearing and a hearing is granted, the abbreviated new drug application holder may participate in the hearing as a nonparty participant as provided for in § 12.89 of this chapter.

(3) Except as provided in paragraphs (c) and (d) of this section, the approval of an abbreviated new drug application for a drug product identified in the notice of opportunity for hearing on the withdrawal of a listed drug will be withdrawn when the agency has completed the withdrawal of approval of the listed drug.

(c)(1) If the holder of an application for a drug identified in the notice of opportunity for hearing has submitted timely comments but does not have an opportunity to participate in a hearing because a hearing is not requested or is settled, the submitted comments will be considered by the agency, which will issue an initial decision. The initial decision will respond to the comments, and contain the agency's decision whether there are grounds to withdraw approval of the listed drug and of the abbreviated new drug applications on which timely comments were submitted. The initial decision will be sent to each abbreviated new drug application holder that has submitted comments.

(2) Abbreviated new drug application holders to whom the initial decision was sent may, within 30 days of the issuance of the initial decision, submit written objections.

(3) The agency may, at its discretion, hold a limited oral hearing to resolve dispositive factual issues that cannot be resolved on the basis of written submissions.

(4) If there are no timely objections to the initial decision, it will become final at the expiration of 30 days.

(5) If timely objections are submitted, they will be reviewed and responded to in a final decision.

(6) The written comments received, the initial decision, the evidence relied on in the comments and in the initial decision, the objections to the initial decision, and, if a limited oral hearing has been held, the transcript of that hearing and any documents submitted therein, shall form the record upon which the agency shall make a final decision.

(7) Except as provided in paragraph (d) of this section, any abbreviated new drug application whose holder submitted comments on the notice of opportunity for hearing shall be withdrawn upon the issuance of a final decision concluding that the listed drug should be withdrawn for grounds as described in § 314.150(a). The final decision shall be in writing and shall constitute final agency action, reviewable in a judicial proceeding.

(8) Documents in the record will be publicly available in accordance with § 10.20(j) of this chapter. Documents available for examination or copying will be placed on public display in the Division of Dockets Management (HFA-305), Food and Drug Administration, room. 1-23, 12420 Parklawn Dr., Rockville, MD 20857, promptly upon receipt in that office.

(d) If the agency determines, based upon information submitted by the holder of an abbreviated new drug application, that the grounds for withdrawal of the listed drug are not applicable to a drug identified in the notice of opportunity for hearing, the final decision will state that the approval of the abbreviated new drug application for such drug is not withdrawn.

[57 FR 17994, Apr. 28, 1992]

§ 314.152 Notice of withdrawal of approval of an application or abbreviated application for a new drug.

If the Food and Drug Administration withdraws approval of an application or abbreviated application for a new drug, FDA will publish a notice in the Federal Register announcing the withdrawal of approval. If the application or abbreviated application was withdrawn for grounds described in

§ 314.150(a) or § 314.151, the notice will announce the removal of the drug from the list of approved drugs published under section 505(j)(6) of the act and shall satisfy the requirement of § 314.162(b).

[57 FR 17994, Apr. 28, 1992]

§ 314.153 Suspension of approval of an abbreviated new drug application.

(a) *Suspension of approval.* The approval of an abbreviated new drug application approved under § 314.105(d) shall be suspended for the period stated when:

(1) The Secretary of the Department of Health and Human Services, under the imminent hazard authority of section 505(e) of the act or the authority of this paragraph, suspends approval of a listed drug referred to in the abbreviated new drug application, for the period of the suspension;

(2) The agency, in the notice described in paragraph (b) of this section, or in any subsequent written notice given an abbreviated new drug application holder by the agency, concludes that the risk of continued marketing and use of the drug is inappropriate, pending completion of proceedings to withdraw or suspend approval under § 314.151 or paragraph (b) of this section; or

(3) The agency, under the procedures set forth in paragraph (b) of this section, issues a final decision stating the determination that the abbreviated application is suspended because the listed drug on which the approval of the abbreviated new drug application depends has been withdrawn from sale for reasons of safety or effectiveness or has been suspended under paragraph (b) of this section. The suspension will take effect on the date stated in the decision and will remain in effect until the agency determines that the marketing of the drug has resumed or that the withdrawal is not for safety or effectiveness reasons.

(b) *Procedures for suspension of abbreviated new drug applications when a listed drug is voluntarily withdrawn for safety or effectiveness reasons.* (1) If a listed drug is voluntarily withdrawn from sale, and the agency determines that the withdrawal from sale was for reasons of safety or effectiveness, the agency will send each holder of an approved abbreviated new drug application that is subject to suspension as a result of this determination a copy of the agency's initial decision setting forth the reasons for the determination. The initial decision will also be placed on file with the Division of Dockets Management (HFA-305), Food and Drug Administration, room 1-23, 12420 Parklawn Dr., Rockville, MD 20857.

(2) Each abbreviated new drug application holder will have 30 days from the issuance of the initial decision to present, in writing, comments and information bearing on the initial decision. If no comments or information is received, the initial decision will become final at the expiration of 30 days.

(3) Comments and information received within 30 days of the issuance of the initial decision will be considered by the agency and responded to in a final decision.

(4) The agency may, in its discretion, hold a limited oral hearing to resolve dispositive factual issues that cannot be resolved on the basis of written submissions.

(5) If the final decision affirms the agency's initial decision that the listed drug was withdrawn for reasons of safety or effectiveness, the decision will be published in the Federal Register in compliance with § 314.152, and will, except as provided in paragraph (b)(6) of this section, suspend approval of all abbreviated new drug applications identified under paragraph (b)(1) of this section and remove from the list the listed drug and any drug whose approval was suspended under this paragraph. The notice will satisfy the requirement of § 314.162(b). The agency's final decision and copies of materials on which it relies will also be filed with the Division of Dockets Management (address in paragraph (b)(1) of this section).

(6) If the agency determines in its final decision that the listed drug was withdrawn for reasons of safety or effectiveness but, based upon information submitted by the holder of an abbreviated new drug application, also determines that the reasons for the withdrawal of the listed drug are not relevant to the safety and effectiveness of the drug subject to such abbreviated new drug applica-

tion, the final decision will state that the approval of such abbreviated new drug application is not suspended.

(7) Documents in the record will be publicly available in accordance with § 10.20(j) of this chapter. Documents available for examination or copying will be placed on public display in the Division of Dockets Management (address in paragraph (b)(1) of this section) promptly upon receipt in that office.

[57 FR 17995, Apr. 28, 1992]

§ 314.160 Approval of an application or abbreviated application for which approval was previously refused, suspended, or withdrawn.

Upon the Food and Drug Administration's own initiative or upon request of an applicant, FDA may, on the basis of new data, approve an application or abbreviated application which it had previously refused, suspended, or withdrawn approval. FDA will publish a notice in the Federal Register announcing the approval.

[57 FR 17995, Apr. 28, 1992]

§ 314.161 Determination of reasons for voluntary withdrawal of a listed drug.

(a) A determination whether a listed drug that has been voluntarily withdrawn from sale was withdrawn for safety or effectiveness reasons may be made by the agency at any time after the drug has been voluntarily withdrawn from sale, but must be made:

(1) Prior to approving an abbreviated new drug application that refers to the listed drug;

(2) Whenever a listed drug is voluntarily withdrawn from sale and abbreviated new drug applications that referred to the listed drug have been approved; and

(3) When a person petitions for such a determination under §§ 10.25(a) and 10.30 of this chapter.

(b) Any person may petition under §§ 10.25(a) and 10.30 of this chapter for a determination whether a listed drug has been voluntarily withdrawn for safety or effectiveness reasons. Any such petition must contain all evidence available to the petitioner concerning the reason that the drug is withdrawn from sale.

(c) If the agency determines that a listed drug is withdrawn from sale for safety or effectiveness reasons, the agency will, except as provided in paragraph (d) of this section, publish a notice of the determination in the Federal Register.

(d) If the agency determines under paragraph (a) of this section that a listed drug is withdrawn from sale for safety and effectiveness reasons and there are approved abbreviated new drug applications that are subject to suspension under section 505(j)(5) of the act, FDA will initiate a proceeding in accordance with § 314.153(b).

(e) A drug that the agency determines is withdrawn for safety or effectiveness reasons will be removed from the list, under § 314.162. The drug may be relisted if the agency has evidence that marketing of the drug has resumed or that the withdrawal is not for safety or effectiveness reasons. A determination that the drug is not withdrawn for safety or effectiveness reasons may be made at any time after its removal from the list, upon the agency's initiative, or upon the submission of a petition under §§ 10.25(a) and 10.30 of this chapter. If the agency determines that the drug is not withdrawn for safety or effectiveness reasons, the agency shall publish a notice of this determination in the Federal Register. The notice will also announce that the drug is relisted, under § 314.162(c). The notice will also serve to reinstate approval of all suspended abbreviated new drug applications that referred to the listed drug.

[57 FR 17995, Apr. 28, 1992]

§ 314.162 Removal of a drug product from the list.

(a) FDA will remove a previously approved new drug product from the list for the period stated when:

(1) The agency withdraws or suspends approval of a new drug application or an abbreviated new drug application under § 314.150(a) or § 314.151 or under the imminent hazard authority of section 505(e) of the act, for the same period as the withdrawal or suspension of the application; or

(2) The agency, in accordance with the procedures in § 314.153(b) or § 314.161, issues a final decision stating that the listed drug was withdrawn from sale for safety or effectiveness reasons, or suspended under § 314.153(b), until the agency determines that the withdrawal from the market has ceased or is not for safety or effectiveness reasons.

(b) FDA will publish in the Federal Register a notice announcing the removal of a drug from the list.

(c) At the end of the period specified in paragraph (a)(1) or (a)(2) of this section, FDA will relist a drug that has been removed from the list. The agency will publish in the Federal Register a notice announcing the relisting of the drug.

[57 FR 17996, Apr. 28, 1992]

§ 314.170 Adulteration and misbranding of an approved drug.

All drugs, including those the Food and Drug Administration approves under section 505 of the act and this part, are subject to the adulteration and misbranding provisions in sections 501, 502, and 503 of the act. FDA is authorized to regulate approved new drugs by regulations issued through informal rulemaking under sections 501, 502, and 503 of the act.

[50 FR 7493, Feb. 22, 1985. Redesignated at 57 FR 17983, Apr. 28, 1992, and amended at 64 FR 402, Jan. 5, 1999]

Subpart E—Hearing Procedures for New Drugs

Source: 50 FR 7493, Feb. 22, 1985, unless otherwise noted. Redesignated at 57 FR 17983, Apr. 28, 1992.

(a) *Notice of opportunity for hearing.* The Director of the Center for Drug Evaluation and Research, Food and Drug Administration, will give the applicant, and all other persons who manufacture or distribute identical, related, or similar drug products as defined in § 310.6 of this chapter, notice and an opportunity for a hearing on the Center's proposal to refuse to approve an application or to withdraw the approval of an application or abbreviated application under section 505(e) of the act. The notice will state the reasons for the action and the proposed grounds for the order.

(1) The notice may be general (that is, simply summarizing in a general way the information resulting in the notice) or specific (that is, either referring to specific requirements in the statute and regulations with which there is a lack of compliance, or providing a detailed description and analysis of the specific facts resulting in the notice).

(2) FDA will publish the notice in the Federal Register and will state that the applicant, and other persons subject to the notice under § 310.6, who wishes to participate in a hearing, has 30 days after the date of publication of the notice to file a written notice of participation and request for hearing. The applicant, or other persons subject to the notice under § 310.6, who fails to file a written notice of participation and request for hearing within 30 days, waives the opportunity for a hearing.

(3) It is the responsibility of every manufacturer and distributor of a drug product to review every notice of opportunity for a hearing published in the Federal Register to determine whether it covers any drug product that person manufactures or distributes. Any person may request an opinion of the applicability of a notice to a specific product that may be identical, related, or similar to a product listed in a notice by writing to the Division of New Drugs and Labeling Compliance, Office of Compliance, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993-0002. A person shall request an opinion within 30 days of the date of publication of the notice to be eligible for an opportunity for a hearing under the notice. If a person requests an opinion, that person's time for filing an appearance and request for a hearing and supporting studies and analyses begins on the date the person receives the opinion from FDA.

(b) FDA will provide the notice of opportunity for a hearing to applicants and to other persons subject to the notice under § 310.6, as follows:

(1) To any person who has submitted an application or abbreviated application, by delivering the notice in person or by sending it by registered or certified mail to the last address shown in the application or abbreviated application.

(2) To any person who has not submitted an application or abbreviated application but who is subject to the notice under § 310.6 of this chapter, by publication of the notice in the Federal Register.

(c)(1) *Notice of participation and request for a hearing, and submission of studies and comments.* The applicant, or any other person subject to the notice under § 310.6, who wishes to participate in a hearing, shall file with the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, (i) within 30 days after the date of the publication of the notice (or of the date of receipt of an opinion requested under paragraph (a)(3) of this section) a written notice of participation and request for a hearing and (ii) within 60 days after the date of publication of the notice, unless a different period of time is specified in the notice of opportunity for a hearing, the studies on which the person relies to justify a hearing as specified in paragraph (d) of this section. The applicant, or other person, may incorporate by reference the raw data underlying a study if the data were previously submitted to FDA as part of an application, abbreviated application, or other report.

(2) FDA will not consider data or analyses submitted after 60 days in determining whether a hearing is warranted unless they are derived from well-controlled studies begun before the date of the notice of opportunity for hearing and the results of the studies were not available within 60 days after the date of publication of the notice. Nevertheless, FDA may consider other studies on the basis of a showing by the person requesting a hearing of inadvertent omission and hardship. The person requesting a hearing shall list in the request for hearing all studies in progress, the results of which the person intends later to submit in support of the request for a hearing. The person shall submit under paragraph (c)(1)(ii) of this section a copy of the complete protocol, a list of the participating investigators, and a brief status report of the studies.

(3) Any other interested person who is not subject to the notice of opportunity for a hearing may also submit comments on the proposal to withdraw approval of the application or abbreviated application. The comments are requested to be submitted within the time and under the conditions specified in this section.

(d) The person requesting a hearing is required to submit under paragraph (c)(1)(ii) of this section the studies (including all protocols and underlying raw data) on which the person relies to justify a hearing with respect to the drug product. Except, a person who requests a hearing on the refusal to approve an application is not required to submit additional studies and analyses if the studies upon which the person relies have been submitted in the application and in the format and containing the summaries required under § 314.50.

(1) If the grounds for FDA's proposed action concern the effectiveness of the drug, each request for hearing is required to be supported only by adequate and well-controlled clinical studies meeting all of the precise requirements of § 314.126 and, for combination drug products, § 300.50, or by other studies not meeting those requirements for which a waiver has been previously granted by FDA under § 314.126. Each person requesting a hearing shall submit all adequate and well-controlled clinical studies on the drug product, including any unfavorable analyses, views, or judgments with respect to the studies. No other data, information, or studies may be submitted.

(2) The submission is required to include a factual analysis of all the studies submitted. If the grounds for FDA's proposed action concern the effectiveness of the drug, the analysis is required to specify how each study accords, on a point-by-point basis, with each criterion required for an adequate well-controlled clinical investigation established under § 314.126 and, if the product is a combination drug product, with each of the requirements for a combination drug established in § 300.50, or the study is required to be accompanied by an appropriate waiver previously granted by FDA. If a study concerns a drug or dosage form or condition of use or mode of administration other than the one in question, that fact is required to be clearly stated. Any study conducted on the final marketed form of the drug product is required to be clearly identified.

(3) Each person requesting a hearing shall submit an analysis of the data upon which the person relies, except that the required information relating either to safety or to effectiveness may be omitted if the notice of opportunity for hearing does not raise any issue with respect to that aspect of the drug; information on compliance with § 300.50 may be omitted if the drug product is not a combination drug product. A financial certification or disclosure statement or both as required by part 54 of this chapter must accompany all clinical data submitted. FDA can most efficiently consider submissions made in the following format.

I. Safety data.

A. Animal safety data.

1. Individual active components.

a. Controlled studies.

b. Partially controlled or uncontrolled studies.

2. Combinations of the individual active components.

a. Controlled studies.

b. Partially controlled or uncontrolled studies.

B. Human safety data.

1. Individual active components.

a. Controlled studies.

b. Partially controlled or uncontrolled studies.

c. Documented case reports.

d. Pertinent marketing experiences that may influence a determination about the safety of each individual active component.

2. Combinations of the individual active components.

a. Controlled studies.

b. Partially controlled or uncontrolled studies.

c. Documented case reports.

d. Pertinent marketing experiences that may influence a determination about the safety of each individual active component.

II. Effectiveness data.

A. Individual active components: Controlled studies, with an analysis showing clearly how each study satisfies, on a point-by-point basis, each of the criteria required by § 314.126.

B. Combinations of individual active components.

1. Controlled studies with an analysis showing clearly how each study satisfies on a point-by-point basis, each of the criteria required by § 314.126.

2. An analysis showing clearly how each requirement of § 300.50 has been satisfied.

III. A summary of the data and views setting forth the medical rationale and purpose for the drug and its ingredients and the scientific basis for the conclusion that the drug and its ingredients have been proven safe and/or effective for the intended use. If there is an absence of controlled studies in the material submitted or the requirements of any element of § 300.50 or § 314.126 have not been fully met, that fact is required to be stated clearly and a waiver obtained under § 314.126 is required to be submitted.

IV. A statement signed by the person responsible for such submission that it includes in full (or incorporates by reference as permitted in § 314.200(c)(2)) all studies and information specified in § 314.200(d).

(WARNING: A willfully false statement is a criminal offense, 18 U.S.C. 1001.)

(e) *Contentions that a drug product is not subject to the new drug requirements.* A notice of opportunity for a hearing encompasses all issues relating to the legal status of each drug product subject to it, including identical, related, and similar drug products as defined in § 310.6. A notice of appearance and request for a hearing under paragraph (c)(1)(i) of this section is required to contain any contention that the product is not a new drug because it is generally recognized as safe and effective within the meaning of section 201(p) of the act, or because it is exempt from part or all of the new drug provisions of the act under the exemption for products marketed before June 25, 1938, contained in section 201(p) of the act or under section 107(c) of the Drug Amendments of 1962, or for any other reason. Each contention is required to be supported by a submission under paragraph (c)(1)(ii) of this section and the Commissioner of Food and Drugs will make an administrative determination on each contention. The failure of any person subject to a notice of opportunity for a hearing, including any person who manufactures or distributes an identical, related, or similar drug product as defined in § 310.6, to submit a notice of participation and request for hearing or to raise all such contentions constitutes a waiver of any contentions not raised.

(1) A contention that a drug product is generally recognized as safe and effective within the meaning of section 201(p) of the act is required to be supported by submission of the same quantity and quality of scientific evidence that is required to obtain approval of an application for the product, unless FDA has waived a requirement for effectiveness (under § 314.126) or safety, or both. The submission should be in the format and with the analyses required under paragraph (d) of this section. A person who fails to submit the required scientific evidence required under paragraph (d) waives the contention. General recognition of safety and effectiveness shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data and information.

(2) A contention that a drug product is exempt from part or all of the new drug provisions of the act under the exemption for products marketed before June 25, 1938, contained in section 201(p) of the act, or under section 107(c) of the Drug Amendments of 1962, is required to be supported by evidence of past and present quantitative formulas, labeling, and evidence of marketing. A person who makes such a contention should submit the formulas, labeling, and evidence of marketing in the following format.

I. Formulation.

A. A copy of each pertinent document or record to establish the exact quantitative formulation of the drug (both active and inactive ingredients) on the date of initial marketing of the drug.

B. A statement whether such formulation has at any subsequent time been changed in any manner. If any such change has been made, the exact date, nature, and rationale for each change in formulation, including any deletion or change in the concentration of any active ingredient and/or inactive ingredient, should be stated, together with a copy of each pertinent document or record to establish the date and nature of each such change, including, but not limited to, the formula which resulted from each such change. If no such change has been made, a copy of representative documents or records showing the formula at representative points in time should be submitted to support the statement.

II. Labeling.

A. A copy of each pertinent document or record to establish the identity of each item of written, printed, or graphic matter used as labeling on the date the drug was initially marketed.

B. A statement whether such labeling has at any subsequent time been discontinued or changed in any manner. If such discontinuance or change has been made, the exact date, nature, and rationale for each discontinuance or change and a copy of each pertinent document or record to establish each such discontinuance or change should be submitted, including, but not limited to, the labeling which resulted from each such discontinuance or change. If no such discontinuance or change has been made, a copy of representative documents or records showing labeling at representative points in time should be submitted to support the statement.

III. Marketing.

A. A copy of each pertinent document or record to establish the exact date the drug was initially marketed.

B. A statement whether such marketing has at any subsequent time been discontinued. If such marketing has been discontinued, the exact date of each such discontinuance should be submitted, together with a copy of each pertinent document or record to establish each such date.

IV. Verification.

A statement signed by the person responsible for such submission, that all appropriate records have been searched and to the best of that person's knowledge and belief it includes a true and accurate presentation of the facts.

(WARNING: A willfully false statement is a criminal offense, 18 U.S.C. 1001.)

(3) The Food and Drug Administration will not find a drug product, including any active ingredient, which is identical, related, or similar, as described in §310.6, to a drug product, including any active ingredient for which an application is or at any time has been effective or deemed approved, or approved under section 505 of the act, to be exempt from part or all of the new drug provisions of the act.

(4) A contention that a drug product is not a new drug for any other reason is required to be supported by submission of the factual records, data, and information that are necessary and appropriate to support the contention.

(5) It is the responsibility of every person who manufactures or distributes a drug product in reliance upon a "grandfather" provision of the act to maintain files that contain the data and information necessary fully to document and support that status.

(f) *Separation of functions.* Separation of functions commences upon receipt of a request for hearing. The Director of the Center for Drug Evaluation and Research, Food and Drug Administration, will prepare an analysis of the request and a proposed order ruling on the matter. The analysis and proposed order, the request for hearing, and any proposed order denying a hearing and response under paragraph (g) (2) or (3) of this section will be submitted to the Office of the Commissioner of Food and Drugs for review and decision. When the Center for Drug Evaluation and Research recommends denial of a hearing on all issues on which a hearing is requested, no representative of the Center will participate or advise in the review and decision by the Commissioner. When the Center for Drug Evaluation and Research recommends that a hearing be granted on one or more issues on which a hearing is requested, separation of functions terminates as to those issues, and representatives of the Center may participate or advise in the review and decision by the Commissioner on those issues. The Commissioner may modify the text of the issues, but may not deny a hearing on those issues. Separation of functions continues with respect to issues on which the Center for Drug Evaluation and Research has recommended denial of a hearing. The Commissioner will neither evaluate nor rule on the Center's recommendation on such issues and such issues will not be included in the notice of hearing. Participants in the hearing may make a motion to the presiding officer for the inclusion of any such issue in the hearing. The ruling on such a motion is subject to review in accordance with § 12.35(b). Failure to so move constitutes a waiver of the right to a hearing on such an issue. Separation of functions on all issues resumes upon issuance of a notice of hearing. The Office of the General Counsel, Department of Health and Human Services, will observe the same separation of functions.

(g) *Summary judgment.* A person who requests a hearing may not rely upon allegations or denials but is required to set forth specific facts showing that there is a genuine and substantial issue of fact that requires a hearing with respect to a particular drug product specified in the request for hearing.

(1) Where a specific notice of opportunity for hearing (as defined in paragraph (a)(1) of this section) is used, the Commissioner will enter summary judgment against a person who requests a hearing, making findings and conclusions, denying a hearing, if it conclusively appears from the face of the data, information, and factual analyses in the request for the hearing that there is no genuine and substantial issue of fact which precludes the refusal to approve the application or abbreviated application or the withdrawal of approval of the application or abbreviated application; for example, no adequate and well-controlled clinical investigations meeting each of the precise elements of § 314.126 and, for a combination drug product, § 300.50 of this chapter, showing effectiveness have been identified. Any order entering summary judgment is required to set forth the Commissioner's findings and conclusions in detail and is required to specify why each study submitted fails to meet the requirements of the statute and regulations or why the request for hearing does not raise a genuine and substantial issue of fact.

(2) When following a general notice of opportunity for a hearing (as defined in paragraph (a)(1) of this section) the Director of the Center for Drug Evaluation and Research concludes that summary judgment against a person requesting a hearing should be considered, the Director will serve upon the person requesting a hearing by registered mail a proposed order denying a hearing. This person has 60 days after receipt of the proposed order to respond with sufficient data, information, and analyses to demonstrate that there is a genuine and substantial issue of fact which justifies a hearing.

(3) When following a general or specific notice of opportunity for a hearing a person requesting a hearing submits data or information of a type required by the statute and regulations, and the Director of the Center for Drug Evaluation and Research concludes that summary judgment against the person should be considered, the Director will serve upon the person by registered mail a proposed order denying a hearing. The person has 60 days after receipt of the proposed order to respond with

sufficient data, information, and analyses to demonstrate that there is a genuine and substantial issue of fact which justifies a hearing.

(4) If review of the data, information, and analyses submitted show that the grounds cited in the notice are not valid, for example, that substantial evidence of effectiveness exists, the Commissioner will enter summary judgment for the person requesting the hearing, and rescind the notice of opportunity for hearing.

(5) If the Commissioner grants a hearing, it will begin within 90 days after the expiration of the time for requesting the hearing unless the parties otherwise agree in the case of denial of approval, and as soon as practicable in the case of withdrawal of approval.

(6) The Commissioner will grant a hearing if there exists a genuine and substantial issue of fact or if the Commissioner concludes that a hearing would otherwise be in the public interest.

(7) If the manufacturer or distributor of an identical, related, or similar drug product requests and is granted a hearing, the hearing may consider whether the product is in fact identical, related, or similar to the drug product named in the notice of opportunity for a hearing.

(8) A request for a hearing, and any subsequent grant or denial of a hearing, applies only to the drug products named in such documents.

(h) FDA will issue a notice withdrawing approval and declaring all products unlawful for drug products subject to a notice of opportunity for a hearing, including any identical, related, or similar drug product under § 310.6, for which an opportunity for a hearing is waived or for which a hearing is denied. The Commissioner may defer or stay the action pending a ruling on any related request for a hearing or pending any related hearing or other administrative or judicial proceeding.

[50 FR 7493, Feb. 22, 1985; 50 FR 14212, Apr. 11, 1985, as amended at 50 FR 21238, May 23, 1985; 55 FR 11580, Mar. 29, 1990; 57 FR 17996, Apr. 28, 1992; 59 FR 14364, Mar. 28, 1994; 63 FR 5252, Feb. 2, 1998; 67 FR 9586, Mar. 4, 2002; 68 FR 24879, May 9, 2003; 69 FR 48775, Aug. 11, 2004; 74 FR 13113, Mar. 26, 2009]

§ 314.201 Procedure for hearings.

Parts 10 through 16 apply to hearings relating to new drugs under section 505 (d) and (e) of the act.

§ 314.235 Judicial review.

(a) The Commissioner of Food and Drugs will certify the transcript and record. In any case in which the Commissioner enters an order without a hearing under § 314.200(g), the record certified by the Commissioner is required to include the requests for hearing together with the data and information submitted and the Commissioner's findings and conclusion.

(b) A manufacturer or distributor of an identical, related, or similar drug product under § 310.6 may seek judicial review of an order withdrawing approval of a new drug application, whether or not a hearing has been held, in a United States court of appeals under section 505(h) of the act.

Subpart G—Miscellaneous Provisions

Source: 50 FR 7493, Feb. 22, 1985, unless otherwise noted. Redesignated at 57 FR 17983, Apr. 28, 1992.

(a) *Imports*. (1) A new drug may be imported into the United States if: (i) It is the subject of an approved application under this part; or (ii) it complies with the regulations pertaining to investigational new drugs under part 312; and it complies with the general regulations pertaining to imports under subpart E of part 1.

(2) A drug substance intended for use in the manufacture, processing, or repacking of a new drug may be imported into the United States if it complies with the labeling exemption in § 201.122 pertaining to shipments of drug substances in domestic commerce.

(b) *Exports*. (1) A new drug may be exported if it is the subject of an approved application under this part or it complies with the regulations pertaining to investigational new drugs under part 312.

(2) A new drug substance that is covered by an application approved under this part for use in the manufacture of an approved drug product may be exported by the applicant or any person listed as a supplier in the approved application, provided the drug substance intended for export meets the specification of, and is shipped with a copy of the labeling required for, the approved drug product.

(3) Insulin or an antibiotic drug may be exported without regard to the requirements in section 802 of the act if the insulin or antibiotic drug meets the requirements of section 801(e)(1) of the act.

[50 FR 7493, Feb. 22, 1985. Redesignated at 57 FR 17983, Apr. 28, 1992, and amended at 64 FR 402, Jan. 5, 1999; 69 FR 18766, Apr. 8, 2004]

§ 314.420 Drug master files.

(a) A drug master file is a submission of information to the Food and Drug Administration by a person (the drug master file holder) who intends it to be used for one of the following purposes: To permit the holder to incorporate the information by reference when the holder submits an investigational new drug application under part 312 or submits an application or an abbreviated application or an amendment or supplement to them under this part, or to permit the holder to authorize other persons to rely on the information to support a submission to FDA without the holder having to disclose the information to the person. FDA ordinarily neither independently reviews drug master files nor approves or disapproves submissions to a drug master file. Instead, the agency customarily reviews the information only in the context of an application under part 312 or this part. A drug master file may contain information of the kind required for any submission to the agency, including information about the following:

(1) [Reserved]

(2) Drug substance, drug substance intermediate, and materials used in their preparation, or drug product;

(3) Packaging materials;

(4) Excipient, colorant, flavor, essence, or materials used in their preparation;

(5) FDA-accepted reference information. (A person wishing to submit information and supporting data in a drug master file (DMF) that is not covered by Types II through IV DMF's must first submit a letter of intent to the Drug Master File Staff, Food and Drug Administration, 5901-B Ammendale Rd., Beltsville, MD 20705-1266.) FDA will then contact the person to discuss the proposed submission.

(b) An investigational new drug application or an application, abbreviated application, amendment, or supplement may incorporate by reference all or part of the contents of any drug master file in support of the submission if the holder authorizes the incorporation in writing. Each incorporation by reference is required to describe the incorporated material by name, reference number, volume, and page number of the drug master file.

(c) A drug master file is required to be submitted in two copies. The agency has prepared guidance that provides information about how to prepare a well-organized drug master file. If the drug master file holder adds, changes, or deletes any information in the file, the holder shall notify in writing, each person authorized to reference that information. Any addition, change, or deletion of information in a drug master file (except the list required under paragraph (d) of this section) is required to be submitted in two copies and to describe by name, reference number, volume, and page number the information affected in the drug master file.

(d) The drug master file is required to contain a complete list of each person currently authorized to incorporate by reference any information in the file, identifying by name, reference number, volume, and page number the information that each person is authorized to incorporate. If the holder restricts the authorization to particular drug products, the list is required to include the name of each drug product and the application number, if known, to which the authorization applies.

(e) The public availability of data and information in a drug master file, including the availability of data and information in the file to a person authorized to reference the file, is determined under part 20 and §314.430.

[50 FR 7493, Feb. 22, 1985, as amended at 50 FR 21238, May 23, 1985; 53 FR 33122, Aug. 30, 1988; 55 FR 28380, July 11, 1990; 65 FR 1780, Jan. 12, 2000; 65 FR 56479, Sept. 19, 2000; 67 FR 9586, Mar. 4, 2002; 69 FR 13473, Mar. 23, 2004]

§314.430 Availability for public disclosure of data and information in an application or abbreviated application.

(a) The Food and Drug Administration will determine the public availability of any part of an application or abbreviated application under this section and part 20 of this chapter. For purposes of this section, the application or abbreviated application includes all data and information submitted with or incorporated by reference in the application or abbreviated application, including investigational new drug applications, drug master files under §314.420, supplements submitted under §314.70 or §314.97, reports under §314.80 or §314.98, and other submissions. For purposes of this section, safety and effectiveness data include all studies and tests of a drug on animals and humans and all studies and tests of the drug for identity, stability, purity, potency, and bioavailability.

(b) FDA will not publicly disclose the existence of an application or abbreviated application before an approval letter is sent to the applicant under §314.105 or tentative approval letter is sent to the applicant under §314.107, unless the existence of the application or abbreviated application has been previously publicly disclosed or acknowledged.

(c) If the existence of an unapproved application or abbreviated application has not been publicly disclosed or acknowledged, no data or information in the application or abbreviated application is available for public disclosure.

(d)(1) If the existence of an application or abbreviated application has been publicly disclosed or acknowledged before the agency sends an approval letter to the applicant, no data or information contained in the application or abbreviated application is available for public disclosure before the agency sends an approval letter, but the Commissioner may, in his or her discretion, disclose a summary of selected portions of the safety and effectiveness data that are appropriate for public consideration of a specific pending issue; for example, for consideration of an open session of an FDA advisory committee.

(2) Notwithstanding paragraph (d)(1) of this section, FDA will make available to the public upon request the information in the investigational new drug application that was required to be filed in Docket Number 95S-0158 in the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, for investigations involving an exception from informed consent under §50.24 of this chapter. Persons wishing to request this information shall submit a request under the Freedom of Information Act.

(e) After FDA sends an approval letter to the applicant, the following data and information in the application or abbreviated application are immediately available for public disclosure, unless the applicant shows that extraordinary circumstances exist. A list of approved applications and abbreviated applications, entitled "Approved Drug Products with Therapeutic Equivalence Evaluations," is available from the Government Printing Office, Washington, DC 20402. This list is updated monthly.

(1) [Reserved]

(2) If the application applies to a new drug, all safety and effectiveness data previously disclosed to the public as set forth in § 20.81 and a summary or summaries of the safety and effectiveness data and information submitted with or incorporated by reference in the application. The summaries do not constitute the full reports of investigations under section 505(b)(1) of the act (21 U.S.C. 355(b)(1)) on which the safety or effectiveness of the drug may be approved. The summaries consist of the following:

(i) For an application approved before July 1, 1975, internal agency records that describe safety and effectiveness data and information, for example, a summary of the basis for approval or internal reviews of the data and information, after deletion of the following:

(a) Names and any information that would identify patients or test subjects or investigators.

(b) Any inappropriate gratuitous comments unnecessary to an objective analysis of the data and information.

(ii) For an application approved on or after July 1, 1975, a Summary Basis of Approval (SBA) document that contains a summary of the safety and effectiveness data and information evaluated by FDA during the drug approval process. The SBA is prepared in one of the following ways:

(a) Before approval of the application, the applicant may prepare a draft SBA which the Center for Drug Evaluation and Research will review and may revise. The draft may be submitted with the application or as an amendment.

(b) The Center for Drug Evaluation and Research may prepare the SBA.

(3) A protocol for a test or study, unless it is shown to fall within the exemption established for trade secrets and confidential commercial information in § 20.61.

(4) Adverse reaction reports, product experience reports, consumer complaints, and other similar data and information after deletion of the following:

(i) Names and any information that would identify the person using the product.

(ii) Names and any information that would identify any third party involved with the report, such as a physician or hospital or other institution.

(5) A list of all active ingredients and any inactive ingredients previously disclosed to the public as set forth in § 20.81.

(6) An assay procedure or other analytical procedure, unless it serves no regulatory or compliance purpose and is shown to fall within the exemption established for trade secrets and confidential commercial information in § 20.61.

(7) All correspondence and written summaries of oral discussions between FDA and the applicant relating to the application, under the provisions of part 20.

(f) All safety and effectiveness data and information which have been submitted in an application and which have not previously been disclosed to the public are available to the public, upon request, at the time any one of the following events occurs unless extraordinary circumstances are shown:

(1) No work is being or will be undertaken to have the application approved.

(2) A final determination is made that the application is not approvable and all legal appeals have been exhausted.

(3) Approval of the application is withdrawn and all legal appeals have been exhausted.

(4) A final determination has been made that the drug is not a new drug.

(5) For applications submitted under section 505(b) of the act, the effective date of the approval of the first abbreviated application submitted under section 505(j) of the act which refers to such drug, or the date on which the approval of an abbreviated application under section 505(j) of the

act which refers to such drug could be made effective if such an abbreviated application had been submitted.

(6) For abbreviated applications submitted under section 505(j) of the act, when FDA sends an approval letter to the applicant.

(g) The following data and information in an application or abbreviated application are not available for public disclosure unless they have been previously disclosed to the public as set forth in § 20.81 of this chapter or they relate to a product or ingredient that has been abandoned and they do not represent a trade secret or confidential commercial or financial information under § 20.61 of this chapter:

(1) Manufacturing methods or processes, including quality control procedures.

(2) Production, sales distribution, and similar data and information, except that any compilation of that data and information aggregated and prepared in a way that does not reveal data or information which is not available for public disclosure under this provision is available for public disclosure.

(3) Quantitative or semiquantitative formulas.

(h) The compilations of information specified in § 20.117 are available for public disclosure.

[50 FR 7493, Feb. 22, 1985, as amended at 50 FR 21238, May 23, 1985; 55 FR 11580, Mar. 29, 1990; 57 FR 17996, Apr. 28, 1992; 61 FR 51530, Oct. 2, 1996; 64 FR 26698, May 13, 1998; 64 FR 402, Jan. 5, 1999; 66 FR 1832, Jan. 10, 2001; 68 FR 24879, May 9, 2003; 69 FR 18766, Apr. 8, 2004; 73 FR 39610, July 10, 2008]

§ 314.440 Addresses for applications and abbreviated applications.

(a) Applicants shall send applications, abbreviated applications, and other correspondence relating to matters covered by this part, except for products listed in paragraph (b) of this section, to the appropriate office identified below:

(1) Except as provided in paragraph (a)(4) of this section, an application under § 314.50 or § 314.54 submitted for filing should be directed to the Central Document Room, 5901-B Ammendale Rd., Beltsville, MD 20705-1266. Applicants may obtain information about folders for binding applications on the Internet at *http://www.fda.gov/cder/ddms/binders.htm*. After FDA has filed the application, the agency will inform the applicant which division is responsible for the application. Amendments, supplements, resubmissions, requests for waivers, and other correspondence about an application that has been filed should be addressed to 5901-B Ammendale Rd., Beltsville, MD 20705-1266, to the attention of the appropriate division.

(2) Except as provided in paragraph (a)(4) of this section, an abbreviated application under § 314.94, and amendments, supplements, and resubmissions should be directed to the Office of Generic Drugs (HFD-600), Center for Drug Evaluation and Research, Food and Drug Administration, Metro Park North VII, 7620 Standish Pl., Rockville, MD 20855. This includes items sent by parcel post or overnight courier service. Correspondence not associated with an abbreviated application should be addressed specifically to the intended office or division and to the person as follows: Office of Generic Drugs, Center for Drug Evaluation and Research, Food and Drug Administration, Attn: [insert name of person], Metro Park North II, HFD-[insert mail code of office or division], 7500 Standish Place, rm. 150, Rockville, MD 20855. The mail code for the Office of Generic Drugs is HFD-600, the mail codes for the Divisions of Chemistry I, II, and III are HFD-620, HFD-640, and HFD-630, respectively, and the mail code for the Division of Bioequivalence is HFD-650.

(3) A request for an opportunity for a hearing under § 314.110 on the question of whether there are grounds for denying approval of an application, except an application under paragraph (b) of this section, should be directed to the Associate Director for Policy (HFD-5).

(4) The field copy of an application, an abbreviated application, amendments, supplements, resubmissions, requests for waivers, and other correspondence about an application and an abbre-

viated application shall be sent to the applicant's home FDA district office, except that a foreign applicant shall send the field copy to the appropriate address identified in paragraphs (a)(1) and (a)(2) of this section.

(b) Applicants shall send applications and other correspondence relating to matters covered by this part for the drug products listed below to the Food and Drug Administration, Center for Biologics Evaluation and Research, Document Control Center, 10903 New Hampshire Ave., Bldg. 71, Rm. G112, Silver Spring, MD 20993-0002, except applicants shall send a request for an opportunity for a hearing under § 314.110 on the question of whether there are grounds for denying approval of an application to the Center for Biologics Evaluation and Research, ATTN: Director, at the same address.

(1) Ingredients packaged together with containers intended for the collection, processing, or storage of blood and blood components;

(2) Plasma volume expanders and hydroxyethyl starch for leukapheresis;

(3) Blood component processing solutions and shelf life extenders; and

(4) Oxygen carriers.

[50 FR 7493, Feb. 22, 1985, as amended at 50 FR 21238, May 23, 1985; 55 FR 11581, Mar. 29, 1990; 57 FR 17997, Apr. 28, 1992; 58 FR 47352, Sept. 8, 1993; 62 FR 43639, Aug. 15, 1997; 69 FR 13473, Mar. 23, 2004; 70 FR 14981, Mar. 24, 2005; 73 FR 39610, July 10, 2008; 74 FR 13113, Mar. 26, 2009; 75 FR 37295, June 29, 2010; 80 FR 18091, Apr. 3, 2015]

§ 314.445 Guidance documents.

(a) FDA has made available guidance documents under § 10.115 of this chapter to help you to comply with certain requirements of this part.

(b) The Center for Drug Evaluation and Research (CDER) maintains a list of guidance documents that apply to CDER's regulations. The list is maintained on the Internet and is published annually in the Federal Register. A request for a copy of the CDER list should be directed to the Office of Training and Communications, Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993-0002.

[65 FR 56480, Sept. 19, 2000, as amended at 74 FR 13113, Mar. 26, 2009]

Subpart H—Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses

Source: 57 FR 58958, Dec. 11, 1992, unless otherwise noted.

This subpart applies to certain new drug products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy).

[57 FR 58958, Dec. 11, 1992, as amended at 64 FR 402, Jan. 5, 1999]

§ 314.510 Approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity.

FDA may grant marketing approval for a new drug product on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. Approval under this section will be subject to the requirement that the applicant study the drug further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate

outcome. Postmarketing studies would usually be studies already underway. When required to be conducted, such studies must also be adequate and well-controlled. The applicant shall carry out any such studies with due diligence.

§ 314.520 Approval with restrictions to assure safe use.

(a) If FDA concludes that a drug product shown to be effective can be safely used only if distribution or use is restricted, FDA will require such postmarketing restrictions as are needed to assure safe use of the drug product, such as:

(1) Distribution restricted to certain facilities or physicians with special training or experience; or

(2) Distribution conditioned on the performance of specified medical procedures.

(b) The limitations imposed will be commensurate with the specific safety concerns presented by the drug product.

§ 314.530 Withdrawal procedures.

(a) For new drugs approved under §§ 314.510 and 314.520, FDA may withdraw approval, following a hearing as provided in part 15 of this chapter, as modified by this section, if:

(1) A postmarketing clinical study fails to verify clinical benefit;

(2) The applicant fails to perform the required postmarketing study with due diligence;

(3) Use after marketing demonstrates that postmarketing restrictions are inadequate to assure safe use of the drug product;

(4) The applicant fails to adhere to the postmarketing restrictions agreed upon;

(5) The promotional materials are false or misleading; or

(6) Other evidence demonstrates that the drug product is not shown to be safe or effective under its conditions of use.

(b) Notice of opportunity for a hearing. The Director of the Center for Drug Evaluation and Research will give the applicant notice of an opportunity for a hearing on the Center's proposal to withdraw the approval of an application approved under § 314.510 or § 314.520. The notice, which will ordinarily be a letter, will state generally the reasons for the action and the proposed grounds for the order.

(c) *Submission of data and information.* (1) If the applicant fails to file a written request for a hearing within 15 days of receipt of the notice, the applicant waives the opportunity for a hearing.

(2) If the applicant files a timely request for a hearing, the agency will publish a notice of hearing in the Federal Register in accordance with §§ 12.32(e) and 15.20 of this chapter.

(3) An applicant who requests a hearing under this section must, within 30 days of receipt of the notice of opportunity for a hearing, submit the data and information upon which the applicant intends to rely at the hearing.

(d) *Separation of functions.* Separation of functions (as specified in § 10.55 of this chapter) will not apply at any point in withdrawal proceedings under this section.

(e) *Procedures for hearings.* Hearings held under this section will be conducted in accordance with the provisions of part 15 of this chapter, with the following modifications:

(1) An advisory committee duly constituted under part 14 of this chapter will be present at the hearing. The committee will be asked to review the issues involved and to provide advice and recommendations to the Commissioner of Food and Drugs.

(2) The presiding officer, the advisory committee members, up to three representatives of the applicant, and up to three representatives of the Center may question any person during or at the conclusion of the person's presentation. No other person attending the hearing may question a per-

son making a presentation. The presiding officer may, as a matter of discretion, permit questions to be submitted to the presiding officer for response by a person making a presentation.

(f) *Judicial review.* The Commissioner's decision constitutes final agency action from which the applicant may petition for judicial review. Before requesting an order from a court for a stay of action pending review, an applicant must first submit a petition for a stay of action under § 10.35 of this chapter.

[57 FR 58958, Dec. 11, 1992, as amended at 64 FR 402, Jan. 5, 1999]

§ 314.540 Postmarketing safety reporting.

Drug products approved under this program are subject to the postmarketing recordkeeping and safety reporting applicable to all approved drug products, as provided in §§ 314.80 and 314.81.

§ 314.550 Promotional materials.

For drug products being considered for approval under this subpart, unless otherwise informed by the agency, applicants must submit to the agency for consideration during the preapproval review period copies of all promotional materials, including promotional labeling as well as advertisements, intended for dissemination or publication within 120 days following marketing approval. After 120 days following marketing approval, unless otherwise informed by the agency, the applicant must submit promotional materials at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.

§ 314.560 Termination of requirements.

If FDA determines after approval that the requirements established in § 314.520, § 314.530, or § 314.550 are no longer necessary for the safe and effective use of a drug product, it will so notify the applicant. Ordinarily, for drug products approved under § 314.510, these requirements will no longer apply when FDA determines that the required postmarketing study verifies and describes the drug product's clinical benefit and the drug product would be appropriate for approval under traditional procedures. For drug products approved under § 314.520, the restrictions would no longer apply when FDA determines that safe use of the drug product can be assured through appropriate labeling. FDA also retains the discretion to remove specific postapproval requirements upon review of a petition submitted by the sponsor in accordance with § 10.30.

Subpart I—Approval of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible

Source: 67 FR 37995, May 31, 2002, unless otherwise noted.

This subpart applies to certain new drug products that have been studied for their safety and efficacy in ameliorating or preventing serious or life-threatening conditions caused by exposure to lethal or permanently disabling toxic biological, chemical, radiological, or nuclear substances. This subpart applies only to those new drug products for which: Definitive human efficacy studies cannot be conducted because it would be unethical to deliberately expose healthy human volunteers to a lethal or permanently disabling toxic biological, chemical, radiological, or nuclear substance; and field trials to study the product's effectiveness after an accidental or hostile exposure have not been feasible. This subpart does not apply to products that can be approved based on efficacy standards described elsewhere in FDA's regulations (e.g., accelerated approval based on surrogate markers or clinical endpoints other than survival or irreversible morbidity), nor does it address the safety evaluation for the products to which it does apply.

§ 314.610 Approval based on evidence of effectiveness from studies in animals.

(a) FDA may grant marketing approval for a new drug product for which safety has been established and for which the requirements of § 314.600 are met based on adequate and well-controlled animal studies when the results of those animal studies establish that the drug product is reasonably likely to produce clinical benefit in humans. In assessing the sufficiency of animal data, the agency may take into account other data, including human data, available to the agency. FDA will rely on the evidence from studies in animals to provide substantial evidence of the effectiveness of these products only when:

(1) There is a reasonably well-understood pathophysiological mechanism of the toxicity of the substance and its prevention or substantial reduction by the product;

(2) The effect is demonstrated in more than one animal species expected to react with a response predictive for humans, unless the effect is demonstrated in a single animal species that represents a sufficiently well-characterized animal model for predicting the response in humans;

(3) The animal study endpoint is clearly related to the desired benefit in humans, generally the enhancement of survival or prevention of major morbidity; and

(4) The data or information on the kinetics and pharmacodynamics of the product or other relevant data or information, in animals and humans, allows selection of an effective dose in humans.

(b) Approval under this subpart will be subject to three requirements:

(1) *Postmarketing studies.* The applicant must conduct postmarketing studies, such as field studies, to verify and describe the drug's clinical benefit and to assess its safety when used as indicated when such studies are feasible and ethical. Such postmarketing studies would not be feasible until an exigency arises. When such studies are feasible, the applicant must conduct such studies with due diligence. Applicants must include as part of their application a plan or approach to postmarketing study commitments in the event such studies become ethical and feasible.

(2) *Approval with restrictions to ensure safe use.* If FDA concludes that a drug product shown to be effective under this subpart can be safely used only if distribution or use is restricted, FDA will require such postmarketing restrictions as are needed to ensure safe use of the drug product, commensurate with the specific safety concerns presented by the drug product, such as:

(i) Distribution restricted to certain facilities or health care practitioners with special training or experience;

(ii) Distribution conditioned on the performance of specified medical procedures, including medical followup; and

(iii) Distribution conditioned on specified recordkeeping requirements.

(3) Information to be provided to patient recipients. For drug products or specific indications approved under this subpart, applicants must prepare, as part of their proposed labeling, labeling to be provided to patient recipients. The patient labeling must explain that, for ethical or feasibility reasons, the drug's approval was based on efficacy studies conducted in animals alone and must give the drug's indication(s), directions for use (dosage and administration), contraindications, a description of any reasonably foreseeable risks, adverse reactions, anticipated benefits, drug interactions, and any other relevant information required by FDA at the time of approval. The patient labeling must be available with the product to be provided to patients prior to administration or dispensing of the drug product for the use approved under this subpart, if possible.

§ 314.620 Withdrawal procedures.

(a) *Reasons to withdraw approval.* For new drugs approved under this subpart, FDA may withdraw approval, following a hearing as provided in part 15 of this chapter, as modified by this section, if:

(1) A postmarketing clinical study fails to verify clinical benefit;

(2) The applicant fails to perform the postmarketing study with due diligence;

(3) Use after marketing demonstrates that postmarketing restrictions are inadequate to ensure safe use of the drug product;

(4) The applicant fails to adhere to the postmarketing restrictions applied at the time of approval under this subpart;

(5) The promotional materials are false or misleading; or

(6) Other evidence demonstrates that the drug product is not shown to be safe or effective under its conditions of use.

(b) *Notice of opportunity for a hearing.* The Director of the Center for Drug Evaluation and Research (CDER) will give the applicant notice of an opportunity for a hearing on CDER's proposal to withdraw the approval of an application approved under this subpart. The notice, which will ordinarily be a letter, will state generally the reasons for the action and the proposed grounds for the order.

(c) *Submission of data and information.* (1) If the applicant fails to file a written request for a hearing within 15 days of receipt of the notice, the applicant waives the opportunity for a hearing.

(2) If the applicant files a timely request for a hearing, the agency will publish a notice of hearing in the Federal Register in accordance with §§ 12.32(e) and 15.20 of this chapter.

(3) An applicant who requests a hearing under this section must, within 30 days of receipt of the notice of opportunity for a hearing, submit the data and information upon which the applicant intends to rely at the hearing.

(d) *Separation of functions.* Separation of functions (as specified in § 10.55 of this chapter) will not apply at any point in withdrawal proceedings under this section.

(e) *Procedures for hearings.* Hearings held under this section will be conducted in accordance with the provisions of part 15 of this chapter, with the following modifications:

(1) An advisory committee duly constituted under part 14 of this chapter will be present at the hearing. The committee will be asked to review the issues involved and to provide advice and recommendations to the Commissioner of Food and Drugs.

(2) The presiding officer, the advisory committee members, up to three representatives of the applicant, and up to three representatives of CDER may question any person during or at the conclusion of the person's presentation. No other person attending the hearing may question a person making a presentation. The presiding officer may, as a matter of discretion, permit questions to be submitted to the presiding officer for response by a person making a presentation.

(f) *Judicial review.* The Commissioner of Food and Drugs' decision constitutes final agency action from which the applicant may petition for judicial review. Before requesting an order from a court for a stay of action pending review, an applicant must first submit a petition for a stay of action under § 10.35 of this chapter.

§ 314.630 Postmarketing safety reporting.

Drug products approved under this subpart are subject to the postmarketing recordkeeping and safety reporting requirements applicable to all approved drug products, as provided in §§ 314.80 and 314.81.

§ 314.640 Promotional materials.

For drug products being considered for approval under this subpart, unless otherwise informed by the agency, applicants must submit to the agency for consideration during the preapproval review period copies of all promotional materials, including promotional labeling as well as advertisements, intended for dissemination or publication within 120 days following marketing approval. After 120 days following marketing approval, unless otherwise informed by the agency, the applicant

must submit promotional materials at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.

§ 314.650 Termination of requirements.

If FDA determines after approval under this subpart that the requirements established in §§ 314.610(b)(2), 314.620, and 314.630 are no longer necessary for the safe and effective use of a drug product, FDA will so notify the applicant. Ordinarily, for drug products approved under § 314.610, these requirements will no longer apply when FDA determines that the postmarketing study verifies and describes the drug product's clinical benefit. For drug products approved under § 314.610, the restrictions would no longer apply when FDA determines that safe use of the drug product can be ensured through appropriate labeling. FDA also retains the discretion to remove specific postapproval requirements upon review of a petition submitted by the sponsor in accordance with § 10.30 of this chapter.

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SUBCHAPTER F—BIOLOGICS

PART 600—BIOLOGICAL PRODUCTS: GENERAL

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 356c, 356e, 360, 360i, 371, 374, 379k-1; 42 U.S.C. 216, 262, 263, 263a, 264, 300aa-25.

Cross references: For U.S. Customs Service regulations relating to viruses, serums, and toxins, see 19 CFR 12.21-12.23. For U.S. Postal Service regulations relating to the admissibility to the United States mails see parts 124 and 125 of the Domestic Mail Manual, that is incorporated by reference in 39 CFR part 111.

Subpart A—General Provisions

§ 600.2 Mailing addresses.

(a) *Licensed biological products regulated by the Center for Biologics Evaluation and Research (CBER).* Unless otherwise stated in paragraph (c) of this section, or as otherwise prescribed by FDA regulation, all submissions to CBER referenced in parts 600 through 680 of this chapter, as applicable, must be sent to: Food and Drug Administration, Center for Biologics Evaluation and Research, Document Control Center, 10903 New Hampshire Ave., Bldg. 71, Rm. G112, Silver Spring, MD 20993-0002. Examples of such submissions include: Biologics license applications (BLAs) and their amendments and supplements, biological product deviation reports, fatality reports, and other correspondence. Biological products samples must not be sent to this address but must be sent to the address in paragraph (c) of this section.

(b) *Licensed biological products regulated by the Center for Drug Evaluation and Research (CDER).* Unless otherwise stated in paragraphs (b)(1), (b)(2), or (c) of this section, or as otherwise prescribed by FDA regulation, all submissions to CDER referenced in parts 600, 601, and 610 of this chapter, as applicable, must be sent to: CDER Central Document Room, Center for Drug Evaluation and Research, Food and Drug Administration, 5901B Ammendale Rd., Beltsville, MD 20705. Examples of such submissions include: BLAs and their amendments and supplements, and other correspondence.

(1) *Biological Product Deviation Reporting (CDER).* All biological product deviation reports required under § 600.14 must be sent to: Division of Compliance Risk Management and Surveillance, Office of Compliance, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993-0002.

(2) *Advertising and Promotional Labeling (CDER).* All advertising and promotional labeling supplements required under §601.12(f) of this chapter must be sent to: Division of Drug Marketing, Advertising and Communication, Center for Drug Evaluation and Research, Food and Drug Administration, 5901-B Ammendale Rd., Beltsville, MD 20705-1266.

(c) *Samples and Protocols for licensed biological products regulated by CBER or CDER.* (1) Biological product samples and/or protocols, other than radioactive biological product samples and protocols, required under §§600.13, 600.22, 601.15, 610.2, 660.6, 660.36, or 660.46 of this chapter must be sent by courier service to: Food and Drug Administration, Center for Biologics Evaluation and Research, ATTN: Sample Custodian, 10903 New Hampshire Ave., Bldg. 75, Rm. G707, Silver Spring, MD 20993-0002. The protocol(s) may be placed in the box used to ship the samples to CBER. A cover letter should not be included when submitting the protocol with the sample unless it contains pertinent information affecting the release of the lot.

(2) Radioactive biological products required under §610.2 of this chapter must be sent by courier service to: Food and Drug Administration, Center for Biologics Evaluation and Research, ATTN: Sample Custodian, c/o White Oak Radiation Safety Program, 10903 New Hampshire Ave., Bldg. 52-72, Rm. G406A, Silver Spring, MD 20993-0002.

(d) Address information for submissions to CBER and CDER other than those listed in parts 600 through 680 of this chapter are included directly in the applicable regulations.

(e) Obtain updated mailing address information for biological products regulated by CBER at *http://www.fda.gov/BiologicsBloodVaccines/default.htm*, or for biological products regulated by CDER at *http://www.fda.gov/Drugs/default.htm*.

[70 FR 14981, Mar. 24, 2005, as amended at 74 FR 13114, Mar. 26, 2009; 78 FR 19585, Apr. 2, 2013; 80 FR 18091, Apr. 3, 2015; 79 FR 33090, June 10, 2014]

§600.3 Definitions.

As used in this subchapter:

(a) *Act* means the Public Health Service Act (58 Stat. 682), approved July 1, 1944.

(b) *Secretary* means the Secretary of Health and Human Services and any other officer or employee of the Department of Health and Human Services to whom the authority involved has been delegated.

(c) *Commissioner of Food and Drugs* means the Commissioner of the Food and Drug Administration.

(d) *Center for Biologics Evaluation and Research* means Center for Biologics Evaluation and Research of the Food and Drug Administration.

(e) *State* means a State or the District of Columbia, Puerto Rico, or the Virgin Islands.

(f) *Possession* includes among other possessions, Puerto Rico and the Virgin Islands.

(g) *Products* includes biological products and trivalent organic arsenicals.

(h) *Biological product* means any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment or cure of diseases or injuries of man:

(1) A virus is interpreted to be a product containing the minute living cause of an infectious disease and includes but is not limited to filterable viruses, bacteria, rickettsia, fungi, and protozoa.

(2) A therapeutic serum is a product obtained from blood by removing the clot or clot components and the blood cells.

(3) A toxin is a product containing a soluble substance poisonous to laboratory animals or to man in doses of 1 milliliter or less (or equivalent in weight) of the product, and having the property, following the injection of non-fatal doses into an animal, of causing to be produced therein another

soluble substance which specifically neutralizes the poisonous substance and which is demonstrable in the serum of the animal thus immunized.

(4) An antitoxin is a product containing the soluble substance in serum or other body fluid of an immunized animal which specifically neutralizes the toxin against which the animal is immune.

(5) A product is analogous:

(i) To a virus if prepared from or with a virus or agent actually or potentially infectious, without regard to the degree of virulence or toxicogenicity of the specific strain used.

(ii) To a therapeutic serum, if composed of whole blood or plasma or containing some organic constituent or product other than a hormone or an amino acid, derived from whole blood, plasma, or serum.

(iii) To a toxin or antitoxin, if intended, irrespective of its source of origin, to be applicable to the prevention, treatment, or cure of disease or injuries of man through a specific immune process.

(i) *Trivalent organic arsenicals* means arsphenamine and its derivatives (or any other trivalent organic arsenic compound) applicable to the prevention, treatment, or cure of diseases or injuries of man.

(j) A product is deemed applicable to the prevention, treatment, or cure of diseases or injuries of man irrespective of the mode of administration or application recommended, including use when intended through administration or application to a person as an aid in diagnosis, or in evaluating the degree of susceptibility or immunity possessed by a person, and including also any other use for purposes of diagnosis if the diagnostic substance so used is prepared from or with the aid of a biological product.

(k) Proper name, as applied to a product, means the name designated in the license for use upon each package of the product.

(l) *Dating period* means the period beyond which the product cannot be expected beyond reasonable doubt to yield its specific results.

(m) *Expiration date* means the calendar month and year, and where applicable, the day and hour, that the dating period ends.

(n) The word *standards* means specifications and procedures applicable to an establishment or to the manufacture or release of products, which are prescribed in this subchapter or established in the biologics license application designed to insure the continued safety, purity, and potency of such products.

(o) The word *continued* as applied to the safety, purity and potency of products is interpreted to apply to the dating period.

(p) The word *safety* means the relative freedom from harmful effect to persons affected, directly or indirectly, by a product when prudently administered, taking into consideration the character of the product in relation to the condition of the recipient at the time.

(q) The word *sterility* is interpreted to mean freedom from viable contaminating microorganisms, as determined by the tests conducted under §610.12 of this chapter.

(r) *Purity* means relative freedom from extraneous matter in the finished product, whether or not harmful to the recipient or deleterious to the product. Purity includes but is not limited to relative freedom from residual moisture or other volatile substances and pyrogenic substances.

(s) The word *potency* is interpreted to mean the specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect a given result.

(t) *Manufacturer* means any legal person or entity engaged in the manufacture of a product subject to license under the act; "Manufacturer" also includes any legal person or entity who is an applicant for a license where the applicant assumes responsibility for compliance with the applicable product and establishment standards.

(u) *Manufacture* means all steps in propagation or manufacture and preparation of products and includes but is not limited to filling, testing, labeling, packaging, and storage by the manufacturer.

(v) *Location* includes all buildings, appurtenances, equipment and animals used, and personnel engaged by a manufacturer within a particular area designated by an address adequate for identification.

(w) *Establishment* has the same meaning as "facility" in section 351 of the Public Health Service Act and includes all locations.

(x) *Lot* means that quantity of uniform material identified by the manufacturer as having been thoroughly mixed in a single vessel.

(y) A *filling* refers to a group of final containers identical in all respects, which have been filled with the same product from the same bulk lot without any change that will affect the integrity of the filling assembly.

(z) *Process* refers to a manufacturing step that is performed on the product itself which may affect its safety, purity or potency, in contrast to such manufacturing steps which do not affect intrinsically the safety, purity or potency of the product.

(aa) *Selling agent or distributor* means any person engaged in the unrestricted distribution, other than by sale at retail, of products subject to license.

(bb) *Container* (referred to also as "final container") is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.

(cc) *Package* means the immediate carton, receptacle, or wrapper, including all labeling matter therein and thereon, and the contents of the one or more enclosed containers. If no package, as defined in the preceding sentence, is used, the container shall be deemed to be the package.

(dd) *Label* means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.

(ee) *Radioactive biological product* means a biological product which is labeled with a radionuclide or intended solely to be labeled with a radionuclide.

(ff) *Amendment* is the submission of information to a pending license application or supplement, to revise or modify the application as originally submitted.

(gg) *Supplement* is a request to approve a change in an approved license application.

(hh) *Distributed* means the biological product has left the control of the licensed manufacturer.

(ii) *Control* means having responsibility for maintaining the continued safety, purity, and potency of the product and for compliance with applicable product and establishment standards, and for compliance with current good manufacturing practices.

(jj) *Assess the effects of the change*, as used in § 601.12 of this chapter, means to evaluate the effects of a manufacturing change on the identity, strength, quality, purity, and potency of a product as these factors may relate to the safety or effectiveness of the product.

(kk) *Specification*, as used in § 601.12 of this chapter, means the quality standard (i.e., tests, analytical procedures, and acceptance criteria) provided in an approved application to confirm the quality of products, intermediates, raw materials, reagents, components, in-process materials, container closure systems, and other materials used in the production of a product. For the purpose of this definition, acceptance criteria means numerical limits, ranges, or other criteria for the tests described.

(ll) *Complete response letter* means a written communication to an applicant from FDA usually describing all of the deficiencies that the agency has identified in a biologics license application or supplement that must be satisfactorily addressed before it can be approved.

(mm) *Resubmission* means a submission by the biologics license applicant or supplement applicant of all materials needed to fully address all deficiencies identified in the complete response letter. A biologics license application or supplement for which FDA issued a complete response letter, but which was withdrawn before approval and later submitted again, is not a resubmission.

[38 FR 32048, Nov. 20, 1973, as amended at 40 FR 31313, July 25, 1975; 55 FR 11014, Mar. 26, 1990; 61 FR 24232, May 14, 1996; 62 FR 39901, July 24, 1997; 64 FR 56449, Oct. 20, 1999; 65 FR 66634, Nov. 7, 2000; 69 FR 18766, Apr. 8, 2004; 70 FR 14982, Mar. 24, 2005; 73 FR 39610, July 10, 2008; 77 FR 26174, May 3, 2012]

Subpart B—Establishment Standards

§ 600.10 Personnel.

(a) [Reserved]

(b) *Personnel*. Personnel shall have capabilities commensurate with their assigned functions, a thorough understanding of the manufacturing operations which they perform, the necessary training and experience relating to individual products, and adequate information concerning the application of the pertinent provisions of this subchapter to their respective functions. Personnel shall include such professionally trained persons as are necessary to insure the competent performance of all manufacturing processes.

(c) *Restrictions on personnel*—(1) *Specific duties.* Persons whose presence can affect adversely the safety and purity of a product shall be excluded from the room where the manufacture of a product is in progress.

(2) *Sterile operations.* Personnel performing sterile operations shall wear clean or sterilized protective clothing and devices to the extent necessary to protect the product from contamination.

(3) *Pathogenic viruses and spore-forming organisms.* Persons working with viruses pathogenic for man or with spore-forming microorganisms, and persons engaged in the care of animals or animal quarters, shall be excluded from areas where other products are manufactured, or such persons shall change outer clothing, including shoes, or wear protective covering prior to entering such areas.

(4) *Live vaccine work areas.* Persons may not enter a live vaccine processing area after having worked with other infectious agents in any other laboratory during the same working day. Only persons actually concerned with propagation of the culture, production of the vaccine, and unit maintenance, shall be allowed in live vaccine processing areas when active work is in progress. Casual visitors shall be excluded from such units at all times and all others having business in such areas shall be admitted only under supervision. Street clothing, including shoes, shall be replaced or covered by suitable laboratory clothing before entering a live vaccine processing unit. Persons caring for animals used in the manufacture of live vaccines shall be excluded from other animal quarters and from contact with other animals during the same working day.

[38 FR 32048, Nov. 20, 1973, as amended at 49 FR 23833, June 8, 1984; 55 FR 11014, Mar. 26, 1990; 62 FR 53538, Oct. 15, 1997; 68 FR 75119, Dec. 30, 2003]

§ 600.11 Physical establishment, equipment, animals, and care.

(a) *Work areas.* All rooms and work areas where products are manufactured or stored shall be kept orderly, clean, and free of dirt, dust, vermin and objects not required for manufacturing. Precautions shall be taken to avoid clogging and back-siphonage of drainage systems. Precautions shall be taken to exclude extraneous infectious agents from manufacturing areas. Work rooms shall be well

lighted and ventilated. The ventilation system shall be arranged so as to prevent the dissemination of microorganisms from one manufacturing area to another and to avoid other conditions unfavorable to the safety of the product. Filling rooms, and other rooms where open, sterile operations are conducted, shall be adequate to meet manufacturing needs and such rooms shall be constructed and equipped to permit thorough cleaning and to keep air-borne contaminants at a minimum. If such rooms are used for other purposes, they shall be cleaned and prepared prior to use for sterile operations. Refrigerators, incubators and warm rooms shall be maintained at temperatures within applicable ranges and shall be free of extraneous material which might affect the safety of the product.

(b) *Equipment*. Apparatus for sterilizing equipment and the method of operation shall be such as to insure the destruction of contaminating microorganisms. The effectiveness of the sterilization procedure shall be no less than that achieved by an attained temperature of 121.5 °C maintained for 20 minutes by saturated steam or by an attained temperature of 170 °C maintained for 2 hours with dry heat. Processing and storage containers, filters, filling apparatus, and other pieces of apparatus and accessory equipment, including pipes and tubing, shall be designed and constructed to permit thorough cleaning and, where possible, inspection for cleanliness. All surfaces that come in contact with products shall be clean and free of surface solids, leachable contaminants, and other materials that will hasten the deterioration of the product or otherwise render it less suitable for the intended use. For products for which sterility is a factor, equipment shall be sterile, unless sterility of the product is assured by subsequent procedures.

(c) *Laboratory and bleeding rooms.* Rooms used for the processing of products, including bleeding rooms, shall be effectively fly-proofed and kept free of flies and vermin. Such rooms shall be so constructed as to insure freedom from dust, smoke and other deleterious substances and to permit thorough cleaning and disinfection. Rooms for animal injection and bleeding, and rooms for smallpox vaccine animals, shall be disinfected and be provided with the necessary water, electrical and other services.

(d) *Animal quarters and stables.* Animal quarters, stables and food storage areas shall be of appropriate construction, fly-proofed, adequately lighted and ventilated, and maintained in a clean, vermin-free and sanitary condition. No manure or refuse shall be stored as to permit the breeding of flies on the premises, nor shall the establishment be located in close proximity to off-property manure or refuse storage capable of engendering fly breeding.

(e) *Restrictions on building and equipment use*—(1) *Work of a diagnostic nature.* Laboratory procedures of a clinical diagnostic nature involving materials that may be contaminated, shall not be performed in space used for the manufacture of products except that manufacturing space which is used only occasionally may be used for diagnostic work provided spore-forming pathogenic microorganisms are not involved and provided the space is thoroughly cleaned and disinfected before the manufacture of products is resumed.

(2) *Spore-forming organisms for supplemental sterilization procedure control test.* Spore-forming organisms used as an additional control in sterilization procedures may be introduced into areas used for the manufacture of products, only for the purposes of the test and only immediately before use for such purposes: Provided, That (i) the organism is not pathogenic for man or animals and does not produce pyrogens or toxins, (ii) the culture is demonstrated to be pure, (iii) transfer of test cultures to culture media shall be limited to the sterility test area or areas designated for work with spore-forming organisms, (iv) each culture be labeled with the name of the microorganism and the statement "Caution: microbial spores. See directions for storage, use and disposition.", and (v) the container of each culture is designed to withstand handling without breaking.

(3) *Work with spore-forming microorganisms.* (i) Manufacturing processes using spore-forming microorganisms conducted in a multiproduct manufacturing site must be performed under appro-

priate controls to prevent contamination of other products and areas within the site. Prevention of spore contamination can be achieved by using a separate dedicated building or by using process containment if manufacturing is conducted in a multiproduct manufacturing building. All product and personnel movement between the area where the spore-forming microorganisms are manufactured and other manufacturing areas must be conducted under conditions that will prevent the introduction of spores into other areas of the facility.

(ii) If process containment is employed in a multiproduct manufacturing area, procedures must be in place to demonstrate adequate removal of the spore-forming microorganism(s) from the manufacturing area for subsequent manufacture of other products. These procedures must provide for adequate removal or decontamination of the spore-forming microorganisms on and within manufacturing equipment, facilities, and ancillary room items as well as the removal of disposable or product dedicated items from the manufacturing area. Environmental monitoring specific for the spore-forming microorganism(s) must be conducted in adjacent areas during manufacturing operations and in the manufacturing area after completion of cleaning and decontamination.

(4) *Live vaccine processing.* Live vaccine processing must be performed under appropriate controls to prevent cross contamination of other products and other manufacturing areas within the building. Appropriate controls must include, at a minimum:

(i)(A) Using a dedicated manufacturing area that is either in a separate building, in a separate wing of a building, or in quarters at the blind end of a corridor and includes adequate space and equipment for all processing steps up to, but not including, filling into final containers; and

(B) Not conducting test procedures that potentially involve the presence of microorganisms other than the vaccine strains or the use of tissue culture cell lines other than primary cultures in space used for processing live vaccine; or

(ii) If manufacturing is conducted in a multiproduct manufacturing building or area, using procedural controls, and where necessary, process containment. Process containment is deemed to be necessary unless procedural controls are sufficient to prevent cross contamination of other products and other manufacturing areas within the building. Process containment is a system designed to mechanically isolate equipment or an area that involves manufacturing using live vaccine organisms. All product, equipment, and personnel movement between distinct live vaccine processing areas and between live vaccine processing areas and other manufacturing areas, up to, but not including, filling in final containers, must be conducted under conditions that will prevent cross contamination of other products and manufacturing areas within the building, including the introduction of live vaccine organisms into other areas. In addition, written procedures and effective processes must be in place to adequately remove or decontaminate live vaccine organisms from the manufacturing area and equipment for subsequent manufacture of other products. Written procedures must be in place for verification that processes to remove or decontaminate live vaccine organisms have been followed.

(5) *Equipment and supplies—contamination*. Equipment and supplies used in work on or otherwise exposed to any pathogenic or potentially pathogenic agent shall be kept separated from equipment and supplies used in the manufacture of products to the extent necessary to prevent cross-contamination.

(f) *Animals used in manufacture*—(1) *Care of animals used in manufacturing.* Caretakers and attendants for animals used for the manufacture of products shall be sufficient in number and have adequate experience to insure adequate care. Animal quarters and cages shall be kept in sanitary condition. Animals on production shall be inspected daily to observe response to production procedures. Animals that become ill for reasons not related to production shall be isolated from other animals and shall not be used for production until recovery is complete. Competent veterinary care shall be provided as needed.

(2) *Quarantine of animals*—(i) *General.* No animal shall be used in processing unless kept under competent daily inspection and preliminary quarantine for a period of at least 7 days before use, or as otherwise provided in this subchapter. Only healthy animals free from detectable communicable diseases shall be used. Animals must remain in overt good health throughout the quarantine periods and particular care shall be taken during the quarantine periods to reject animals of the equine genus which may be infected with glanders and animals which may be infected with tuberculosis.

(ii) *Quarantine of monkeys.* In addition to observing the pertinent general quarantine requirements, monkeys used as a source of tissue in the manufacture of vaccine shall be maintained in quarantine for at least 6 weeks prior to use, except when otherwise provided in this part. Only monkeys that have reacted negatively to tuberculin at the start of the quarantine period and again within 2 weeks prior to use shall be used in the manufacture of vaccine. Due precaution shall be taken to prevent cross-infection from any infected or potentially infected monkeys on the premises. Monkeys to be used in the manufacture of a live vaccine shall be maintained throughout the quarantine period in cages closed on all sides with solid materials except the front which shall be screened, with no more than two monkeys housed in one cage. Cage mates shall not be interchanged.

(3) *Immunization against tetanus.* Horses and other animals susceptible to tetanus, that are used in the processing steps of the manufacture of biological products, shall be treated adequately to maintain immunity to tetanus.

(4) *Immunization and bleeding of animals used as a source of products.* Toxins or other nonviable antigens administered in the immunization of animals used in the manufacture of products shall be sterile. Viable antigens, when so used, shall be free of contaminants, as determined by appropriate tests prior to use. Injections shall not be made into horses within 6 inches of bleeding site. Horses shall not be bled for manufacturing purposes while showing persistent general reaction or local reaction near the site of bleeding. Blood shall not be used if it was drawn within 5 days of injecting the animals with viable microorganisms. Animals shall not be bled for manufacturing purposes when they have an intercurrent disease. Blood intended for use as a source of a biological product shall be collected in clean, sterile vessels. When the product is intended for use by injection, such vessels shall also be pyrogen-free.

(5) [Reserved]

(6) *Reporting of certain diseases.* In cases of actual or suspected infection with foot and mouth disease, glanders, tetanus, anthrax, gas gangrene, equine infectious anemia; equine encephalomyelitis, or any of the pock diseases among animals intended for use or used in the manufacture of products, the manufacturer shall immediately notify the Director, Center for Biologics Evaluation and Research or the Director, Center for Drug Evaluation and Research (see mailing addresses in §600.2(a) or (b)).

(7) *Monkeys used previously for experimental or test purposes.* Monkeys that have been used previously for experimental or test purposes with live microbiological agents shall not be used as a source of kidney tissue for the manufacture of vaccine. Except as provided otherwise in this subchapter, monkeys that have been used previously for other experimental or test purposes may be used as a source of kidney tissue upon their return to a normal condition, provided all quarantine requirements have been met.

(8) *Necropsy examination of monkeys.* Each monkey used in the manufacture of vaccine shall be examined at necropsy under the direction of a qualified pathologist, physician, or veterinarian having experience with diseases of monkeys, for evidence of ill health, particularly for (i) evidence of tuberculosis, (ii) presence of herpes-like lesions, including eruptions or plaques on or around the lips, in the buccal cavity or on the gums, and (iii) signs of conjunctivitis. If there are any such signs or other significant gross pathological lesions, the tissue shall not be used in the manufacture of vaccine.

(g) *Filling procedures.* Filling procedures shall be such as will not affect adversely the safety, purity or potency of the product.

(h) *Containers and closures.* All final containers and closures shall be made of material that will not hasten the deterioration of the product or otherwise render it less suitable for the intended use. All final containers and closures shall be clean and free of surface solids, leachable contaminants and other materials that will hasten the deterioration of the product or otherwise render it less suitable for the intended use. After filling, sealing shall be performed in a manner that will maintain the integrity of the product during the dating period. In addition, final containers and closures for products intended for use by injection shall be sterile and free from pyrogens. Except as otherwise provided in the regulations of this subchapter, final containers for products intended for use by injection shall be colorless and sufficiently transparent to permit visual examination of the contents under normal light. As soon as possible after filling final containers shall be labeled as prescribed in §610.60 et seq. of this chapter, except that final containers may be stored without such prescribed labeling provided they are stored in a sealed receptacle labeled both inside and outside with at least the name of the product, the lot number, and the filling identification.

[38 FR 32048, Nov. 20, 1973, as amended at 41 FR 10428, Mar. 11, 1976; 49 FR 23833, June 8, 1984; 55 FR 11013, Mar. 26, 1990; 68 FR 75119, Dec. 30, 2003; 70 FR 14982, Mar. 24, 2005; 72 FR 59003, Oct. 18, 2007; 80 FR 18092, Apr. 3, 2015]

§600.12 Records.

(a) *Maintenance of records.* Records shall be made, concurrently with the performance, of each step in the manufacture and distribution of products, in such a manner that at any time successive steps in the manufacture and distribution of any lot may be traced by an inspector. Such records shall be legible and indelible, shall identify the person immediately responsible, shall include dates of the various steps, and be as detailed as necessary for clear understanding of each step by one experienced in the manufacture of products.

(b) *Records retention*—(1) *General.* Records shall be retained for such interval beyond the expiration date as is necessary for the individual product, to permit the return of any clinical report of unfavorable reactions. The retention period shall be no less than five years after the records of manufacture have been completed or six months after the latest expiration date for the individual product, whichever represents a later date.

(2) *Records of recall.* Complete records shall be maintained pertaining to the recall from distribution of any product upon notification by the Director, Center for Biologics Evaluation and Research or the Director, Center for Drug Evaluation and Research, to recall for failure to conform with the standards prescribed in the regulations of this subchapter, because of deterioration of the product or for any other factor by reason of which the distribution of the product would constitute a danger to health.

(3) *Suspension of requirement for retention.* The Director, Center for Biologics Evaluation and Research or the Director, Center for Drug Evaluation and Research, may authorize the suspension of the requirement to retain records of a specific manufacturing step upon a showing that such records no longer have significance for the purposes for which they were made: Provided, That a summary of such records shall be retained.

(c) *Records of sterilization of equipment and supplies.* Records relating to the mode of sterilization, date, duration, temperature and other conditions relating to each sterilization of equipment and supplies used in the processing of products shall be made by means of automatic recording devices or by means of a system of recording which gives equivalent assurance of the accuracy and reliability of the record. Such records shall be maintained in a manner that permits an identification of the product with the particular manufacturing process to which the sterilization relates.

(d) *Animal necropsy records.* A necropsy record shall be kept on each animal from which a biological product has been obtained and which dies or is sacrificed while being so used.

(e) *Records in case of divided manufacturing responsibility.* If two or more establishments participate in the manufacture of a product, the records of each such establishment must show plainly the degree of its responsibility. In addition, each participating manufacturer shall furnish to the manufacturer who prepares the product in final form for sale, barter or exchange, a copy of all records relating to the manufacturing operations performed by such participating manufacturer insofar as they concern the safety, purity and potency of the lots of the product involved, and the manufacturer who prepares the product in final form shall retain a complete record of all the manufacturing operations relating to the product.

[38 FR 32048, Nov. 20, 1973, as amended at 49 FR 23833, June 8, 1984; 55 FR 11013, Mar. 26, 1990; 70 FR 14982, Mar. 24, 2005]

§ 600.13 Retention samples.

Manufacturers shall retain for a period of at least 6 months after the expiration date, unless a different time period is specified in additional standards, a quantity of representative material of each lot of each product, sufficient for examination and testing for safety and potency, except Whole Blood, Cryoprecipitated AHF, Platelets, Red Blood Cells, Plasma, and Source Plasma and Allergenic Products prepared to a physician's prescription. Samples so retained shall be selected at random from either final container material, or from bulk and final containers, provided they include at least one final container as a final package, or package-equivalent of such filling of each lot of the product as intended for distribution. Such sample material shall be stored at temperatures and under conditions which will maintain the identity and integrity of the product. Samples retained as required in this section shall be in addition to samples of specific products required to be submitted to the Center for Biologics Evaluation and Research or the Center for Drug Evaluation and Research (see mailing addresses in § 600.2). Exceptions may be authorized by the Director, Center for Biologics Evaluation and Research or the Director, Center for Drug Evaluation and Research, when the lot yields relatively few final containers and when such lots are prepared by the same method in large number and in close succession.

[41 FR 10428, Mar. 11, 1976, as amended at 49 FR 23833, June 8, 1984; 50 FR 4133, Jan. 29, 1985; 55 FR 11013, Mar. 26, 1990; 70 FR 14982, Mar. 24, 2005]

§ 600.14 Reporting of biological product deviations by licensed manufacturers.

(a) *Who must report under this section?* (1) You, the manufacturer who holds the biological product license and who had control over the product when the deviation occurred, must report under this section. If you arrange for another person to perform a manufacturing, holding, or distribution step, while the product is in your control, that step is performed under your control. You must establish, maintain, and follow a procedure for receiving information from that person on all deviations, complaints, and adverse events concerning the affected product.

(2) Exceptions:

(i) Persons who manufacture only in vitro diagnostic products that are not subject to licensing under section 351 of the Public Health Service Act do not report biological product deviations for those products under this section but must report in accordance with part 803 of this chapter;

(ii) Persons who manufacture blood and blood components, including licensed manufacturers, unlicensed registered blood establishments, and transfusion services, do not report biological product deviations for those products under this section but must report under § 606.171 of this chapter;

(iii) Persons who manufacture Source Plasma or any other blood component and use that Source Plasma or any other blood component in the further manufacture of another licensed biological product must report:

(A) Under §606.171 of this chapter, if a biological product deviation occurs during the manufacture of that Source Plasma or any other blood component; or

(B) Under this section, if a biological product deviation occurs after the manufacture of that Source Plasma or any other blood component, and during manufacture of the licensed biological product.

(b) *What do I report under this section?* You must report any event, and information relevant to the event, associated with the manufacturing, to include testing, processing, packing, labeling, or storage, or with the holding or distribution, of a licensed biological product, if that event meets all the following criteria:

(1) Either:

(i) Represents a deviation from current good manufacturing practice, applicable regulations, applicable standards, or established specifications that may affect the safety, purity, or potency of that product; or

(ii) Represents an unexpected or unforeseeable event that may affect the safety, purity, or potency of that product; and

(2) Occurs in your facility or another facility under contract with you; and

(3) Involves a distributed biological product.

(c) *When do I report under this section?* You should report a biological product deviation as soon as possible but you must report at a date not to exceed 45-calendar days from the date you, your agent, or another person who performs a manufacturing, holding, or distribution step under your control, acquire information reasonably suggesting that a reportable event has occurred.

(d) *How do I report under this section?* You must report on Form FDA-3486.

(e) *Where do I report under this section?* (1) For biological products regulated by the Center for Biologics Evaluation and Research (CBER), send the completed Form FDA 3486 to the CBER Document Control Center (see mailing address in §600.2(a)), or submit electronically using CBER's electronic Web-based application.

(2) For biological products regulated by the Center for Drug Evaluation and Research (CDER), send the completed Form FDA-3486 to the Division of Compliance Risk Management and Surveillance (HFD-330) (see mailing addresses in §600.2). CDER does not currently accept electronic filings.

(3) If you make a paper filing, you should identify on the envelope that a biological product deviation report (BPDR) is enclosed.

(f) *How does this regulation affect other FDA regulations?* This part supplements and does not supersede other provisions of the regulations in this chapter. All biological product deviations, whether or not they are required to be reported under this section, should be investigated in accordance with the applicable provisions of parts 211 and 820 of this chapter.

[65 FR 66634, Nov. 7, 2000, as amended at 70 FR 14982, Mar. 24, 2005; 80 FR 18092, Apr. 3, 2015]

§600.15 Temperatures during shipment.

The following products shall be maintained during shipment at the specified temperatures:

(a) *Products*.

Product	Temperature
Cryoprecipitated AHF	−18 °C or colder.
Measles and Rubella Virus Vaccine Live	10 °C or colder.
Measles Live and Smallpox Vaccine	Do.

Measles, Mumps, and Rubella Virus Vaccine Live	Do.
Measles and Mumps Virus Vaccine Live	Do.
Measles Virus Vaccine Live	Do.
Mumps Virus Vaccine Live	Do.
Fresh Frozen Plasma	−18 °C or colder.
Liquid Plasma	1 to 10 °C.
Plasma	−18 °C or colder.
Platelet Rich Plasma	Between 1 and 10 °C if the label indicates storage between 1 and 6 °C, or all reasonable methods to maintain the temperature as close as possible to a range between 20 and 24 °C, if the label indicates storage between 20 and 24 °C.
Platelets	Between 1 and 10 °C if the label indicates storage between 1 and 6 °C, or all reasonable methods to maintain the temperature as close as possible to a range between 20 to 24 °C, if the label indicates storage between 20 and 24 °C.
Poliovirus Vaccine Live Oral Trivalent	0 °C or colder.
Poliovirus Vaccine Live Oral Type I	Do.
Poliovirus Vaccine Live Oral Type II	Do.
Poliovirus Vaccine Live Oral Type III	Do.
Red Blood Cells (liquid product)	Between 1 and 10 °C.
Red Blood Cells Frozen	−65 °C or colder.
Rubella and Mumps Virus Vaccine Live	10 °C or colder.
Rubella Virus Vaccine Live	Do.
Smallpox Vaccine (Liquid Product)	0 °C or colder.
Source Plasma	−5 °C or colder.
Source Plasma Liquid	10 °C or colder.
Whole Blood	Blood that is transported from the collecting facility to the processing facility shall be transported in an environment capable of continuously cooling the blood toward a temperature range of 1 to 10 °C, or at a temperature as close as possible to 20 to 24 °C for a period not to exceed 6 hours. Blood transported from the storage facility shall be placed in an appropriate environment to maintain a temperature range between 1 to 10 °C during shipment.
Yellow Fever Vaccine	0 °C or colder.

(b) *Exemptions*. Exemptions or modifications shall be made only upon written approval, in the form of a supplement to the biologics license application, approved by the Director, Center for Biologics Evaluation and Research.

[39 FR 39872, Nov. 12, 1974, as amended at 49 FR 23833, June 8, 1984; 50 FR 4133, Jan. 29, 1985; 50 FR 9000, Mar. 6, 1985; 55 FR 11013, Mar. 26, 1990; 59 FR 49351, Sept. 28, 1994; 64 FR 56449, Oct. 20, 1999]

Subpart C—Establishment Inspection

§ 600.20 Inspectors.

Inspections shall be made by an officer of the Food and Drug Administration having special knowledge of the methods used in the manufacture and control of products and designated for such purposes by the Commissioner of Food and Drugs, or by any officer, agent, or employee of the Department of Health and Human Services specifically designated for such purpose by the Secretary.

[38 FR 32048, Nov. 20, 1973]

§ 600.21 Time of inspection.

Link to an amendment published at 83 FR 3589, Jan. 26, 2018.

The inspection of an establishment for which a biologics license application is pending need not be made until the establishment is in operation and is manufacturing the complete product for which a biologics license is desired. In case the license is denied following inspection for the original license, no reinspection need be made until assurance has been received that the faulty conditions which were the basis of the denial have been corrected. An inspection of each licensed establishment and its additional location(s) shall be made at least once every 2 years. Inspections may be made with or without notice, and shall be made during regular business hours unless otherwise directed.

[38 FR 32048, Nov. 20, 1973, as amended at 48 FR 26314, June 7, 1983; 64 FR 56449, Oct. 20, 1999]

Effective date note: At 83 FR 3589, Jan. 26, 2018, § 600.21 was amended by removing the last three sentences, effective June 11, 2018.

§ 600.22 Duties of inspector.

Link to an amendment published at 83 FR 3589, Jan. 26, 2018.

The inspector shall:

(a) Call upon the active head of the establishment, stating the object of his visit,

(b) Interrogate the proprietor or other personnel of the establishment as he may deem necessary,

(c) Examine the details of location, construction, equipment and maintenance, including stables, barns, warehouses, manufacturing laboratories, bleeding clinics maintained for the collection of human blood, shipping rooms, record rooms, and any other structure or appliance used in any part of the manufacture of a product,

(d) Investigate as fully as he deems necessary the methods of propagation, processing, testing, storing, dispensing, recording, or other details of manufacture and distribution of each licensed product, or product for which a license has been requested, including observation of these procedures in actual operation,

(e) Obtain and cause to be sent to the Director, Center for Biologics Evaluation and Research or the Director, Center for Drug Evaluation and Research (see mailing addresses in § 600.2(c)), adequate samples for the examination of any product or ingredient used in its manufacture,

(f) Bring to the attention of the manufacturer any fault observed in the course of inspection in location, construction, manufacturing methods, or administration of a licensed establishment which might lead to impairment of a product,

(g) Inspect and copy, as circumstances may require, any records required to be kept pursuant to §600.12,

(h) Certify as to the condition of the establishment and of the manufacturing methods followed and make recommendations as to action deemed appropriate with respect to any application for license or any license previously issued.

[38 FR 32048, Nov. 20, 1973, as amended at 49 FR 23833, June 8, 1984; 55 FR 11013, Mar. 26, 1990; 70 FR 14982, Mar. 24, 2005; 80 FR 18092, Apr. 3, 2015]

Effective date note: At 83 FR 3589, Jan. 26, 2018, §600.22 was removed, effective June 11, 2018.

Subpart D—Reporting of Adverse Experiences

Source: 59 FR 54042, Oct. 27, 1994, unless otherwise noted.

(a) *Definitions*. The following definitions of terms apply to this section:

Adverse experience. Any adverse event associated with the use of a biological product in humans, whether or not considered product related, including the following: An adverse event occurring in the course of the use of a biological product in professional practice; an adverse event occurring from overdose of the product whether accidental or intentional; an adverse event occurring from abuse of the product; an adverse event occurring from withdrawal of the product; and any failure of expected pharmacological action.

Blood Component. As defined in §606.3(c) of this chapter.

Disability. A substantial disruption of a person's ability to conduct normal life functions.

Individual case safety report (ICSR). A description of an adverse experience related to an individual patient or subject.

ICSR attachments. Documents related to the adverse experience described in an ICSR, such as medical records, hospital discharge summaries, or other documentation.

Life-threatening adverse experience. Any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred, i.e., it does not include an adverse experience that, had it occurred in a more severe form, might have caused death.

Serious adverse experience. Any adverse experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Unexpected adverse experience: Any adverse experience that is not listed in the current labeling for the biological product. This includes events that may be symptomatically and pathophysiologically related to an event listed in the labeling, but differ from the event because of greater severity

or specificity. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the labeling only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the labeling only listed cerebral vascular accidents. "Unexpected," as used in this definition, refers to an adverse experience that has not been previously observed (i.e., included in the labeling) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

(b) Review of adverse experiences. Any person having a biologics license under §601.20 of this chapter must promptly review all adverse experience information pertaining to its product obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from commercial marketing experience, postmarketing clinical investigations, postmarketing epidemiological/surveillance studies, reports in the scientific literature, and unpublished scientific papers. Applicants are not required to resubmit to FDA adverse product experience reports forwarded to the applicant by FDA; applicants, however, must submit all followup information on such reports to FDA. Any person subject to the reporting requirements under paragraph (c) of this section must also develop written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse experiences to FDA.

(c) Reporting requirements. The applicant must submit to FDA postmarketing 15-day Alert reports and periodic safety reports pertaining to its biological product as described in this section. These reports must be submitted to the Agency in electronic format as described in paragraph (h)(1) of this section, except as provided in paragraph (h)(2) of this section.

(1)(i) Postmarketing 15-day "Alert reports". The applicant must report each adverse experience that is both serious and unexpected, whether foreign or domestic, as soon as possible but no later than 15 calendar days from initial receipt of the information by the applicant.

(ii) Postmarketing 15-day "Alert reports"—followup. The applicant must promptly investigate all adverse experiences that are the subject of these postmarketing 15-day Alert reports and must submit followup reports within 15 calendar days of receipt of new information or as requested by FDA. If additional information is not obtainable, records should be maintained of the unsuccessful steps taken to seek additional information.

(iii) Submission of reports. The requirements of paragraphs (c)(1)(i) and (c)(1)(ii) of this section, concerning the submission of postmarketing 15-day Alert reports, also apply to any person whose name appears on the label of a licensed biological product as a manufacturer, packer, distributor, shared manufacturer, joint manufacturer, or any other participant involved in divided manufacturing. To avoid unnecessary duplication in the submission to FDA of reports required by paragraphs (c)(1)(i) and (c)(1)(ii) of this section, obligations of persons other than the applicant of the final biological product may be met by submission of all reports of serious adverse experiences to the applicant of the final product. If a person elects to submit adverse experience reports to the applicant rather than to FDA, the person must submit, by any appropriate means, each report to the applicant within 5 calendar days of initial receipt of the information by the person, and the applicant must then comply with the requirements of this section. Under this circumstance, a person who elects to submit reports to the applicant of the final product shall maintain a record of this action which must include:

(A) A copy of all adverse biological product experience reports submitted to the applicant of the final product;

(B) The date the report was received by the person;

(C) The date the report was submitted to the applicant of the final product; and—

(D) The name and address of the applicant of the final product.

(2) Periodic adverse experience reports. (i) The applicant must report each adverse experience not reported under paragraph (c)(1)(i) of this section at quarterly intervals, for 3 years from the date of issuance of the biologics license, and then at annual intervals. The applicant must submit each quarterly report within 30 days of the close of the quarter (the first quarter beginning on the date of issuance of the biologics license) and each annual report within 60 days of the anniversary date of the issuance of the biologics license. Upon written notice, FDA may extend or reestablish the requirement that an applicant submit quarterly reports, or require that the applicant submit reports under this section at different times than those stated. Followup information to adverse experiences submitted in a periodic report may be submitted in the next periodic report.

(ii) Each periodic report is required to contain:

(A) Descriptive information. (1) A narrative summary and analysis of the information in the report;

(2) An analysis of the 15-day Alert reports submitted during the reporting interval (all 15-day Alert reports being appropriately referenced by the applicant's patient identification code for nonvaccine biological product reports or by the unique case identification number for vaccine reports, adverse reaction term(s), and date of submission to FDA);

(3) A history of actions taken since the last report because of adverse experiences (for example, labeling changes or studies initiated);

(4) An index consisting of a line listing of the applicant's patient identification code for nonvaccine biological product reports or by the unique case identification number for vaccine reports and adverse reaction term(s) for ICSRs submitted under paragraph (c)(2)(ii)(B) of this section; and

(B) ICSRs for serious, expected and, nonserious adverse experiences. An ICSR for each adverse experience not reported under paragraph (c)(1)(i) of this section (all serious, expected and nonserious adverse experiences). All such ICSRs must be submitted to FDA (either individually or in one or more batches) within the timeframe specified in paragraph (c)(2)(i) of this section. ICSRs must only be submitted to FDA once.

(iii) Periodic reporting, except for information regarding 15-day Alert reports, does not apply to adverse experience information obtained from postmarketing studies (whether or not conducted under an investigational new drug application), from reports in the scientific literature, and from foreign marketing experience.

(d) Scientific literature. A 15-day Alert report based on information in the scientific literature must be accompanied by a copy of the published article. The 15-day Alert reporting requirements in paragraph (c)(1)(i) of this section (i.e., serious, unexpected adverse experiences) apply only to reports found in scientific and medical journals either as case reports or as the result of a formal clinical trial.

(e) Postmarketing studies. Applicants are not required to submit a 15-day Alert report under paragraph (c) of this section for an adverse experience obtained from a postmarketing clinical study (whether or not conducted under a biological investigational new drug application) unless the applicant concludes that there is a reasonable possibility that the product caused the adverse experience.

(f) Information reported on ICSRs for nonvaccine biological products. ICSRs for nonvaccine biological products include the following information:

(1) Patient information.

(i) Patient identification code;

(ii) Patient age at the time of adverse experience, or date of birth;

(iii) Patient gender; and

(iv) Patient weight.

(2) Adverse experience.

(i) Outcome attributed to adverse experience;

(ii) Date of adverse experience;

(iii) Date of report;

(iv) Description of adverse experience (including a concise medical narrative);

(v) Adverse experience term(s);

(vi) Description of relevant tests, including dates and laboratory data; and

(vii) Other relevant patient history, including preexisting medical conditions.

(3) Suspect medical product(s).

(i) Name;

(ii) Dose, frequency, and route of administration used;

(iii) Therapy dates;

(iv) Diagnosis for use (indication);

(v) Whether the product is a combination product as defined in § 3.2(e) of this chapter;

(vi) Whether the product is a prescription or nonprescription product;

(vii) Whether adverse experience abated after product use stopped or dose reduced;

(viii) Whether adverse experience reappeared after reintroduction of the product;

(ix) Lot number;

(x) Expiration date;

(xi) National Drug Code (NDC) number, or other unique identifier; and

(xii) Concomitant medical products and therapy dates.

(4) Initial reporter information.

(i) Name, address, and telephone number;

(ii) Whether the initial reporter is a health care professional; and

(iii) Occupation, if a health care professional.

(5) Applicant information.

(i) Applicant name and contact office address;

(ii) Telephone number;

(iii) Report source, such as spontaneous, literature, or study;

(iv) Date the report was received by applicant;

(v) Application number and type;

(vi) Whether the ICSR is a 15-day "Alert report";

(vii) Whether the ICSR is an initial report or followup report; and

(viii) Unique case identification number, which must be the same in the initial report and any subsequent followup report(s).

(g) Information reported on ICSRs for vaccine products. ICSRs for vaccine products include the following information:

(1) Patient information.

(i) Patient name, address, telephone number;

(ii) Patient age at the time of vaccination, or date of birth;

(iii) Patient gender; and

(iv) Patient birth weight for children under age 5.

(2) Adverse experience.

(i) Outcome attributed to adverse experience;

(ii) Date and time of adverse experience;

(iii) Date of report;

(iv) Description of adverse experience (including a concise medical narrative);

(v) Adverse experience term(s);

(vi) Illness at the time of vaccination;

(vii) Description of relevant tests, including dates and laboratory data; and

(viii) Other relevant patient history, including preexisting medical conditions.

(3) Suspect medical product(s), including vaccines administered on the same date.

(i) Name;

(ii) Dose, frequency, and route or site of administration used;

(iii) Number of previous vaccine doses;

(iv) Vaccination date(s) and time(s);

(v) Diagnosis for use (indication);

(vi) Whether the product is a combination product (as defined in § 3.2(e) of this chapter);

(vii) Whether the adverse experience abated after product use stopped or dose reduced;

(viii) Whether the adverse experience reappeared after reintroduction of the product;

(ix) Lot number;

(x) Expiration date;

(xi) National Drug Code (NDC) number, or other unique identifier; and

(xii) Concomitant medical products and therapy dates.

(4) Vaccine(s) administered in the 4 weeks prior to the vaccination date.

(i) Name of vaccine;

(ii) Manufacturer;

(iii) Lot number;

(iv) Route or site of administration;

(v) Date given; and

(vi) Number of previous doses.

(5) Initial reporter information.

(i) Name, address, and telephone number;

(ii) Whether the initial reporter is a health care professional; and

(iii) Occupation, if a health care professional.

(6) Facility and personnel where vaccine was administered.

(i) Name of person who administered vaccine;

(ii) Name of responsible physician at facility where vaccine was administered; and

(iii) Name, address (including city, county, and state), and telephone number of facility where vaccine was administered.

(7) Applicant information.

(i) Applicant name and contact office address;

(ii) Telephone number;

(iii) Report source, such as spontaneous, literature, or study;

(iv) Date received by applicant;

(v) Application number and type;

(vi) Whether the ICSR is a 15-day "Alert report";

(vii) Whether the ICSR is an initial report or followup report; and

(viii) Unique case identification number, which must be the same in the initial report and any subsequent followup report(s).

(h) Electronic format for submissions. (1) Safety report submissions, including ICSRs, ICSR attachments, and the descriptive information in periodic reports, must be in an electronic format that FDA can process, review, and archive. FDA will issue guidance on how to provide the electronic submission (e.g., method of transmission, media, file formats, preparation and organization of files).

(2) Persons subject to the requirements of paragraph (c) of this section may request, in writing, a temporary waiver of the requirements in paragraph (h)(1) of this section. These waivers will be granted on a limited basis for good cause shown. FDA will issue guidance on requesting a waiver of the requirements in paragraph (h)(1) of this section. Requests for waivers must be submitted in accordance with § 600.90.

(i) Multiple reports. An applicant should not include in reports under this section any adverse experience that occurred in clinical trials if they were previously submitted as part of the biologics license application. If a report refers to more than one biological product marketed by an applicant, the applicant should submit the report to the biologics license application for the product listed first in the report.

(j) Patient privacy. For nonvaccine biological products, an applicant should not include in reports under this section the names and addresses of individual patients; instead, the applicant should assign a unique code for identification of the patient. The applicant should include the name of the reporter from whom the information was received as part of the initial reporter information, even when the reporter is the patient. The names of patients, health care professionals, hospitals, and geographical identifiers in adverse experience reports are not releasable to the public under FDA's public information regulations in part 20 of this chapter. For vaccine adverse experience reports, these data will become part of the CDC Privacy Act System 09-20-0136, "Epidemiologic Studies and Surveillance of Disease Problems." Information identifying the person who received the vaccine or that person's legal representative will not be made available to the public, but may be available to the vaccinee or legal representative.

(k) Recordkeeping. The applicant must maintain for a period of 10 years records of all adverse experiences known to the applicant, including raw data and any correspondence relating to the adverse experiences.

(l) Revocation of biologics license. If an applicant fails to establish and maintain records and make reports required under this section with respect to a licensed biological product, FDA may revoke the biologics license for such a product in accordance with the procedures of § 601.5 of this chapter.

(m) Exemptions. Manufacturers of the following listed products are not required to submit adverse experience reports under this section:

(1) Whole blood or components of whole blood.

(2) In vitro diagnostic products, including assay systems for the detection of antibodies or antigens to retroviruses. These products are subject to the reporting requirements for devices.

(n) Disclaimer. A report or information submitted by an applicant under this section (and any release by FDA of that report or information) does not necessarily reflect a conclusion by the applicant or FDA that the report or information constitutes an admission that the biological product caused or contributed to an adverse effect. An applicant need not admit, and may deny, that the report or information submitted under this section constitutes an admission that the biological product caused or contributed to an adverse effect. For purposes of this provision, this paragraph also includes any person reporting under paragraph (c)(1)(iii) of this section.

[59 FR 54042, Oct. 27, 1994, as amended at 62 FR 34168, June 25, 1997; 62 FR 52252, Oct. 7, 1997; 63 FR 14612, Mar. 26, 1998; 64 FR 56449, Oct. 20, 1999; 70 FR 14982, Mar. 24, 2005; 79 FR 33090, June 10, 2014]

§600.81 Distribution reports.

(a) *Reporting requirements*. The applicant must submit to the Center for Biologics Evaluation and Research or the Center for Drug Evaluation and Research, information about the quantity of the product distributed under the biologics license, including the quantity distributed to distributors. The interval between distribution reports must be 6 months. Upon written notice, FDA may require that the applicant submit distribution reports under this section at times other than every 6 months. The distribution report must consist of the bulk lot number (from which the final container was filled), the fill lot numbers for the total number of dosage units of each strength or potency distributed (e.g., fifty thousand per 10-milliliter vials), the label lot number (if different from fill lot number), labeled date of expiration, number of doses in fill lot/label lot, date of release of fill lot/label lot for distribution at that time. If any significant amount of a fill lot/label lot is returned, include this information. Disclosure of financial or pricing data is not required. As needed, FDA may require submission of more detailed product distribution information. Upon written notice, FDA may require that the applicant submit reports under this section at times other than those stated. Requests by an applicant to submit reports at times other than those stated should be made as a request for a waiver under §600.90.

(b)(1) *Electronic format*. Except as provided for in paragraph (b)(2) of this section, the distribution reports required under paragraph (a) of this section must be submitted to the Agency in an electronic format that FDA can process, review, and archive. FDA will issue guidance on how to provide the electronic submission (e.g., method of transmission, media, file formats, preparation and organization of files).

(2) *Waivers*. An applicant may request, in writing, a temporary waiver of the requirements in paragraph (b)(1) of this section. These waivers will be granted on a limited basis for good cause shown. FDA will issue guidance on requesting a waiver of the requirements in paragraph (b)(1) of this section. Requests for waivers must be submitted in accordance with §600.90.

[59 FR 54042, Oct. 27, 1994, as amended at 64 FR 56449, Oct. 20, 1999; 70 FR 14983, Mar. 24, 2005; 79 FR 33091, June 10, 2014]

§600.82 Notification of a permanent discontinuance or an interruption in manufacturing.

(a) *Notification of a permanent discontinuance or an interruption in manufacturing*. (1) An applicant of a biological product, other than blood or blood components for transfusion, which is licensed under section 351 of the Public Health Service Act, and which may be dispensed only under prescription under section 503(b)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 353(b)(1)), must notify FDA in writing of a permanent discontinuance of manufacture of the biological product or an interruption in manufacturing of the biological product that is likely to lead to a meaningful disruption in supply of that biological product in the United States if:

(i) The biological product is life supporting, life sustaining, or intended for use in the prevention or treatment of a debilitating disease or condition, including any such biological product used in emergency medical care or during surgery; and

(ii) The biological product is not a radiopharmaceutical biological product.

(2) An applicant of blood or blood components for transfusion, which is licensed under section 351 of the Public Health Service Act, and which may be dispensed only under prescription under section 503(b) of the Federal Food, Drug, and Cosmetic Act, must notify FDA in writing of a permanent discontinuance of manufacture of any product listed in its license or an interruption in manufacturing of any such product that is likely to lead to a significant disruption in supply of that product in the United States if:

(i) The product is life supporting, life sustaining, or intended for use in the prevention or treatment of a debilitating disease or condition, including any such product used in emergency medical care or during surgery; and

(ii) The applicant is a manufacturer of a significant percentage of the U.S. blood supply.

(b) *Submission and timing of notification.* Notifications required by paragraph (a) of this section must be submitted to FDA electronically in a format that FDA can process, review, and archive:

(1) At least 6 months prior to the date of the permanent discontinuance or interruption in manufacturing; or

(2) If 6 months' advance notice is not possible because the permanent discontinuance or interruption in manufacturing was not reasonably anticipated 6 months in advance, as soon as practicable thereafter, but in no case later than 5 business days after such a permanent discontinuance or interruption in manufacturing occurs.

(c) Information included in notification. Notifications required by paragraph (a) of this section must include the following information:

(1) The name of the biological product subject to the notification, including the National Drug Code for such biological product, or an alternative standard for identification and labeling that has been recognized as acceptable by the Center Director;

(2) The name of the applicant of the biological product;

(3) Whether the notification relates to a permanent discontinuance of the biological product or an interruption in manufacturing of the biological product;

(4) A description of the reason for the permanent discontinuance or interruption in manufacturing; and

(5) The estimated duration of the interruption in manufacturing.

(d)(1) *Public list of biological product shortages.* FDA will maintain a publicly available list of biological products that are determined by FDA to be in shortage. This biological product shortages list will include the following information:

(i) The names and National Drug Codes for such biological products, or the alternative standards for identification and labeling that have been recognized as acceptable by the Center Director;

(ii) The name of each applicant for such biological products;

(iii) The reason for the shortage, as determined by FDA, selecting from the following categories: Requirements related to complying with good manufacturing practices; regulatory delay; shortage of an active ingredient; shortage of an inactive ingredient component; discontinuation of the manufacture of the biological product; delay in shipping of the biological product; demand increase for the biological product; or other reason; and

(iv) The estimated duration of the shortage.

(2) *Confidentiality*. FDA may choose not to make information collected to implement this paragraph available on the biological product shortages list or available under section 506C(c) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 356c(c)) if FDA determines that disclosure of such

information would adversely affect the public health (such as by increasing the possibility of hoarding or other disruption of the availability of the biological product to patients). FDA will also not provide information on the public shortages list or under section 506C(c) of the Federal Food, Drug, and Cosmetic Act that is protected by 18 U.S.C. 1905 or 5 U.S.C. 552(b)(4), including trade secrets and commercial or financial information that is considered confidential or privileged under § 20.61 of this chapter.

(e) *Noncompliance letters.* If an applicant fails to submit a notification as required under paragraph (a) of this section and in accordance with paragraph (b) of this section, FDA will issue a letter to the applicant informing it of such failure.

(1) Not later than 30 calendar days after the issuance of such a letter, the applicant must submit to FDA a written response setting forth the basis for noncompliance and providing the required notification under paragraph (a) of this section and including the information required under paragraph (c) of this section; and

(2) Not later than 45 calendar days after the issuance of a letter under this paragraph, FDA will make the letter and the applicant's response to the letter public, unless, after review of the applicant's response, FDA determines that the applicant had a reasonable basis for not notifying FDA as required under paragraph (a) of this section.

(f) *Definitions*. The following definitions of terms apply to this section:

Biological product shortage or *shortage* means a period of time when the demand or projected demand for the biological product within the United States exceeds the supply of the biological product.

Intended for use in the prevention or treatment of a debilitating disease or condition means a biological product intended for use in the prevention or treatment of a disease or condition associated with mortality or morbidity that has a substantial impact on day-to-day functioning.

Life supporting or *life sustaining* means a biological product that is essential to, or that yields information that is essential to, the restoration or continuation of a bodily function important to the continuation of human life.

Meaningful disruption means a change in production that is reasonably likely to lead to a reduction in the supply of a biological product by a manufacturer that is more than negligible and affects the ability of the manufacturer to fill orders or meet expected demand for its product, and does not include interruptions in manufacturing due to matters such as routine maintenance or insignificant changes in manufacturing so long as the manufacturer expects to resume operations in a short period of time.

Significant disruption means a change in production that is reasonably likely to lead to a reduction in the supply of blood or blood components by a manufacturer that substantially affects the ability of the manufacturer to fill orders or meet expected demand for its product, and does not include interruptions in manufacturing due to matters such as routine maintenance or insignificant changes in manufacturing so long as the manufacturer expects to resume operations in a short period of time.

[80 FR 38939, July 8, 2015]

§ 600.90 Waivers.

(a) An applicant may ask the Food and Drug Administration to waive under this section any requirement that applies to the applicant under §§ 600.80 and 600.81. A waiver request under this section is required to be submitted with supporting documentation. The waiver request is required to contain one of the following:

(1) An explanation why the applicant's compliance with the requirement is unnecessary or cannot be achieved,

(2) A description of an alternative submission that satisfies the purpose of the requirement, or

(3) Other information justifying a waiver.

(b) FDA may grant a waiver if it finds one of the following:

(1) The applicant's compliance with the requirement is unnecessary or cannot be achieved,

(2) The applicant's alternative submission satisfies the requirement, or

(3) The applicant's submission otherwise justifies a waiver.

[59 FR 54042, Oct. 27, 1994, as amended at 79 FR 33092, June 10, 2014]

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PART 601—LICENSING

Subpart A—General Provisions

Authority: 15 U.S.C. 1451-1561; 21 U.S.C. 321, 351, 352, 353, 355, 356b, 360, 360c-360f, 360h-360j, 371, 374, 379e, 381; 42 U.S.C. 216, 241, 262, 263, 264; sec 122, Pub. L. 105-115, 111 Stat. 2322 (21 U.S.C. 355 note).

Source: 38 FR 32052, Nov. 20, 1973, unless otherwise noted.

Cross references: For U.S. Customs Service regulations relating to viruses, serums, and toxins, see 19 CFR 12.21-12.23. For U.S. Postal Service regulations relating to the admissibility to the United States mails see parts 124 and 125 of the Domestic Mail Manual, that is incorporated by reference in 39 CFR part 111.

Subpart A—General Provisions

§ 601.2 Applications for biologics licenses; procedures for filing.

(a) *General.* To obtain a biologics license under section 351 of the Public Health Service Act for any biological product, the manufacturer shall submit an application to the Director, Center for Biologics Evaluation and Research or the Director, Center for Drug Evaluation and Research (see mailing addresses in § 600.2(a) or (b) of this chapter), on forms prescribed for such purposes, and shall submit data derived from nonclinical laboratory and clinical studies which demonstrate that the manufactured product meets prescribed requirements of safety, purity, and potency; with respect to each nonclinical laboratory study, either a statement that the study was conducted in compliance with the requirements set forth in part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance; statements regarding each clinical investigation involving human subjects contained in the application, that it either was conducted in compliance with the requirements for institutional review set forth in part 56 of this chapter; or was not subject to such requirements in accordance with § 56.104 or § 56.105, and was conducted in compliance with requirements for informed consent set forth in part 50 of this chapter. A full description of manufacturing methods; data establishing stability of the product through the dating period; sample(s) representative of the product for introduction or delivery for introduction into interstate commerce; summaries of results of tests performed on the lot(s) represented by the submitted sample(s); specimens of the labels, enclosures, and containers, and if applicable, any Medication Guide required under part 208 of this chapter proposed to be used for the product; and the address of each location involved in the manufacture of the biological product shall be listed in the biologics license application. The applicant shall also include a financial certification or disclo-

sure statement(s) or both for clinical investigators as required by part 54 of this chapter. An application for a biologics license shall not be considered as filed until all pertinent information and data have been received by the Food and Drug Administration. The applicant shall also include either a claim for categorical exclusion under § 25.30 or § 25.31 of this chapter or an environmental assessment under § 25.40 of this chapter. The applicant, or the applicant's attorney, agent, or other authorized official shall sign the application. An application for any of the following specified categories of biological products subject to licensure shall be handled as set forth in paragraph (c) of this section:

(1) Therapeutic DNA plasmid products;

(2) Therapeutic synthetic peptide products of 40 or fewer amino acids;

(3) Monoclonal antibody products for in vivo use; and

(4) Therapeutic recombinant DNA-derived products.

(b) [Reserved]

(c)(1) To obtain marketing approval for a biological product subject to licensure which is a therapeutic DNA plasmid product, therapeutic synthetic peptide product of 40 or fewer amino acids, monoclonal antibody product for in vivo use, or therapeutic recombinant DNA-derived product, an applicant shall submit a biologics license application in accordance with paragraph (a) of this section except that the following sections in parts 600 through 680 of this chapter shall not be applicable to such products: §§ 600.10(b) and (c), 600.11, 600.12, 600.13, 610.53, and 610.62 of this chapter.

(2) To the extent that the requirements in this paragraph (c) conflict with other requirements in this subchapter, this paragraph (c) shall supersede other requirements.

(d) Approval of a biologics license application or issuance of a biologics license shall constitute a determination that the establishment(s) and the product meet applicable requirements to ensure the continued safety, purity, and potency of such products. Applicable requirements for the maintenance of establishments for the manufacture of a product subject to this section shall include but not be limited to the good manufacturing practice requirements set forth in parts 210, 211, 600, 606, and 820 of this chapter.

(e) Any establishment and product license for a biological product issued under section 351 of the Public Health Service Act (42 U.S.C. 201 et seq.) that has not been revoked or suspended as of December 20, 1999, shall constitute an approved biologics license application in effect under the same terms and conditions set forth in such product license and such portions of the establishment license relating to such product.

(f) *Withdrawal from sale of approved biological products.* A holder of a biologics license application (BLA) must report to FDA, in accordance with the requirements of §§ 207.61 and 207.65, the withdrawal from sale of an approved biological product. The information must be submitted to FDA within 30 working days of the biological product's withdrawal from sale. The following information must be submitted: The holder's name; product name; BLA number; the National Drug Code; and the date on which the product is expected to be no longer in commercial distribution. The reason for the withdrawal of the biological product is requested but not required to be submitted.

[64 FR 56450, Oct. 20, 1999, as amended at 70 FR 14983, Mar. 24, 2005; 80 FR 18092, Apr. 3, 2015; 80 FR 37974, July 2, 2015; 81 FR 60221, Aug. 31, 2016]

§ 601.3 Complete response letter to the applicant.

(a) *Complete response letter.* The Food and Drug Administration will send the biologics license applicant or supplement applicant a complete response letter if the agency determines that it will not approve the biologics license application or supplement in its present form.

(1) *Description of specific deficiencies.* A complete response letter will describe all of the deficiencies that the agency has identified in a biologics license application or supplement, except as stated in paragraph (a)(2) of this section.

(2) *Inadequate data.* If FDA determines, after a biologics license application or supplement is filed, that the data submitted are inadequate to support approval, the agency might issue a complete response letter without first conducting required inspections, testing submitted product lots, and/or reviewing proposed product labeling.

(3) *Recommendation of actions for approval.* When possible, a complete response letter will recommend actions that the applicant might take to place its biologics license application or supplement in condition for approval.

(b) *Applicant actions.* After receiving a complete response letter, the biologics license applicant or supplement applicant must take either of the following actions:

(1) *Resubmission*. Resubmit the application or supplement, addressing all deficiencies identified in the complete response letter.

(2) *Withdrawal*. Withdraw the application or supplement. A decision to withdraw the application or supplement is without prejudice to a subsequent submission.

(c) *Failure to take action.* (1) FDA may consider a biologics license applicant or supplement applicant's failure to either resubmit or withdraw the application or supplement within 1 year after issuance of a complete response letter to be a request by the applicant to withdraw the application or supplement, unless the applicant has requested an extension of time in which to resubmit the application or supplement. FDA will grant any reasonable request for such an extension. FDA may consider an applicant's failure to resubmit the application or supplement within the extended time period or request an additional extension to be a request by the applicant to withdraw the application.

(2) If FDA considers an applicant's failure to take action in accordance with paragraph (c)(1) of this section to be a request to withdraw the application, the agency will notify the applicant in writing. The applicant will have 30 days from the date of the notification to explain why the application or supplement should not be withdrawn and to request an extension of time in which to resubmit the application or supplement. FDA will grant any reasonable request for an extension. If the applicant does not respond to the notification within 30 days, the application or supplement will be deemed to be withdrawn.

[73 FR 39611, July 10, 2008]

§601.4 Issuance and denial of license.

(a) A biologics license shall be issued upon a determination by the Director, Center for Biologics Evaluation and Research or the Director, Center for Drug Evaluation and Research that the establishment(s) and the product meet the applicable requirements established in this chapter. A biologics license shall be valid until suspended or revoked.

(b) If the Commissioner determines that the establishment or product does not meet the requirements established in this chapter, the biologics license application shall be denied and the applicant shall be informed of the grounds for, and of an opportunity for a hearing on, the decision. If the applicant so requests, the Commissioner shall issue a notice of opportunity for hearing on the matter pursuant to §12.21(b) of this chapter.

[42 FR 4718, Jan. 25, 1977, as amended at 42 FR 15676, Mar. 22, 1977; 42 FR 19142, Apr. 12, 1977; 64 FR 56450, Oct. 20, 1999; 70 FR 14983, Mar. 24, 2005]

§601.5 Revocation of license.

(a) A biologics license shall be revoked upon application of the manufacturer giving notice of intention to discontinue the manufacture of all products manufactured under such license or to discontinue the manufacture of a particular product for which a license is held and waiving an opportunity for a hearing on the matter.

(b)(1) The Commissioner shall notify the licensed manufacturer of the intention to revoke the biologics license, setting forth the grounds for, and offering an opportunity for a hearing on the proposed revocation if the Commissioner finds any of the following:

(i) Authorized Food and Drug Administration employees after reasonable efforts have been unable to gain access to an establishment or a location for the purpose of carrying out the inspection required under § 600.21 of this chapter,

(ii) Manufacturing of products or of a product has been discontinued to an extent that a meaningful inspection or evaluation cannot be made,

(iii) The manufacturer has failed to report a change as required by § 601.12 of this chapter,

(iv) The establishment or any location thereof, or the product for which the license has been issued, fails to conform to the applicable standards established in the license and in this chapter designed to ensure the continued safety, purity, and potency of the manufactured product,

(v) The establishment or the manufacturing methods have been so changed as to require a new showing that the establishment or product meets the requirements established in this chapter in order to protect the public health, or

(vi) The licensed product is not safe and effective for all of its intended uses or is misbranded with respect to any such use.

(2) Except as provided in § 601.6 of this chapter, or in cases involving willfulness, the notification required in this paragraph shall provide a reasonable period for the licensed manufacturer to demonstrate or achieve compliance with the requirements of this chapter, before proceedings will be instituted for the revocation of the license. If compliance is not demonstrated or achieved and the licensed manufacturer does not waive the opportunity for a hearing, the Commissioner shall issue a notice of opportunity for hearing on the matter under § 12.21(b) of this chapter.

[64 FR 56451, Oct. 20, 1999]

§ 601.6 Suspension of license.

(a) Whenever the Commissioner has reasonable grounds to believe that any of the grounds for revocation of a license exist and that by reason thereof there is a danger to health, the Commissioner may notify the licensed manufacturer that the biologics license is suspended and require that the licensed manufacturer do the following:

(1) Notify the selling agents and distributors to whom such product or products have been delivered of such suspension, and

(2) Furnish to the Center for Biologics Evaluation and Research or the Center for Drug Evaluation and Research, complete records of such deliveries and notice of suspension.

(b) Upon suspension of a license, the Commissioner shall either:

(1) Proceed under the provisions of § 601.5(b) of this chapter to revoke the license, or

(2) If the licensed manufacturer agrees, hold revocation in abeyance pending resolution of the matters involved.

[64 FR 56451, Oct. 20, 1999, as amended at 70 FR 14983, Mar. 24, 2005]

§ 601.7 Procedure for hearings.

(a) A notice of opportunity for hearing, notice of appearance and request for hearing, and grant or denial of hearing for a biological drug pursuant to this part, for which the exemption from the Federal Food, Drug, and Cosmetic Act in § 310.4 of this chapter has been revoked, shall be subject to the provisions of § 314.200 of this chapter except to the extent that the notice of opportunity for hearing on the matter issued pursuant to § 12.21(b) of this chapter specifically provides otherwise.

(b) Hearings pursuant to §§ 601.4 through 601.6 shall be governed by part 12 of this chapter.

(c) When a license has been suspended pursuant to § 601.6 and a hearing request has been granted, the hearing shall proceed on an expedited basis.

[42 FR 4718, Jan. 25, 1977, as amended at 42 FR 15676, Mar. 22, 1977; 42 FR 19143, Apr. 12, 1977]

§ 601.8 Publication of revocation.

The Commissioner, following revocation of a biologics license under 21 CFR 601.5(b), will publish a notice in the Federal Register with a statement of the specific grounds for the revocation.

[74 FR 20585, May 5, 2009]

§ 601.9 Licenses; reissuance.

(a) *Compliance with requirements.* A biologics license, previously suspended or revoked, may be reissued or reinstated upon a showing of compliance with requirements and upon such inspection and examination as may be considered necessary by the Director, Center for Biologics Evaluation and Research or the Director, Center for Drug Evaluation and Research.

(b) *Exclusion of noncomplying location.* A biologics license, excluding a location or locations that fail to comply with the requirements in this chapter, may be issued without further application and concurrently with the suspension or revocation of the license for noncompliance at the excluded location or locations.

(c) *Exclusion of noncomplying product(s).* In the case of multiple products included under a single biologics license application, a biologics license may be issued, excluding the noncompliant product(s), without further application and concurrently with the suspension or revocation of the biologics license for a noncompliant product(s).

[64 FR 56451, Oct. 20, 1999, as amended at 70 FR 14983, Mar. 24, 2005]

Subpart C—Biologics Licensing

§ 601.12 Changes to an approved application.

(a) *General*. (1) As provided by this section, an applicant must inform the Food and Drug Administration (FDA) (see mailing addresses in § 600.2 of this chapter) about each change in the product, production process, quality controls, equipment, facilities, responsible personnel, or labeling established in the approved license application(s).

(2) Before distributing a product made using a change, an applicant must assess the effects of the change and demonstrate through appropriate validation and/or other clinical and/or nonclinical laboratory studies the lack of adverse effect of the change on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product.

(3) Notwithstanding the requirements of paragraphs (b), (c), and (f) of this section, an applicant must make a change provided for in those paragraphs in accordance with a regulation or guidance that provides for a less burdensome notification of the change (for example, by submission of a supplement that does not require approval prior to distribution of the product or in an annual report).

(4) The applicant must promptly revise all promotional labeling and advertising to make it consistent with any labeling change implemented in accordance with paragraphs (f)(1) and (f)(2) of this section.

(5) A supplement or annual report must include a list of all changes contained in the supplement or annual report. For supplements, this list must be provided in the cover letter.

(b) *Changes requiring supplement submission and approval prior to distribution of the product made using the change (major changes).* (1) A supplement shall be submitted for any change in the product, production process, quality controls, equipment, facilities, or responsible personnel that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product.

(2) These changes include, but are not limited to:

(i) Except as provided in paragraphs (c) and (d) of this section, changes in the qualitative or quantitative formulation, including inactive ingredients, or in the specifications provided in the approved application;

(ii) Changes requiring completion of an appropriate human study to demonstrate the equivalence of the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product;

(iii) Changes in the virus or adventitious agent removal or inactivation method(s);

(iv) Changes in the source material or cell line;

(v) Establishment of a new master cell bank or seed; and

(vi) Changes which may affect product sterility assurance, such as changes in product or component sterilization method(s), or an addition, deletion, or substitution of steps in an aseptic processing operation.

(3) The applicant must obtain approval of the supplement from FDA prior to distribution of the product made using the change. Except for submissions under paragraph (e) of this section, the following shall be contained in the supplement:

(i) A detailed description of the proposed change;

(ii) The product(s) involved;

(iii) The manufacturing site(s) or area(s) affected;

(iv) A description of the methods used and studies performed to evaluate the effect of the change on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product;

(v) The data derived from such studies;

(vi) Relevant validation protocols and data; and

(vii) A reference list of relevant standard operating procedures (SOP's).

(4) An applicant may ask FDA to expedite its review of a supplement for public health reasons or if a delay in making the change described in it would impose an extraordinary hardship on the applicant. Such a supplement and its mailing cover should be plainly marked: "Prior Approval Supplement-Expedited Review Requested.

(c) *Changes requiring supplement submission at least 30 days prior to distribution of the product made using the change.* (1) A supplement shall be submitted for any change in the product, production process, quality controls, equipment, facilities, or responsible personnel that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product. The supplement shall be labeled "Supplement—Changes Being Effected in 30 Days" or, if applicable under paragraph (c)(5) of this section, "Supplement—Changes Being Effected."

(2) These changes include, but are not limited to:

(i) [Reserved]

(ii) An increase or decrease in production scale during finishing steps that involves different equipment; and

(iii) Replacement of equipment with that of similar, but not identical, design and operating principle that does not affect the process methodology or process operating parameters.

(iv) Relaxation of an acceptance criterion or deletion of a test to comply with an official compendium that is consistent with FDA statutory and regulatory requirements.

(3) Pending approval of the supplement by FDA, and except as provided in paragraph (c)(5) of this section, distribution of the product made using the change may begin not less than 30 days after receipt of the supplement by FDA. The information listed in paragraph (b)(3)(i) through (b)(3)(vii) of this section shall be contained in the supplement.

(4) If within 30 days following FDA's receipt of the supplement, FDA informs the applicant that either:

(i) The change requires approval prior to distribution of the product in accordance with paragraph (b) of this section; or

(ii) Any of the information required under paragraph (c)(3) of this section is missing; the applicant shall not distribute the product made using the change until FDA determines that compliance with this section is achieved.

(5) In certain circumstances, FDA may determine that, based on experience with a particular type of change, the supplement for such change is usually complete and provides the proper information, and on particular assurances that the proposed change has been appropriately submitted, the product made using the change may be distributed immediately upon receipt of the supplement by FDA. These circumstances may include substantial similarity with a type of change regularly involving a "Supplement—Changes Being Effected" supplement or a situation in which the applicant presents evidence that the proposed change has been validated in accordance with an approved protocol for such change under paragraph (e) of this section.

(6) If the agency disapproves the supplemental application, it may order the manufacturer to cease distribution of the products made with the manufacturing change.

(d) *Changes to be described in an annual report (minor changes).* (1) Changes in the product, production process, quality controls, equipment, facilities, or responsible personnel that have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product shall be documented by the applicant in an annual report submitted each year within 60 days of the anniversary date of approval of the application. The Director, Center for Biologics Evaluation and Research or the Director, Center for Drug Evaluation and Research, may approve a written request for an alternative date to combine annual reports for multiple approved applications into a single annual report submission.

(2) These changes include, but are not limited to:

(i) Any change made to comply with a change to an official compendium, except a change described in paragraph (c)(2)(iv) of this section, that is consistent with FDA statutory and regulatory requirements.

(ii) The deletion or reduction of an ingredient intended only to affect the color of the product, except that a change intended only to affect Blood Grouping Reagents requires supplement submission and approval prior to distribution of the product made using the change in accordance with the requirements set forth in paragraph (b) of this section;

(iii) An extension of an expiration dating period based upon full shelf life data on production batches obtained from a protocol approved in the application;

(iv) A change within the container closure system for a nonsterile product, based upon a showing of equivalency to the approved system under a protocol approved in the application or published in an official compendium;

(v) A change in the size and/or shape of a container containing the same number of dosage units for a nonsterile solid dosage form product, without a change from one container closure system to another;

(vi) The addition by embossing, debossing, or engraving of a code imprint to a solid dosage form biological product other than a modified release dosage form, or a minor change in an existing code imprint; and

(vii) The addition or revision of an alternative analytical procedure that provides the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application, or deletion of an alternative analytical procedure.

(3) The following information for each change shall be contained in the annual report:

(i) A list of all products involved; and

(ii) A full description of the manufacturing and controls changes including: the manufacturing site(s) or area(s) involved; the date the change was made; a cross-reference to relevant validation protocols and/or SOP's; and relevant data from studies and tests performed to evaluate the effect of the change on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product.

(iii) A statement by the holder of the approved application or license that the effects of the change have been assessed.

(4) The applicant shall submit the report to the FDA office responsible for reviewing the application. The report shall include all the information required under this paragraph for each change made during the annual reporting interval which ends on the anniversary date in the order in which they were implemented.

(e) An applicant may submit one or more protocols describing the specific tests and validation studies and acceptable limits to be achieved to demonstrate the lack of adverse effect for specified types of manufacturing changes on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product. Any such protocols, or change to a protocol, shall be submitted as a supplement requiring approval from FDA prior to distribution of the product which, if approved, may justify a reduced reporting category for the particular change because the use of the protocol for that type of change reduces the potential risk of an adverse effect.

(f) *Labeling changes.* (1) Labeling changes requiring supplement submission—FDA approval must be obtained before distribution of the product with the labeling change. Except as described in paragraphs (f)(2) and (f)(3) of this section, an applicant shall submit a supplement describing a proposed change in the package insert, package label, container label, or, if applicable, a Medication Guide required under part 208 of this chapter, and include the information necessary to support the proposed change. An applicant cannot use paragraph (f)(2) of this section to make any change to the information required in § 201.57(a) of this chapter. An applicant may report the minor changes to the information specified in paragraph (f)(3)(i)(D) of this section in an annual report. The supplement shall clearly highlight the proposed change in the labeling. The applicant shall obtain approval from FDA prior to distribution of the product with the labeling change.

(2) *Labeling changes requiring supplement submission—product with a labeling change that may be distributed before FDA approval.* (i) An applicant shall submit, at the time such change is made, a supplement for any change in the package insert, package label, or container label to reflect newly

acquired information, except for changes to the package insert required in § 201.57(a) of this chapter (which must be made under paragraph (f)(1) of this section), to accomplish any of the following:

(A) To add or strengthen a contraindication, warning, precaution, or adverse reaction for which the evidence of a causal association satisfies the standard for inclusion in the labeling under § 201.57(c) of this chapter;

(B) To add or strengthen a statement about abuse, dependence, psychological effect, or overdosage;

(C) To add or strengthen an instruction about dosage and administration that is intended to increase the safety of the use of the product; and

(D) To delete false, misleading, or unsupported indications for use or claims for effectiveness.

(E) Any labeling change normally requiring a supplement submission and approval prior to distribution of the product that FDA specifically requests be submitted under this provision.

(ii) Pending approval of the supplement by FDA, the applicant may distribute a product with a package insert, package label, or container label bearing such change at the time the supplement is submitted. The supplement shall clearly identify the change being made and include necessary supporting data. The supplement and its mailing cover shall be plainly marked: "Special Labeling Supplement—Changes Being Effected."

(3) *Labeling changes requiring submission in an annual report.* (i) An applicant shall submit any final printed package insert, package label, container label, or Medication Guide required under part 208 of this chapter incorporating the following changes in an annual report submitted to FDA each year as provided in paragraph (d)(1) of this section:

(A) Editorial or similar minor changes;

(B) A change in the information on how the product is supplied that does not involve a change in the dosage strength or dosage form;

(C) A change in the information specified in § 208.20(b)(8)(iii) and (b)(8)(iv) of this chapter for a Medication Guide; and

(D) A change to the information required in § 201.57(a) of this chapter as follows:

(1) Removal of a listed section(s) specified in § 201.57(a)(5) of this chapter; and

(2) Changes to the most recent revision date of the labeling as specified in § 201.57(a)(15) of this chapter.

(E) A change made pursuant to an exception or alternative granted under § 201.26 or § 610.68 of this chapter.

(ii) The applicant may distribute a product with a package insert, package label, or container label bearing such change at the time the change is made.

(4) *Advertisements and promotional labeling.* Advertisements and promotional labeling shall be submitted to the Center for Biologics Evaluation and Research or Center for Drug Evaluation and Research in accordance with the requirements set forth in § 314.81(b)(3)(i) of this chapter.

(5) The submission and grant of a written request for an exception or alternative under § 201.26 or § 610.68 of this chapter satisfies the requirements in paragraphs (f)(1) through (f)(2) of this section.

(6) For purposes of paragraph (f)(2) of this section, information will be considered newly acquired if it consists of data, analyses, or other information not previously submitted to the agency, which may include (but are not limited to) data derived from new clinical studies, reports of adverse events, or new analyses of previously submitted data (e.g., meta-analyses) if the studies, events or analyses reveal risks of a different type or greater severity or frequency than previously included in submissions to FDA.

(g) *Failure to comply.* In addition to other remedies available in law and regulations, in the event of repeated failure of the applicant to comply with this section, FDA may require that the applicant submit a supplement for any proposed change and obtain approval of the supplement by FDA prior to distribution of the product made using the change.

(h) *Administrative review.* Under § 10.75 of this chapter, an applicant may request internal FDA review of FDA employee decisions under this section.

[62 FR 39901, July 24, 1997, as amended at 63 FR 66399, Dec. 1, 1998. Redesignated at 65 FR 59718, Oct. 6, 2000, and amended at 69 FR 18766, Apr. 8, 2004; 70 FR 14983, Mar. 24, 2005; 71 FR 3997, Jan. 24, 2006; 72 FR 73600, Dec. 28, 2007; 73 FR 49609, Aug. 22, 2008; 73 FR 68333, Nov. 18, 2008; 80 FR 18092, Apr. 3, 2015]

§ 601.14 Regulatory submissions in electronic format.

(a) *General*. Electronic format submissions must be in a form that FDA can process, review, and archive. FDA will periodically issue guidance on how to provide the electronic submission (e.g., method of transmission, media, file formats, preparation and organization of files.)

(b) *Labeling*. The content of labeling required under § 201.100(d)(3) of this chapter (commonly referred to as the package insert or professional labeling), including all text, tables, and figures, must be submitted to the agency in electronic format as described in paragraph (a) of this section. This requirement is in addition to the provisions of §§ 601.2(a) and 601.12(f) that require applicants to submit specimens of the labels, enclosures, and containers, or to submit other final printed labeling. Submissions under this paragraph must be made in accordance with part 11 of this chapter except for the requirements of § 11.10(a), (c) through (h), and (k), and the corresponding requirements of § 11.30.

[68 FR 69020, Dec. 11, 2003]

§ 601.15 Foreign establishments and products: samples for each importation.

Random samples of each importation, obtained by the District Director of Customs and forwarded to the Director, Center for Biologics Evaluation and Research or the Director, Center for Drug Evaluation and Research (see mailing addresses in § 600.2(c) of this chapter) must be at least two final containers of each lot of product. A copy of the associated documents which describe and identify the shipment must accompany the shipment for forwarding with the samples to the Director, Center for Biologics Evaluation and Research or the Director, Center for Drug Evaluation and Research (see mailing addresses in § 600.2(c)). For shipments of 20 or less final containers, samples need not be forwarded, provided a copy of an official release from the Center for Biologics Evaluation and Research or Center for Drug Evaluation and Research accompanies each shipment.

[70 FR 14983, Mar. 24, 2005, as amended at 80 FR 18092, Apr. 3, 2015]

§ 601.20 Biologics licenses; issuance and conditions.

(a) Examination—compliance with requirements. A biologics license application shall be approved only upon examination of the product and upon a determination that the product complies with the standards established in the biologics license application and the requirements prescribed in the regulations in this chapter including but not limited to the good manufacturing practice requirements set forth in parts 210, 211, 600, 606, and 820 of this chapter.

(b) *Availability of product.* No biologics license shall be issued unless:

(1) The product intended for introduction into interstate commerce is available for examination, and

(2) Such product is available for inspection during all phases of manufacture.

(c) *Manufacturing process—impairment of assurances.* No product shall be licensed if any part of the process of or relating to the manufacture of such product, in the judgment of the Director, Center for Biologics Evaluation and Research or the Director, Center for Drug Evaluation and Research, would impair the assurances of continued safety, purity, and potency as provided by the regulations contained in this chapter.

(d) *Inspection—compliance with requirements.* A biologics license shall be issued or a biologics license application approved only after inspection of the establishment(s) listed in the biologics license application and upon a determination that the establishment(s) complies with the standards established in the biologics license application and the requirements prescribed in applicable regulations.

(e) *One biologics license to cover all locations.* One biologics license shall be issued to cover all locations meeting the establishment standards identified in the approved biologics license application and each location shall be subject to inspection by FDA officials.

[64 FR 56451, Oct. 20, 1999, as amended at 70 FR 14983, Mar. 24, 2005]

§ 601.21 Products under development.

A biological product undergoing development, but not yet ready for a biologics license, may be shipped or otherwise delivered from one State or possession into another State or possession provided such shipment or delivery is not for introduction or delivery for introduction into interstate commerce, except as provided in sections 505(i) and 520(g) of the Federal Food, Drug, and Cosmetic Act, as amended, and the regulations thereunder (21 CFR parts 312 and 812).

[64 FR 56451, Oct. 20, 1999]

§ 601.22 Products in short supply; initial manufacturing at other than licensed location.

A biologics license issued to a manufacturer and covering all locations of manufacture shall authorize persons other than such manufacturer to conduct at places other than such locations the initial, and partial manufacturing of a product for shipment solely to such manufacturer only to the extent that the names of such persons and places are registered with the Commissioner of Food and Drugs and it is found upon application of such manufacturer, that the product is in short supply due either to the peculiar growth requirements of the organism involved or to the scarcity of the animal required for manufacturing purposes, and such manufacturer has established with respect to such persons and places such procedures, inspections, tests or other arrangements as will ensure full compliance with the applicable regulations of this subchapter related to continued safety, purity, and potency. Such persons and places shall be subject to all regulations of this subchapter except §§ 601.2 to 601.6, 601.9, 601.10, 601.20, 601.21 to 601.33, and 610.60 to 610.65 of this chapter. For persons and places authorized under this section to conduct the initial and partial manufacturing of a product for shipment solely to a manufacturer of a product subject to licensure under § 601.2(c), the following additional regulations shall not be applicable: §§ 600.10(b) and (c), 600.11, 600.12, 600.13, and 610.53 of this chapter. Failure of such manufacturer to maintain such procedures, inspections, tests, or other arrangements, or failure of any person conducting such partial manufacturing to comply with applicable regulations shall constitute a ground for suspension or revocation of the authority conferred pursuant to this section on the same basis as provided in §§ 601.6 to 601.8 with respect to the suspension and the revocation of licenses.

[42 FR 4718, Jan. 25, 1977, as amended at 61 FR 24233, May 14, 1996; 64 FR 56452, Oct. 20, 1999; 80 FR 37974, July 2, 2015]

§ 601.27 Pediatric studies.

(a) *Required assessment.* Except as provided in paragraphs (b), (c), and (d) of this section, each application for a new active ingredient, new indication, new dosage form, new dosing regimen, or new

route of administration shall contain data that are adequate to assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. Where the course of the disease and the effects of the product are similar in adults and pediatric patients, FDA may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled effectiveness studies in adults, usually supplemented with other information in pediatric patients, such as pharmacokinetic studies. In addition, studies may not be needed in each pediatric age group, if data from one age group can be extrapolated to another. Assessments required under this section for a product that represents a meaningful therapeutic benefit over existing treatments must be carried out using appropriate formulations for the age group(s) for which the assessment is required.

(b) *Deferred submission.* (1) FDA may, on its own initiative or at the request of an applicant, defer submission of some or all assessments of safety and effectiveness described in paragraph (a) of this section until after licensing of the product for use in adults. Deferral may be granted if, among other reasons, the product is ready for approval in adults before studies in pediatric patients are complete, pediatric studies should be delayed until additional safety or effectiveness data have been collected. If an applicant requests deferred submission, the request must provide an adequate justification for delaying pediatric studies, a description of the planned or ongoing studies, and evidence that the studies are being or will be conducted with due diligence and at the earliest possible time.

(2) If FDA determines that there is an adequate justification for temporarily delaying the submission of assessments of pediatric safety and effectiveness, the product may be licensed for use in adults subject to the requirement that the applicant submit the required assessments within a specified time.

(c) *Waivers*—(1) *General*. FDA may grant a full or partial waiver of the requirements of paragraph (a) of this section on its own initiative or at the request of an applicant. A request for a waiver must provide an adequate justification.

(2) *Full waiver.* An applicant may request a waiver of the requirements of paragraph (a) of this section if the applicant certifies that:

(i) The product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is not likely to be used in a substantial number of pediatric patients;

(ii) Necessary studies are impossible or highly impractical because, e.g., the number of such patients is so small or geographically dispersed; or

(iii) There is evidence strongly suggesting that the product would be ineffective or unsafe in all pediatric age groups.

(3) Partial waiver. An applicant may request a waiver of the requirements of paragraph (a) of this section with respect to a specified pediatric age group, if the applicant certifies that:

(i) The product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group, and is not likely to be used in a substantial number of patients in that age group;

(ii) Necessary studies are impossible or highly impractical because, e.g., the number of patients in that age group is so small or geographically dispersed;

(iii) There is evidence strongly suggesting that the product would be ineffective or unsafe in that age group; or

(iv) The applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed.

(4) *FDA action on waiver.* FDA shall grant a full or partial waiver, as appropriate, if the agency finds that there is a reasonable basis on which to conclude that one or more of the grounds for waiver

specified in paragraphs (c)(2) or (c)(3) of this section have been met. If a waiver is granted on the ground that it is not possible to develop a pediatric formulation, the waiver will cover only those pediatric age groups requiring that formulation. If a waiver is granted because there is evidence that the product would be ineffective or unsafe in pediatric populations, this information will be included in the product's labeling.

(5) *Definition of "meaningful therapeutic benefit".* For purposes of this section, a product will be considered to offer a meaningful therapeutic benefit over existing therapies if FDA estimates that:

(i) If approved, the product would represent a significant improvement in the treatment, diagnosis, or prevention of a disease, compared to marketed products adequately labeled for that use in the relevant pediatric population. Examples of how improvement might be demonstrated include, e.g., evidence of increased effectiveness in treatment, prevention, or diagnosis of disease; elimination or substantial reduction of a treatment-limiting drug reaction; documented enhancement of compliance; or evidence of safety and effectiveness in a new subpopulation; or

(ii) The product is in a class of products or for an indication for which there is a need for additional therapeutic options.

(d) *Exemption for orphan drugs.* This section does not apply to any product for an indication or indications for which orphan designation has been granted under part 316, subpart C, of this chapter.

[63 FR 66671, Dec. 2, 1998]

§ 601.28 Annual reports of postmarketing pediatric studies.

Sponsors of licensed biological products shall submit the following information each year within 60 days of the anniversary date of approval of each product under the license to the Director, Center for Biologics Evaluation and Research or the Director, Center for Drug Evaluation and Research (see mailing addresses in § 600.2(a) or (b) of this chapter):

(a) *Summary*. A brief summary stating whether labeling supplements for pediatric use have been submitted and whether new studies in the pediatric population to support appropriate labeling for the pediatric population have been initiated. Where possible, an estimate of patient exposure to the drug product, with special reference to the pediatric population (neonates, infants, children, and adolescents) shall be provided, including dosage form.

(b) *Clinical data.* Analysis of available safety and efficacy data in the pediatric population and changes proposed in the labeling based on this information. An assessment of data needed to ensure appropriate labeling for the pediatric population shall be included.

(c) *Status reports.* A statement on the current status of any postmarketing studies in the pediatric population performed by, or on behalf of, the applicant. The statement shall include whether postmarketing clinical studies in pediatric populations were required or agreed to, and, if so, the status of these studies shall be reported to FDA in annual progress reports of postmarketing studies under § 601.70 rather than under this section.

[65 FR 59718, Oct. 6, 2000, as amended at 65 FR 64618, Oct. 30, 2000; 70 FR 14984, Mar. 24, 2005; 80 FR 18092, Apr. 3, 2015]

§ 601.29 Guidance documents.

(a) FDA has made available guidance documents under § 10.115 of this chapter to help you comply with certain requirements of this part.

(b) The Center for Biologics Evaluation and Research (CBER) maintains a list of guidance documents that apply to the center's regulations. The lists are maintained on the Internet and are published annually in the Federal Register. You may request a copy of the CBER list from the Food and Drug Administration, Center for Biologics Evaluation and Research, Office of Communication, Out-

reach and Development, 10903 New Hampshire Ave., Bldg. 71, Rm. 3103, Silver Spring, MD 20993-0002.

[65 FR 56480, Sept. 19, 2000, as amended at 70 FR 14984, Mar. 24, 2005; 80 FR 18092, Apr. 3, 2015]

Subpart D—Diagnostic Radiopharmaceuticals

Source: 64 FR 26668, May 17, 1999, unless otherwise noted.

This subpart applies to radiopharmaceuticals intended for in vivo administration for diagnostic and monitoring use. It does not apply to radiopharmaceuticals intended for therapeutic purposes. In situations where a particular radiopharmaceutical is proposed for both diagnostic and therapeutic uses, the radiopharmaceutical must be evaluated taking into account each intended use.

§601.31 Definition.

For purposes of this part, *diagnostic radiopharmaceutical means:*

(a) An article that is intended for use in the diagnosis or monitoring of a disease or a manifestation of a disease in humans and that exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons; or

(b) Any nonradioactive reagent kit or nuclide generator that is intended to be used in the preparation of such article as defined in paragraph (a) of this section.

§601.32 General factors relevant to safety and effectiveness.

FDA's determination of the safety and effectiveness of a diagnostic radiopharmaceutical includes consideration of the following:

(a) The proposed use of the diagnostic radiopharmaceutical in the practice of medicine;

(b) The pharmacological and toxicological activity of the diagnostic radiopharmaceutical (including any carrier or ligand component of the diagnostic radiopharmaceutical); and

(c) The estimated absorbed radiation dose of the diagnostic radiopharmaceutical.

§601.33 Indications.

(a) For diagnostic radiopharmaceuticals, the categories of proposed indications for use include, but are not limited to, the following:

(1) Structure delineation;

(2) Functional, physiological, or biochemical assessment;

(3) Disease or pathology detection or assessment; and

(4) Diagnostic or therapeutic patient management.

(b) Where a diagnostic radiopharmaceutical is not intended to provide disease-specific information, the proposed indications for use may refer to a biochemical, physiological, anatomical, or pathological process or to more than one disease or condition.

§601.34 Evaluation of effectiveness.

(a) The effectiveness of a diagnostic radiopharmaceutical is assessed by evaluating its ability to provide useful clinical information related to its proposed indications for use. The method of this evaluation varies depending upon the proposed indication(s) and may use one or more of the following criteria:

(1) The claim of structure delineation is established by demonstrating in a defined clinical setting the ability to locate anatomical structures and to characterize their anatomy.

(2) The claim of functional, physiological, or biochemical assessment is established by demonstrating in a defined clinical setting reliable measurement of function(s) or physiological, biochemical, or molecular process(es).

(3) The claim of disease or pathology detection or assessment is established by demonstrating in a defined clinical setting that the diagnostic radiopharmaceutical has sufficient accuracy in identifying or characterizing the disease or pathology.

(4) The claim of diagnostic or therapeutic patient management is established by demonstrating in a defined clinical setting that the test is useful in diagnostic or therapeutic patient management.

(5) For a claim that does not fall within the indication categories identified in §601.33, the applicant or sponsor should consult FDA on how to establish the effectiveness of the diagnostic radiopharmaceutical for the claim.

(b) The accuracy and usefulness of the diagnostic information is determined by comparison with a reliable assessment of actual clinical status. A reliable assessment of actual clinical status may be provided by a diagnostic standard or standards of demonstrated accuracy. In the absence of such diagnostic standard(s), the actual clinical status must be established in another manner, e.g., patient followup.

§601.35 Evaluation of safety.

(a) Factors considered in the safety assessment of a diagnostic radiopharmaceutical include, among others, the following:

(1) The radiation dose;

(2) The pharmacology and toxicology of the radiopharmaceutical, including any radionuclide, carrier, or ligand;

(3) The risks of an incorrect diagnostic determination;

(4) The adverse reaction profile of the drug;

(5) Results of human experience with the radiopharmaceutical for other uses; and

(6) Results of any previous human experience with the carrier or ligand of the radiopharmaceutical when the same chemical entity as the carrier or ligand has been used in a previously studied product.

(b) The assessment of the adverse reaction profile includes, but is not limited to, an evaluation of the potential of the diagnostic radiopharmaceutical, including the carrier or ligand, to elicit the following:

(1) Allergic or hypersensitivity responses,

(2) Immunologic responses,

(3) Changes in the physiologic or biochemical function of the target and nontarget tissues, and

(4) Clinically detectable signs or symptoms.

(c)(1) To establish the safety of a diagnostic radiopharmaceutical, FDA may require, among other information, the following types of data:

(A) Pharmacology data,

(B) Toxicology data,

(C) Clinical adverse event data, and

(D) Radiation safety assessment.

(2) The amount of new safety data required will depend on the characteristics of the product and available information regarding the safety of the diagnostic radiopharmaceutical, and its carrier or ligand, obtained from other studies and uses. Such information may include, but is not limited to,

the dose, route of administration, frequency of use, half-life of the ligand or carrier, half-life of the radionuclide, and results of clinical and preclinical studies. FDA will establish categories of diagnostic radiopharmaceuticals based on defined characteristics relevant to risk and will specify the amount and type of safety data that are appropriate for each category (e.g., required safety data may be limited for diagnostic radiopharmaceuticals with a well established, low-risk profile). Upon reviewing the relevant product characteristics and safety information, FDA will place each diagnostic radiopharmaceutical into the appropriate safety risk category.

(d) *Radiation safety assessment.* The radiation safety assessment must establish the radiation dose of a diagnostic radiopharmaceutical by radiation dosimetry evaluations in humans and appropriate animal models. The maximum tolerated dose need not be established.

Subpart E—Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses

Source: 57 FR 58959, Dec. 11, 1992, unless otherwise noted.

This subpart applies to certain biological products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy).

§ 601.41 Approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity.

FDA may grant marketing approval for a biological product on the basis of adequate and well-controlled clinical trials establishing that the biological product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. Approval under this section will be subject to the requirement that the applicant study the biological product further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome. Postmarketing studies would usually be studies already underway. When required to be conducted, such studies must also be adequate and well-controlled. The applicant shall carry out any such studies with due diligence.

§ 601.42 Approval with restrictions to assure safe use.

(a) If FDA concludes that a biological product shown to be effective can be safely used only if distribution or use is restricted, FDA will require such postmarketing restrictions as are needed to assure safe use of the biological product, such as:

(1) Distribution restricted to certain facilities or physicians with special training or experience; or

(2) Distribution conditioned on the performance of specified medical procedures.

(b) The limitations imposed will be commensurate with the specific safety concerns presented by the biological product.

§ 601.43 Withdrawal procedures.

(a) For biological products approved under § 601.41 or § 601.42, FDA may withdraw approval, following a hearing as provided in part 15 of this chapter, as modified by this section, if:

(1) A postmarketing clinical study fails to verify clinical benefit;

(2) The applicant fails to perform the required postmarketing study with due diligence;

(3) Use after marketing demonstrates that postmarketing restrictions are inadequate to ensure safe use of the biological product;

(4) The applicant fails to adhere to the postmarketing restrictions agreed upon;

(5) The promotional materials are false or misleading; or

(6) Other evidence demonstrates that the biological product is not shown to be safe or effective under its conditions of use.

(b) *Notice of opportunity for a hearing.* The Director of the Center for Biologics Evaluation and Research or the Director of the Center for Drug Evaluation and Research will give the applicant notice of an opportunity for a hearing on the Center's proposal to withdraw the approval of an application approved under § 601.41 or § 601.42. The notice, which will ordinarily be a letter, will state generally the reasons for the action and the proposed grounds for the order.

(c) *Submission of data and information.* (1) If the applicant fails to file a written request for a hearing within 15 days of receipt of the notice, the applicant waives the opportunity for a hearing.

(2) If the applicant files a timely request for a hearing, the agency will publish a notice of hearing in the Federal Register in accordance with §§ 12.32(e) and 15.20 of this chapter.

(3) An applicant who requests a hearing under this section must, within 30 days of receipt of the notice of opportunity for a hearing, submit the data and information upon which the applicant intends to rely at the hearing.

(d) *Separation of functions.* Separation of functions (as specified in § 10.55 of this chapter) will not apply at any point in withdrawal proceedings under this section.

(e) *Procedures for hearings.* Hearings held under this section will be conducted in accordance with the provisions of part 15 of this chapter, with the following modifications:

(1) An advisory committee duly constituted under part 14 of this chapter will be present at the hearing. The committee will be asked to review the issues involved and to provide advice and recommendations to the Commissioner of Food and Drugs.

(2) The presiding officer, the advisory committee members, up to three representatives of the applicant, and up to three representatives of the Center may question any person during or at the conclusion of the person's presentation. No other person attending the hearing may question a person making a presentation. The presiding officer may, as a matter of discretion, permit questions to be submitted to the presiding officer for response by a person making a presentation.

(f) *Judicial review.* The Commissioner's decision constitutes final agency action from which the applicant may petition for judicial review. Before requesting an order from a court for a stay of action pending review, an applicant must first submit a petition for a stay of action under § 10.35 of this chapter.

[57 FR 58959, Dec. 11, 1992, as amended at 68 FR 34797, June 11, 2003; 70 FR 14984, Mar. 24, 2005]

§ 601.44 Postmarketing safety reporting.

Biological products approved under this program are subject to the postmarketing recordkeeping and safety reporting applicable to all approved biological products.

§ 601.45 Promotional materials.

For biological products being considered for approval under this subpart, unless otherwise informed by the agency, applicants must submit to the agency for consideration during the preapproval review period copies of all promotional materials, including promotional labeling as well as advertisements, intended for dissemination or publication within 120 days following marketing approval. After 120 days following marketing approval, unless otherwise informed by the agency, the

applicant must submit promotional materials at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.

§601.46 Termination of requirements.

If FDA determines after approval that the requirements established in §601.42, §601.43, or §601.45 are no longer necessary for the safe and effective use of a biological product, it will so notify the applicant. Ordinarily, for biological products approved under §601.41, these requirements will no longer apply when FDA determines that the required postmarketing study verifies and describes the biological product's clinical benefit and the biological product would be appropriate for approval under traditional procedures. For biological products approved under §601.42, the restrictions would no longer apply when FDA determines that safe use of the biological product can be assured through appropriate labeling. FDA also retains the discretion to remove specific postapproval requirements upon review of a petition submitted by the sponsor in accordance with §10.30.

Subpart F—Confidentiality of Information

§601.50 Confidentiality of data and information in an investigational new drug notice for a biological product.

(a) The existence of an IND notice for a biological product will not be disclosed by the Food and Drug Administration unless it has previously been publicly disclosed or acknowledged.

(b) The availability for public disclosure of all data and information in an IND file for a biological product shall be handled in accordance with the provisions established in §601.51.

(c) Notwithstanding the provisions of §601.51, the Food and Drug Administration shall disclose upon request to an individual on whom an investigational biological product has been used a copy of any adverse reaction report relating to such use.

[39 FR 44656, Dec. 24, 1974]

§601.51 Confidentiality of data and information in applications for biologics licenses.

(a) For purposes of this section the biological product file includes all data and information submitted with or incorporated by reference in any application for a biologics license, IND's incorporated into any such application, master files, and other related submissions. The availability for public disclosure of any record in the biological product file shall be handled in accordance with the provisions of this section.

(b) The existence of a biological product file will not be disclosed by the Food and Drug Administration before a biologics license application has been approved unless it has previously been publicly disclosed or acknowledged. The Food and Drug Administration will maintain a list available for public disclosure of biological products for which a license application has been approved.

(c) If the existence of a biological product file has not been publicly disclosed or acknowledged, no data or information in the biological product file is available for public disclosure.

(d)(1) If the existence of a biological product file has been publicly disclosed or acknowledged before a license has been issued, no data or information contained in the file is available for public disclosure before such license is issued, but the Commissioner may, in his discretion, disclose a summary of such selected portions of the safety and effectiveness data as are appropriate for public consideration of a specific pending issue, e.g., at an open session of a Food and Drug Administration advisory committee or pursuant to an exchange of important regulatory information with a foreign government.

(2) Notwithstanding paragraph (d)(1) of this section, FDA will make available to the public upon request the information in the IND that was required to be filed in Docket Number 95S-0158 in the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm.

1061, Rockville, MD 20852, for investigations involving an exception from informed consent under § 50.24 of this chapter. Persons wishing to request this information shall submit a request under the Freedom of Information Act.

(e) After a license has been issued, the following data and information in the biological product file are immediately available for public disclosure unless extraordinary circumstances are shown:

(1) All safety and effectiveness data and information.

(2) A protocol for a test or study, unless it is shown to fall within the exemption established for trade secrets and confidential commercial or financial information in § 20.61 of this chapter.

(3) Adverse reaction reports, product experience reports, consumer complaints, and other similar data and information, after deletion of:

(i) Names and any information that would identify the person using the product.

(ii) Names and any information that would identify any third party involved with the report, such as a physician or hospital or other institution.

(4) A list of all active ingredients and any inactive ingredients previously disclosed to the public, as defined in § 20.81 of this chapter.

(5) An assay method or other analytical method, unless it serves no regulatory or compliance purpose and it is shown to fall within the exemption established in § 20.61 of this chapter.

(6) All correspondence and written summaries of oral discussions relating to the biological product file, in accordance with the provisions of part 20 of this chapter.

(7) All records showing the manufacturer's testing of a particular lot, after deletion of data or information that would show the volume of the drug produced, manufacturing procedures and controls, yield from raw materials, costs, or other material falling within § 20.61 of this chapter.

(8) All records showing the testing of and action on a particular lot by the Food and Drug Administration.

(f) The following data and information in a biological product file are not available for public disclosure unless they have been previously disclosed to the public as defined in § 20.81 of this chapter or they relate to a product or ingredient that has been abandoned and they no longer represent a trade secret or confidential commercial or financial information as defined in § 20.61 of this chapter:

(1) Manufacturing methods or processes, including quality control procedures.

(2) Production, sales, distribution, and similar data and information, except that any compilation of such data and information aggregated and prepared in a way that does not reveal data or information which is not available for public disclosure under this provision is available for public disclosure.

(3) Quantitative or semiquantitative formulas.

(g) For purposes of this regulation, safety and effectiveness data include all studies and tests of a biological product on animals and humans and all studies and tests on the drug for identity, stability, purity, potency, and bioavailability.

[39 FR 44656, Dec. 24, 1974, as amended at 42 FR 15676, Mar. 22, 1977; 49 FR 23833, June 8, 1984; 55 FR 11013, Mar. 26, 1990; 61 FR 51530, Oct. 2, 1996; 64 FR 56452, Oct. 20, 1999; 68 FR 24879, May 9, 2003; 69 FR 13717, Mar. 24, 2004; 70 FR 14984, Mar. 24, 2005]

Subpart G—Postmarketing Studies

Source: 65 FR 64618, Oct. 30, 2000, unless otherwise noted.

(a) *General requirements.* This section applies to all required postmarketing studies (e.g., accelerated approval clinical benefit studies, pediatric studies) and postmarketing studies that an applicant has committed, in writing, to conduct either at the time of approval of an application or a supplement to an application, or after approval of an application or a supplement. Postmarketing studies within the meaning of this section are those that concern:

(1) Clinical safety;

(2) Clinical efficacy;

(3) Clinical pharmacology; and

(4) Nonclinical toxicology.

(b) *What to report.* Each applicant of a licensed biological product shall submit a report to FDA on the status of postmarketing studies for each approved product application. The status of these postmarketing studies shall be reported annually until FDA notifies the applicant, in writing, that the agency concurs with the applicant's determination that the study commitment has been fulfilled, or that the study is either no longer feasible or would no longer provide useful information. Each annual progress report shall be accompanied by a completed transmittal Form FDA-2252, and shall include all the information required under this section that the applicant received or otherwise obtained during the annual reporting interval which ends on the U.S. anniversary date. The report must provide the following information for each postmarketing study:

(1) *Applicant's name.*

(2) *Product name.* Include the approved product's proper name and the proprietary name, if any.

(3) *Biologics license application (BLA) and supplement number.*

(4) *Date of U.S. approval of BLA.*

(5) *Date of postmarketing study commitment.*

(6) *Description of postmarketing study commitment.* The description must include sufficient information to uniquely describe the study. This information may include the purpose of the study, the type of study, the patient population addressed by the study and the indication(s) and dosage(s) that are to be studied.

(7) *Schedule for completion and reporting of the postmarketing study commitment.* The schedule should include the actual or projected dates for submission of the study protocol to FDA, completion of patient accrual or initiation of an animal study, completion of the study, submission of the final study report to FDA, and any additional milestones or submissions for which projected dates were specified as part of the commitment. In addition, it should include a revised schedule, as appropriate. If the schedule has been previously revised, provide both the original schedule and the most recent, previously submitted revision.

(8) Current status of the postmarketing study commitment. The status of each postmarketing study should be categorized using one of the following terms that describes the study's status on the anniversary date of U.S. approval of the application or other agreed upon date:

(i) *Pending*. The study has not been initiated, but does not meet the criterion for delayed.

(ii) *Ongoing*. The study is proceeding according to or ahead of the original schedule described under paragraph (b)(7) of this section.

(iii) *Delayed*. The study is behind the original schedule described under paragraph (b)(7) of this section.

(iv) *Terminated*. The study was ended before completion but a final study report has not been submitted to FDA.

(v) *Submitted*. The study has been completed or terminated and a final study report has been submitted to FDA.

(9) *Explanation of the study's status.* Provide a brief description of the status of the study, including the patient accrual rate (expressed by providing the number of patients or subjects enrolled to date, and the total planned enrollment), and an explanation of the study's status identified under paragraph (b)(8) of this section. If the study has been completed, include the date the study was completed and the date the final study report was submitted to FDA, as applicable. Provide a revised schedule, as well as the reason(s) for the revision, if the schedule under paragraph (b)(7) of this section has changed since the previous report.

(c) *When to report.* Annual progress reports for postmarketing study commitments entered into by applicants shall be reported to FDA within 60 days of the anniversary date of the U.S. approval of the application for the product.

(d) *Where to report.* Submit two copies of the annual progress report of postmarketing studies to the Center for Biologics Evaluation and Research or Center for Drug Evaluation and Research (see mailing addresses in § 600.2(a) or (b) of this chapter).

(e) *Public disclosure of information.* Except for the information described in this paragraph, FDA may publicly disclose any information concerning a postmarketing study, within the meaning of this section, if the agency determines that the information is necessary to identify an applicant or to establish the status of the study including the reasons, if any, for failure to conduct, complete, and report the study. Under this section, FDA will not publicly disclose trade secrets, as defined in § 20.61 of this chapter, or information, described in § 20.63 of this chapter, the disclosure of which would constitute an unwarranted invasion of personal privacy.

[65 FR 64618, Oct. 30, 2000, as amended at 70 FR 14984, Mar. 24, 2005; 80 FR 18092, Apr. 3, 2015]

Subpart H—Approval of Biological Products When Human Efficacy Studies Are Not Ethical or Feasible

Source: 67 FR 37996, May 31, 2002, unless otherwise noted.

This subpart applies to certain biological products that have been studied for their safety and efficacy in ameliorating or preventing serious or life-threatening conditions caused by exposure to lethal or permanently disabling toxic biological, chemical, radiological, or nuclear substances. This subpart applies only to those biological products for which: Definitive human efficacy studies cannot be conducted because it would be unethical to deliberately expose healthy human volunteers to a lethal or permanently disabling toxic biological, chemical, radiological, or nuclear substance; and field trials to study the product's efficacy after an accidental or hostile exposure have not been feasible. This subpart does not apply to products that can be approved based on efficacy standards described elsewhere in FDA's regulations (e.g., accelerated approval based on surrogate markers or clinical endpoints other than survival or irreversible morbidity), nor does it address the safety evaluation for the products to which it does apply.

§ 601.91 Approval based on evidence of effectiveness from studies in animals.

(a) FDA may grant marketing approval for a biological product for which safety has been established and for which the requirements of § 601.90 are met based on adequate and well-controlled animal studies when the results of those animal studies establish that the biological product is reasonably likely to produce clinical benefit in humans. In assessing the sufficiency of animal data, the agency may take into account other data, including human data, available to the agency. FDA will rely on the evidence from studies in animals to provide substantial evidence of the effectiveness of these products only when:

(1) There is a reasonably well-understood pathophysiological mechanism of the toxicity of the substance and its prevention or substantial reduction by the product;

(2) The effect is demonstrated in more than one animal species expected to react with a response predictive for humans, unless the effect is demonstrated in a single animal species that represents a sufficiently well-characterized animal model for predicting the response in humans;

(3) The animal study endpoint is clearly related to the desired benefit in humans, generally the enhancement of survival or prevention of major morbidity; and

(4) The data or information on the kinetics and pharmacodynamics of the product or other relevant data or information, in animals and humans, allows selection of an effective dose in humans.

(b) Approval under this subpart will be subject to three requirements:

(1) *Postmarketing studies.* The applicant must conduct postmarketing studies, such as field studies, to verify and describe the biological product's clinical benefit and to assess its safety when used as indicated when such studies are feasible and ethical. Such postmarketing studies would not be feasible until an exigency arises. When such studies are feasible, the applicant must conduct such studies with due diligence. Applicants must include as part of their application a plan or approach to postmarketing study commitments in the event such studies become ethical and feasible.

(2) *Approval with restrictions to ensure safe use.* If FDA concludes that a biological product shown to be effective under this subpart can be safely used only if distribution or use is restricted, FDA will require such postmarketing restrictions as are needed to ensure safe use of the biological product, commensurate with the specific safety concerns presented by the biological product, such as:

(i) Distribution restricted to certain facilities or health care practitioners with special training or experience;

(ii) Distribution conditioned on the performance of specified medical procedures, including medical followup; and

(iii) Distribution conditioned on specified recordkeeping requirements.

(3) *Information to be provided to patient recipients.* For biological products or specific indications approved under this subpart, applicants must prepare, as part of their proposed labeling, labeling to be provided to patient recipients. The patient labeling must explain that, for ethical or feasibility reasons, the biological product's approval was based on efficacy studies conducted in animals alone and must give the biological product's indication(s), directions for use (dosage and administration), contraindications, a description of any reasonably foreseeable risks, adverse reactions, anticipated benefits, drug interactions, and any other relevant information required by FDA at the time of approval. The patient labeling must be available with the product to be provided to patients prior to administration or dispensing of the biological product for the use approved under this subpart, if possible.

§601.92 Withdrawal procedures.

(a) *Reasons to withdraw approval.* For biological products approved under this subpart, FDA may withdraw approval, following a hearing as provided in part 15 of this chapter, as modified by this section, if:

(1) A postmarketing clinical study fails to verify clinical benefit;

(2) The applicant fails to perform the postmarketing study with due diligence;

(3) Use after marketing demonstrates that postmarketing restrictions are inadequate to ensure safe use of the biological product;

(4) The applicant fails to adhere to the postmarketing restrictions applied at the time of approval under this subpart;

(5) The promotional materials are false or misleading; or

(6) Other evidence demonstrates that the biological product is not shown to be safe or effective under its conditions of use.

(b) *Notice of opportunity for a hearing.* The Director of the Center for Biologics Evaluation and Research or the Director of the Center for Drug Evaluation and Research will give the applicant notice of an opportunity for a hearing on the proposal to withdraw the approval of an application approved under this subpart. The notice, which will ordinarily be a letter, will state generally the reasons for the action and the proposed grounds for the order.

(c) *Submission of data and information.* (1) If the applicant fails to file a written request for a hearing within 15 days of receipt of the notice, the applicant waives the opportunity for a hearing.

(2) If the applicant files a timely request for a hearing, the agency will publish a notice of hearing in the Federal Register in accordance with §§ 12.32(e) and 15.20 of this chapter.

(3) An applicant who requests a hearing under this section must, within 30 days of receipt of the notice of opportunity for a hearing, submit the data and information upon which the applicant intends to rely at the hearing.

(d) *Separation of functions.* Separation of functions (as specified in § 10.55 of this chapter) will not apply at any point in withdrawal proceedings under this section.

(e) *Procedures for hearings.* Hearings held under this section will be conducted in accordance with the provisions of part 15 of this chapter, with the following modifications:

(1) An advisory committee duly constituted under part 14 of this chapter will be present at the hearing. The committee will be asked to review the issues involved and to provide advice and recommendations to the Commissioner of Food and Drugs.

(2) The presiding officer, the advisory committee members, up to three representatives of the applicant, and up to three representatives of CBER may question any person during or at the conclusion of the person's presentation. No other person attending the hearing may question a person making a presentation. The presiding officer may, as a matter of discretion, permit questions to be submitted to the presiding officer for response by a person making a presentation.

(f) *Judicial review.* The Commissioner of Food and Drugs' decision constitutes final agency action from which the applicant may petition for judicial review. Before requesting an order from a court for a stay of action pending review, an applicant must first submit a petition for a stay of action under § 10.35 of this chapter.

[67 FR 37996, May 31, 2002, as amended at 70 FR 14984, Mar. 24, 2005]

§ 601.93 Postmarketing safety reporting.

Biological products approved under this subpart are subject to the postmarketing recordkeeping and safety reporting applicable to all approved biological products.

§ 601.94 Promotional materials.

For biological products being considered for approval under this subpart, unless otherwise informed by the agency, applicants must submit to the agency for consideration during the preapproval review period copies of all promotional materials, including promotional labeling as well as advertisements, intended for dissemination or publication within 120 days following marketing approval. After 120 days following marketing approval, unless otherwise informed by the agency, the applicant must submit promotional materials at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.

§ 601.95 Termination of requirements.

If FDA determines after approval under this subpart that the requirements established in §§ 601.91(b)(2), 601.92, and 601.93 are no longer necessary for the safe and effective use of a biological product, FDA will so notify the applicant. Ordinarily, for biological products approved under § 601.91, these requirements will no longer apply when FDA determines that the postmarketing study verifies and describes the biological product's clinical benefit. For biological products approved under § 601.91, the restrictions would no longer apply when FDA determines that safe use of the biological product can be ensured through appropriate labeling. FDA also retains the discretion to remove specific postapproval requirements upon review of a petition submitted by the sponsor in accordance with § 10.30 of this chapter.

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PART 610—GENERAL BIOLOGICAL PRODUCTS STANDARDS

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 360, 360c, 360d, 360h, 360i, 371, 372, 374, 381; 42 U.S.C. 216, 262, 263, 263a, 264.

Source: 38 FR 32056, Nov. 20, 1973, unless otherwise noted.

Cross references: For U.S. Customs Service regulations relating to viruses, serums, and toxins, see 19 CFR 12.21-12.23. For U.S. Postal Service regulations relating to the admissibility to the United States mails see parts 124 and 125 of the Domestic Mail Manual, that is incorporated by reference in 39 CFR part 111.

Subpart A—Release Requirements

§ 610.1 Tests prior to release required for each lot.

No lot of any licensed product shall be released by the manufacturer prior to the completion of tests for conformity with standards applicable to such product. Each applicable test shall be made on each lot after completion of all processes of manufacture which may affect compliance with the standard to which the test applies. The results of all tests performed shall be considered in determining whether or not the test results meet the test objective, except that a test result may be disregarded when it is established that the test is invalid due to causes unrelated to the product.

§ 610.2 Requests for samples and protocols; official release.

(a) *Licensed biological products regulated by CBER.* Samples of any lot of any licensed product together with the protocols showing results of applicable tests, may at any time be required to be sent to the Director, Center for Biologics Evaluation and Research (see mailing addresses in § 600.2(c) of this chapter). Upon notification by the Director, Center for Biologics Evaluation and Research, a manufacturer shall not distribute a lot of a product until the lot is released by the Director, Center for Biologics Evaluation and Research: Provided, That the Director, Center for Biologics Evaluation and Research, shall not issue such notification except when deemed necessary for the safety, purity, or potency of the product.

(b) *Licensed biological products regulated by CDER.* Samples of any lot of any licensed product together with the protocols showing results of applicable tests, may at any time be required to be sent to the Director, Center for Drug Evaluation and Research (see mailing addresses in § 600.2(c) of this chapter) for official release. Upon notification by the Director, Center for Drug Evaluation and Research, a manufacturer shall not distribute a lot of a biological product until the lot is released by the Director, Center for Drug Evaluation and Research: Provided, That the Director, Center for Drug Evaluation and Research shall not issue such notification except when deemed necessary for the safety, purity, or potency of the product.

[40 FR 31313, July 25, 1975, as amended at 49 FR 23834, June 8, 1984; 50 FR 10941, Mar. 19, 1985; 55 FR 11013, 11014, Mar. 26, 1990; 67 FR 9587, Mar. 4, 2002; 70 FR 14984, Mar. 24, 2005; 80 FR 18093, Apr. 3, 2015]

Subpart B—General Provisions

§610.9 Equivalent methods and processes.

Modification of any particular test method or manufacturing process or the conditions under which it is conducted as required in this part or in the additional standards for specific biological products in parts 620 through 680 of this chapter shall be permitted only under the following conditions:

(a) The applicant presents evidence, in the form of a license application, or a supplement to the application submitted in accordance with §601.12(b) or (c), demonstrating that the modification will provide assurances of the safety, purity, potency, and effectiveness of the biological product equal to or greater than the assurances provided by the method or process specified in the general standards or additional standards for the biological product; and

(b) Approval of the modification is received in writing from the Director, Center for Biologics Evaluation and Research or the Director, Center for Drug Evaluation and Research.

[62 FR 39903, July 24, 1997, as amended at 70 FR 14984, Mar. 24, 2005]

§610.10 Potency.

Tests for potency shall consist of either in vitro or in vivo tests, or both, which have been specifically designed for each product so as to indicate its potency in a manner adequate to satisfy the interpretation of potency given by the definition in §600.3(s) of this chapter.

§610.11-610.11a [Reserved]

§610.12 Sterility.

(a) *The test.* Except as provided in paragraph (h) of this section, manufacturers of biological products must perform sterility testing of each lot of each biological product's final container material or other material, as appropriate and as approved in the biologics license application or supplement for that product.

(b) *Test requirements.* (1) The sterility test must be appropriate to the material being tested such that the material does not interfere with or otherwise hinder the test.

(2) The sterility test must be validated to demonstrate that the test is capable of reliably and consistently detecting the presence of viable contaminating microorganisms.

(3) The sterility test and test components must be verified to demonstrate that the test method can consistently detect the presence of viable contaminating microorganisms.

(c) *Written procedures.* Manufacturers must establish, implement, and follow written procedures for sterility testing that describe, at a minimum, the following:

(1) The sterility test method to be used;

(i) If culture-based test methods are used, include, at a minimum:

(A) Composition of the culture media;

(B) Growth-promotion test requirements; and

(C) Incubation conditions (time and temperature).

(ii) If non-culture-based test methods are used, include, at a minimum:

(A) Composition of test components;

(B) Test parameters, including acceptance criteria; and

(C) Controls used to verify the method's ability to detect the presence of viable contaminating microorganisms.

(2) The method of sampling, including the number, volume, and size of articles to be tested;

(3) Written specifications for the acceptance or rejection of each lot; and

(4) A statement of any other function critical to the particular sterility test method to ensure consistent and accurate results.

(d) *The sample.* The sample must be appropriate to the material being tested, considering, at a minimum:

(1) The size and volume of the final product lot;

(2) The duration of manufacturing of the drug product;

(3) The final container configuration and size;

(4) The quantity or concentration of inhibitors, neutralizers, and preservatives, if present, in the tested material;

(5) For a culture-based test method, the volume of test material that results in a dilution of the product that is not bacteriostatic or fungistatic; and

(6) For a non-culture-based test method, the volume of test material that results in a dilution of the product that does not inhibit or otherwise hinder the detection of viable contaminating microorganisms.

(e) *Verification.* (1) For culture-based test methods, studies must be conducted to demonstrate that the performance of the test organisms and culture media are suitable to consistently detect the presence of viable contaminating microorganisms, including tests for each lot of culture media to verify its growth-promoting properties over the shelf-life of the media.

(2) For non-culture-based test methods, within the test itself, appropriate controls must be used to demonstrate the ability of the test method to continue to consistently detect the presence of viable contaminating microorganisms.

(f) *Repeat test procedures.* (1) If the initial test indicates the presence of microorganisms, the product does not comply with the sterility test requirements unless a thorough investigation by the quality control unit can ascribe definitively the microbial presence to a laboratory error or faulty materials used in conducting the sterility testing.

(2) If the investigation described in paragraph (f)(1) of this section finds that the initial test indicated the presence of microorganisms due to laboratory error or the use of faulty materials, a sterility test may be repeated one time. If no evidence of microorganisms is found in the repeat test, the product examined complies with the sterility test requirements. If evidence of microorganisms is found in the repeat test, the product examined does not comply with the sterility test requirements.

(3) If a repeat test is conducted, the same test method must be used for both the initial and repeat tests, and the repeat test must be conducted with comparable product that is reflective of the initial sample in terms of sample location and the stage in the manufacturing process from which it was obtained.

(g) *Records*. The records related to the test requirements of this section must be prepared and maintained as required by §§ 211.167 and 211.194 of this chapter.

(h) *Exceptions*. Sterility testing must be performed on final container material or other appropriate material as defined in the approved biologics license application or supplement and as described in this section, except as follows:

(1) This section does not require sterility testing for Whole Blood, Cryoprecipitated Antihemophilic Factor, Platelets, Red Blood Cells, Plasma, Source Plasma, Smallpox Vaccine, Reagent Red Blood Cells, Anti-Human Globulin, and Blood Grouping Reagents.

(2) A manufacturer is not required to comply with the sterility test requirements if the Director of the Center for Biologics Evaluation and Research or the Director of the Center for Drug Evaluation and Research, as appropriate, determines that data submitted in the biologics license application or supplement adequately establish that the route of administration, the method of preparation, or any other aspect of the product precludes or does not necessitate a sterility test to assure the safety, purity, and potency of the product.

[77 FR 26174, May 3, 2012]

§610.13 Purity.

Products shall be free of extraneous material except that which is unavoidable in the manufacturing process described in the approved biologics license application. In addition, products shall be tested as provided in paragraphs (a) and (b) of this section.

(a)(1) *Test for residual moisture.* Each lot of dried product shall be tested for residual moisture and shall meet and not exceed established limits as specified by an approved method on file in the biologics license application. The test for residual moisture may be exempted by the Director, Center for Biologics Evaluation and Research or the Director, Center for Drug Evaluation and Research, when deemed not necessary for the continued safety, purity, and potency of the product.

(2) *Records*. Appropriate records for residual moisture under paragraph (a)(1) of this section shall be prepared and maintained as required by the applicable provisions of §§211.188 and 211.194 of this chapter.

(b) *Test for pyrogenic substances.* Each lot of final containers of any product intended for use by injection shall be tested for pyrogenic substances by intravenous injection into rabbits as provided in paragraphs (b) (1) and (2) of this section: Provided, That notwithstanding any other provision of Subchapter F of this chapter, the test for pyrogenic substances is not required for the following products: Products containing formed blood elements; Cryoprecipitate; Plasma; Source Plasma; Normal Horse Serum; bacterial, viral, and rickettsial vaccines and antigens; toxoids; toxins; allergenic extracts; venoms; diagnostic substances and trivalent organic arsenicals.

(1) *Test dose.* The test dose for each rabbit shall be at least 3 milliliters per kilogram of body weight of the rabbit and also shall be at least equivalent proportionately, on a body weight basis, to the maximum single human dose recommended, but need not exceed 10 milliliters per kilogram of body weight of the rabbit, except that: (i) Regardless of the human dose recommended, the test dose per kilogram of body weight of each rabbit shall be at least 1 milliliter for immune globulins derived from human blood; (ii) for Streptokinase, the test dose shall be at least equivalent proportionately, on a body weight basis, to the maximum single human dose recommended.

(2) *Test procedure, results, and interpretation; standards to be met.* The test for pyrogenic substances shall be performed according to the requirements specified in United States Pharmacopeia XX.

(3) *Retest*. If the lot fails to meet the test requirements prescribed in paragraph (b)(2) of this section, the test may be repeated once using five other rabbits. The temperature rises recorded for all eight rabbits used in testing shall be included in determining whether the requirements are met. The lot meets the requirements for absence of pyrogens if not more than three of the eight rabbits show individual rises in temperature of 0.6 °C or more, and if the sum of the eight individual maximum temperature rises does not exceed 3.7 °C.

[38 FR 32056, Nov. 20, 1973, as amended at 40 FR 29710, July 15, 1975; 41 FR 10429, Mar. 11, 1976; 41 FR 41424, Sept. 22, 1976; 44 FR 40289, July 10, 1979; 46 FR 62845, Dec. 29, 1981; 49 FR 15187, Apr. 18, 1984;

50 FR 4134, Jan. 29, 1985; 55 FR 28381, July 11, 1990; 64 FR 56453, Oct. 20, 1999; 67 FR 9587, Mar. 4, 2002; 70 FR 14985, Mar. 24, 2005]

§610.14 Identity.

The contents of a final container of each filling of each lot shall be tested for identity after all labeling operations shall have been completed. The identity test shall be specific for each product in a manner that will adequately identify it as the product designated on final container and package labels and circulars, and distinguish it from any other product being processed in the same laboratory. Identity may be established either through the physical or chemical characteristics of the product, inspection by macroscopic or microscopic methods, specific cultural tests, or in vitro or in vivo immunological tests.

§610.15 Constituent materials.

(a) *Ingredients, preservatives, diluents, adjuvants.* All ingredients used in a licensed product, and any diluent provided as an aid in the administration of the product, shall meet generally accepted standards of purity and quality. Any preservative used shall be sufficiently nontoxic so that the amount present in the recommended dose of the product will not be toxic to the recipient, and in the combination used it shall not denature the specific substances in the product to result in a decrease below the minimum acceptable potency within the dating period when stored at the recommended temperature. Products in multiple-dose containers shall contain a preservative, except that a preservative need not be added to Yellow Fever Vaccine; Poliovirus Vaccine Live Oral; viral vaccines labeled for use with the jet injector; dried vaccines when the accompanying diluent contains a preservative; or to an Allergenic Product in 50 percent or more volume in volume (v/v) glycerin. An adjuvant shall not be introduced into a product unless there is satisfactory evidence that it does not affect adversely the safety or potency of the product. The amount of aluminum in the recommended individual dose of a biological product shall not exceed:

(1) 0.85 milligrams if determined by assay;

(2) 1.14 milligrams if determined by calculation on the basis of the amount of aluminum compound added; or

(3) 1.25 milligrams determined by assay provided that data demonstrating that the amount of aluminum used is safe and necessary to produce the intended effect are submitted to and approved by the Director, Center for Biologics Evaluation and Research or the Director, Center for Drug Evaluation and Research (see mailing addresses in §600.2(a) or (b) of this chapter).

(b) *Extraneous protein; cell culture produced vaccines.* Extraneous protein known to be capable of producing allergenic effects in human subjects shall not be added to a final virus medium of cell culture produced vaccines intended for injection. If serum is used at any stage, its calculated concentration in the final medium shall not exceed 1:1,000,000.

(c) *Antibiotics*. A minimum concentration of antibiotics, other than penicillin, may be added to the production substrate of viral vaccines.

(d) The Director of the Center for Biologics Evaluation and Research or the Director of the Center for Drug Evaluation and Research may approve an exception or alternative to any requirement in this section. Requests for such exceptions or alternatives must be in writing.

[38 FR 32056, Nov. 20, 1973, as amended at 46 FR 51903, Oct. 23, 1981; 48 FR 13025, Mar. 29, 1983; 48 FR 37023, Aug. 16, 1983; 49 FR 23834, June 8, 1984; 50 FR 4134, Jan. 29, 1985; 51 FR 15607, Apr. 25, 1986; 55 FR 11013, Mar. 26, 1990; 70 FR 14985, Mar. 24, 2005; 76 FR 20518, Apr. 13, 2011; 80 FR 18093, Apr. 3, 2015]

§610.16 Total solids in serums.

Except as otherwise provided by regulation, no liquid serum or antitoxin shall contain more than 20 percent total solids.

§610.17 Permissible combinations.

Licensed products may not be combined with other licensed products either therapeutic, prophylactic or diagnostic, except as a license is obtained for the combined product. Licensed products may not be combined with nonlicensable therapeutic, prophylactic, or diagnostic substances except as a license is obtained for such combination.

§610.18 Cultures.

(a) *Storage and maintenance.* Cultures used in the manufacture of products shall be stored in a secure and orderly manner, at a temperature and by a method that will retain the initial characteristics of the organisms and insure freedom from contamination and deterioration.

(b*) Identity and verification.* Each culture shall be clearly identified as to source strain. A complete identification of the strain shall be made for each new stock culture preparation. Primary and subsequent seed lots shall be identified by lot number and date of preparation. Periodic tests shall be performed as often as necessary to verify the integrity of the strain characteristics and freedom from extraneous organisms. Results of all periodic tests for verification of cultures and determination of freedom from extraneous organisms shall be recorded and retained.

(c) *Cell lines used for manufacturing biological products*—(1) *General requirements.* Cell lines used for manufacturing biological products shall be:

(i) Identified by history;

(ii) Described with respect to cytogenetic characteristics and tumorigenicity;

(iii) Characterized with respect to in vitro growth characteristics and life potential; and

(iv) Tested for the presence of detectable microbial agents.

(2) *Tests*. Tests that are necessary to assure the safety, purity, and potency of a product may be required by the Director, Center for Biologics Evaluation and Research or the Director, Center for Drug Evaluation and Research.

(3) *Applicability*. This paragraph applies to diploid and nondiploid cell lines. Primary cell cultures that are not subcultivated and primary cell cultures that are subsequently subcultivated for only a very limited number of population doublings are not subject to the provisions of this paragraph (c).

(d) *Records*. The records appropriate for cultures under this section shall be prepared and maintained as required by the applicable provisions of §§ 211.188 and 211.194 of this chapter.

[38 FR 32056, Nov. 20, 1973, as amended at 51 FR 44453, Dec. 10, 1986; 55 FR 11013, Mar. 26, 1990; 67 FR 9587, Mar. 4, 2002; 70 FR 14985, Mar. 24, 2005]

Subpart D—[Reserve]

§§610.20-610.21 [Reserved]

Subpart D—Mycoplasma

§610.30 Test for Mycoplasma.

Except as provided otherwise in this subchapter, prior to clarification or filtration in the case of live virus vaccines produced from in vitro living cell cultures, and prior to inactivation in the case of inactivated virus vaccines produced from such living cell cultures, each virus harvest pool and control fluid pool shall be tested for the presence of *Mycoplasma*, as follows:

Samples of the virus for this test shall be stored either (1) between 2 and 8 °C for no longer than 24 hours, or (2) at −20 °C or lower if stored for longer than 24 hours. The test shall be performed on samples of the viral harvest pool and on control fluid pool obtained at the time of viral harvest, as follows: No less than 2.0 ml. of each sample shall be inoculated in evenly distributed amounts over the surface of no less than 10 plates of at least two agar

media. No less than 1.0 ml. of sample shall be inoculated into each of four tubes containing 10 ml. of a semisolid broth medium. The media shall be such as have been shown to be capable of detecting known Mycoplasma and each test shall include control cultures of at least two known strains of Mycoplasma, one of which must be M. pneumoniae. One half of the plates and two tubes of broth shall be incubated aerobically at 36 °C ±1 °C and the remaining plates and tubes shall be incubated anaerobically at 36 °C ±1 °C in an environment of 5-10 percent CO2 in N2. Aerobic incubation shall be for a period of no less than 14 days and the broth in the two tubes shall be tested after 3 days and 14 days, at which times 0.5 ml. of broth from each of the two tubes shall be combined and subinoculated on to no less than 4 additional plates and incubated aerobically. Anaerobic incubation shall be for no less than 14 days and the broth in the two tubes shall be tested after 3 days and 14 days, at which times 0.5 ml. of broth from each of the two tubes shall be combined and subinoculated onto no less than four additional plates and incubated anaerobically. All inoculated plates shall be incubated for no less than 14 days, at which time observation for growth of Mycoplasma shall be made at a magnification of no less than 300×. If the Dienes Methylene Blue-Azure dye or an equivalent staining procedure is used, no less than a one square cm. plug of the agar shall be excised from the inoculated area and examined for the presence of Mycoplasma. The presence of the Mycoplasma shall be determined by comparison of the growth obtained from the test samples with that of the control cultures, with respect to typical colonial and microscopic morphology. The virus pool is satisfactory for vaccine manufacture if none of the tests on the samples show evidence of the presence of Mycoplasma.

[38 FR 32056, Nov. 20, 1973, as amended at 63 FR 16685, Apr. 6, 1998]

Subpart E—Testing Requirements for Relevant Transfusion-Transmitted Infections

§610.39 Definitions.

The definitions set out in §630.3 of this chapter apply to this subpart.

[80 FR 29896, May 22, 2015]

§610.40 Test requirements.

(a) *Human blood and blood components.* Except as specified in paragraphs (c) and (d) of this section, you, an establishment that collects blood and blood components for transfusion or for use in manufacturing a product, including donations intended as a component of, or used to manufacture, a medical device, must comply with the following requirements:

(1) Test each donation for evidence of infection due to the relevant transfusion-transmitted infections described in §630.3(h)(1)(i) through (iii) of this chapter (HIV, HBV, and HCV).

(2) Test each donation for evidence of infection due to the relevant transfusion-transmitted infections described in §630.3(h)(1)(iv) through (vii) of this chapter (HTLV, syphilis, West Nile virus, and Chagas disease). The following exceptions apply:

(i) To identify evidence of infection with syphilis in donors of Source Plasma, you must test donors for evidence of such infection in accordance with §640.65(b) of this chapter, and not under this section.

(ii) You are not required to test donations of Source Plasma for evidence of infection due to the relevant transfusion-transmitted infections described in §630.3(h)(1)(iv), (vi), and (vii) of this chapter (HTLV, West Nile virus, and Chagas disease).

(iii) For each of the relevant transfusion-transmitted infections described in §630.3(h)(1)(iv) through (vii) of this chapter (HTLV, syphilis, West Nile virus, and Chagas disease):

(A) If, based on evidence related to the risk of transmission of that relevant transfusion-transmitted infection, testing each donation is not necessary to reduce adequately and appropriately the risk

of transmission of such infection by blood or a blood component, you may adopt an adequate and appropriate alternative testing procedure that has been found acceptable for this purpose by FDA.

(B) If, based on evidence related to the risk of transmission of that relevant transfusion-transmitted infection, testing previously required for that infection is no longer necessary to reduce adequately and appropriately the risk of transmission of such infection by blood or a blood component, you may stop such testing in accordance with procedures found acceptable for this purpose by FDA.

(3) For each of the relevant transfusion-transmitted infections described in §630.3(h)(1)(viii) through (x) of this chapter (CJD, vCJD, malaria) and §630.3(h)(2) of this chapter (other transfusion-transmitted infections):

(i) You must test for evidence of infection when the following conditions are met:

(A) A test(s) for the relevant transfusion-transmitted infection is licensed, approved or cleared by FDA for use as a donor screening test and is available for such use; and

(B) Testing for the relevant transfusion-transmitted infection is necessary to reduce adequately and appropriately the risk of transmission of the relevant transfusion-transmitted infection by blood, or blood component, or blood derivative product manufactured from the collected blood or blood component.

(ii) You must perform this testing on each donation, unless one of the following exceptions applies:

(A) Testing of each donation is not necessary to reduce adequately and appropriately the risk of transmission of such infection by blood, blood component, or blood derivative product manufactured from the collected blood or blood component. When evidence related to the risk of transmission of such infection supports this determination, you may adopt an adequate and appropriate alternative testing procedure that has been found acceptable for this purpose by FDA.

(B) Testing of each donation is not necessary to reduce adequately and appropriately the risk of transmission of such infection by blood, blood component, or blood derivative product manufactured from the collected blood or blood component. When evidence related to the risk of transmission of such infection supports this determination, you may stop such testing in accordance with procedures found acceptable for this purpose by FDA.

(4) Evidence related to the risk of transmission of a relevant transfusion-transmitted infection that would support a determination that testing is not necessary, or that testing of each donation is not necessary, to reduce adequately and appropriately the risk of transmission of such infection by blood or blood component, as described in paragraphs (a)(2)(iii)(A) and (B) of this section, or by blood, blood component, or blood derivative, as described in paragraphs (a)(3)(ii)(A) and (B) of this section, includes epidemiological or other scientific evidence. It may include evidence related to the seasonality or geographic limitation of risk of transmission of such infection by blood or blood component, or other information related to when and how a donation is at risk of transmitting a relevant transfusion-transmitted infection. It may also include evidence related to the effectiveness of manufacturing steps (for example, the use of pathogen reduction technology) that reduce the risk of transmission of the relevant transfusion-transmitted infection by blood, blood components, or blood derivatives, as applicable.

(b) *Testing using one or more licensed, approved, or cleared screening tests.* To perform testing for evidence of infection due to relevant transfusion-transmitted infections as required in paragraph (a) of this section, you must use screening tests that FDA has licensed, approved, or cleared for such use, in accordance with the manufacturer's instructions. You must perform one or more such tests as necessary to reduce adequately and appropriately the risk of transmission of relevant transfusion-transmitted infections.

(c) *Exceptions to testing for dedicated donations, medical devices, and samples.*—(1) *Dedicated donations.* (i) You must test donations of human blood and blood components from a donor whose donations are dedicated to and used solely by a single identified recipient under paragraphs (a), (b), and (e) of this section; except that, if the donor makes multiple donations for a single identified recipient, you may perform such testing only on the first donation in each 30-day period. If an untested dedicated donation is made available for any use other than transfusion to the single, identified recipient, then this exemption from the testing required under this section no longer applies.

(ii) Each donation must be labeled as required under §606.121 of this chapter and with a label entitled "INTENDED RECIPIENT INFORMATION LABEL" containing the name and identifying information of the recipient. Each donation must also have the following label, as appropriate:

Donor Testing Status	**Label**
Tests negative	Label as required under §606.121
Tested negative within the last 30 days	"DONOR TESTED WITHIN THE LAST 30 DAYS"

(2) *Medical device.* (i) You are not required to test donations of human blood or blood components intended solely as a component of, or used to prepare, a medical device for evidence of infection due to the relevant transfusion-transmitted infections listed in §630.3(h)(iv) of this chapter unless the final device contains viable leukocytes.

(ii) Donations of human blood and blood components intended solely as a component of, or used to prepare, a medical device must be labeled "Caution: For Further Manufacturing Use as a Component of, or to Prepare, a Medical Device."

(3) *Samples*. You are not required to test samples of blood, blood components, plasma, or sera if used or distributed for clinical laboratory testing or research purposes and not intended for administration to humans or in the manufacture of a product.

(d) Autologous donations. You, an establishment that collects human blood or blood components from autologous donors, or you, an establishment that is a consignee of a collecting establishment, are not required to test donations of human blood or blood components from autologous donors for evidence of infection due to relevant transfusion-transmitted infections listed in paragraph (a) of this section, except:

(1) If you allow any autologous donation to be used for allogeneic transfusion, you must assure that all autologous donations are tested under this section.

(2) If you ship autologous donations to another establishment that allows autologous donations to be used for allogeneic transfusion, you must assure that all autologous donations shipped to that establishment are tested under this section.

(3) If you ship autologous donations to another establishment that does not allow autologous donations to be used for allogeneic transfusion, you must assure that, at a minimum, the first donation in each 30-day period is tested under this section.

(4) Each autologous donation must be labeled as required under §606.121 of this chapter and with the following label, as appropriate:

Donor Testing Status	**Label**
Untested	"DONOR UNTESTED"
Tests negative	Label as required under §606.121
Reactive on current collection/reactive in the last 30 days	"BIOHAZARD" legend in §610.40(h)(2)(ii)(B)

Tested negative within the last 30 days	"DONOR TESTED WITHIN THE LAST 30 DAYS"

(e) *Further testing.* You must further test each donation, including autologous donations, found to be reactive by a donor screening test performed under paragraphs (a) and (b) of this section using a licensed, approved, or cleared supplemental test, when available. If no such supplemental test is available, you must perform one or more licensed, approved, or cleared tests as adequate and appropriate to provide additional information concerning the reactive donor's infection status. Except:

(1) For autologous donations:

(i) You must further test under this section, at a minimum, the first reactive donation in each 30 calendar day period; or

(ii) If you have a record for that donor of a positive result on further testing performed under this section, you do not have to further test an autologous donation.

(2) You are not required to perform further testing of a donation found to be reactive by a treponemal donor screening test for syphilis.

(f) *Testing responsibility.* Required testing under this section, must be performed by a laboratory registered in accordance with part 607 of this chapter and either certified to perform such testing on human specimens under the Clinical Laboratory Improvement Amendments of 1988 (42 U.S.C. 263a) under 42 CFR part 493 or has met equivalent requirements as determined by the Centers for Medicare and Medicaid Services in accordance with those provisions.

(g) *Release or shipment prior to testing.* Human blood or blood components that are required to be tested for evidence of infection due to relevant transfusion-transmitted infections designated in paragraph (a) of this section may be released or shipped prior to completion of testing in the following circumstances provided that you label the blood or blood components under §606.121(h) of this chapter, you complete the tests for evidence of infection due to relevant transfusion-transmitted infections as soon as possible after release or shipment, and that you provide the results promptly to the consignee:

(1) Only in appropriately documented medical emergency situations; or

(2) For further manufacturing use as approved in writing by FDA.

(h) *Restrictions on shipment or use*—(1) *Reactive screening test.* You must not ship or use human blood or blood components that have a reactive screening test for evidence of infection due to relevant transfusion-transmitted infection(s) designated in paragraph (a) of this section or that are collected from a donor with a previous record of a reactive screening test for evidence of infection due to relevant transfusion-transmitted infection(s) designated in paragraph (a) of this section, except as provided in paragraphs (h)(2)(i) through (h)(2)(vii) of this section.

(2) *Exceptions.* (i) You may ship or use blood or blood components intended for autologous use, including reactive donations, as described in paragraph (d) of this section.

(ii) You must not ship or use human blood or blood components that have a reactive screening test for evidence of infection due to a relevant transfusion-transmitted infection(s) designated in paragraph (a) of this section or that are collected from a donor deferred under §610.41(a) unless you meet the following conditions:

(A) Except for autologous donations, you must obtain from FDA written approval for the shipment or use;

(B) You must appropriately label such blood or blood components as required under §606.121 of this chapter, and with the "BIOHAZARD" legend;

(C) Except for autologous donations, you must label such human blood and blood components as reactive for the appropriate screening test for evidence of infection due to the identified relevant transfusion-transmitted infection(s);

(D) If the blood or blood components are intended for further manufacturing use into injectable products, you must include a statement on the container label indicating the exempted use specifically approved by FDA.

(E) Each blood or blood component with a reactive screening test and intended solely as a component of, or used to prepare a medical device, must be labeled with the following label, as appropriate:

Type of Medical Device	Label
A medical device other than an in vitro diagnostic reagent	"Caution: For Further Manufacturing Use as a Component of a Medical Device For Which There Are No Alternative Sources"
An in vitro diagnostic reagent	"Caution: For Further Manufacturing Into In Vitro Diagnostic Reagents For Which There Are No Alternative Sources"

(iii) The restrictions on shipment or use do not apply to samples of blood, blood components, plasma, or sera if used or distributed for clinical laboratory testing or research purposes, and not intended for administration in humans or in the manufacture of a product.

(iv) You may use human blood or blood components from a donor with a previous record of a reactive screening test(s) for evidence of infection due to a relevant transfusion-transmitted infection(s) designated in paragraph (a) of this section, if:

(A) At the time of donation, the donor is shown or was previously shown to be eligible by a requalification method or process found acceptable for such purposes by FDA under §610.41(b); and

(B) tests performed under paragraphs (a) and (b) of this section are nonreactive.

(v) Anti-HBc reactive donations, otherwise nonreactive when tested as required under this section, may be used for further manufacturing into plasma derivatives without prior FDA approval or a "BIOHAZARD" legend as required under paragraphs (h)(2)(ii)(A) and (h)(2)(ii)(B) of this section.

(vi) You may use human blood or blood components, excluding Source Plasma, that test reactive by a screening test for syphilis as required under paragraph (a) of this section if, the donation is further tested by an adequate and appropriate test which demonstrates that the reactive screening test is a biological false positive. You must label the blood or blood components with both test results.

(vii) You may use Source Plasma from a donor who tests reactive by a screening test for syphilis as required under §640.65(a)(2)(ii) and (b)(1)(i) of this chapter, if the donor meets the requirements of §640.65(b)(2)(i) through (b)(2)(iv) of this chapter.

[66 FR 31162, June 11, 2001, as amended at 77 FR 18, Jan. 3, 2012; 80 FR 29896, May 22, 2015]

§610.41 Donor deferral.

(a) You, an establishment that collects human blood or blood components, must defer donors testing reactive by a screening test for evidence of infection due to a relevant transfusion-transmitted infection(s) under §610.40(a), from future donations of human blood and blood components, except:

(1) You are not required to defer a donor who tests reactive for anti-HBc or anti-HTLV, types I and II, on only one occasion. However, you must defer the donor if further testing for HBV or HTLV has been performed under §610.40(e) and the donor is found to be positive, or if a second, licensed, cleared, or approved screening test for HBV or HTLV has been performed on the same donation under §610.40(a) and is reactive, or if the donor tests reactive for anti-HBc or anti-HTLV, types I and II, on more than one occasion;

(2) A deferred donor who tests reactive for evidence of infection due to a relevant transfusion-transmitted infection(s) under §610.40(a) may serve as a donor for blood or blood components shipped or used under §610.40(h)(2)(ii);

(3) A deferred donor who showed evidence of infection due to hepatitis B surface antigen (HBsAg) when previously tested under §610.40(a), (b), and (e) subsequently may donate Source Plasma

for use in the preparation of Hepatitis B Immune Globulin (Human) provided the current donation tests nonreactive for HBsAg and the donor is otherwise determined to be eligible;

(4) A deferred donor, who otherwise is determined to be eligible for donation and tests reactive for anti-HBc or for evidence of infection due to HTLV, types I and II, may serve as a donor of Source Plasma;

(5) A deferred donor who tests reactive for a relevant transfusion-transmitted infections(s) under §610.40(a), may serve as an autologous donor under §610.40(d).

(b) A deferred donor subsequently may be found to be eligible as a donor of blood or blood components by a requalification method or process found acceptable for such purposes by FDA. Such a donor is considered no longer deferred.

(c) You must comply with the requirements under §§610.46 and 610.47 when a donor tests reactive by a screening test for HIV or HCV required under §610.40(a) and (b), or when you are aware of other reliable test results or information indicating evidence of HIV or HCV infection.

[66 FR 31164, June 11, 2001, as amended at 72 FR 48798, Aug. 24, 2007; 80 FR 29897, May 22, 2015]

§610.42 Restrictions on use for further manufacture of medical devices.

(a) In addition to labeling requirements in subchapter H of this chapter, when a medical device contains human blood or a blood component as a component of the final device, and the human blood or blood component was found to be reactive by a screening test performed under §610.40(a) and (b), then you must include in the device labeling a statement of warning indicating that the product was manufactured from a donation found to be reactive by a screening test for evidence of infection due to the identified relevant transfusion-transmitted infection(s).

(b) FDA may approve an exception or alternative to the statement of warning required in paragraph (a) of this section based on evidence that the reactivity of the human blood or blood component in the medical device presents no significant health risk through use of the medical device.

[66 FR 31164, June 11, 2001, as amended at 80 FR 29897, May 22, 2015]

§610.44 Use of reference panels by manufacturers of test kits.

(a) When available and appropriate to verify acceptable sensitivity and specificity, you, a manufacturer of test kits, must use a reference panel you obtain from FDA or from an FDA designated source to test lots of the following products. You must test each lot of the following products, unless FDA informs you that less frequent testing is appropriate, based on your consistent prior production of products of acceptable sensitivity and specificity:

(1) A test kit approved for use in testing donations of human blood and blood components for evidence of infection due to relevant transfusion-transmitted infections under §610.40(a); and

(2) Human immunodeficiency virus (HIV) test kit approved for use in the diagnosis, prognosis, or monitoring of this relevant transfusion-transmitted infection.

(b) You must not distribute a lot that is found to be not acceptable for sensitivity and specificity under §610.44(a). FDA may approve an exception or alternative to this requirement. Applicants must submit such requests in writing. However, in limited circumstances, such requests may be made orally and permission may be given orally by FDA. Oral requests and approvals must be promptly followed by written requests and written approvals.

[66 FR 31164, June 11, 2001, as amended at 80 FR 29897, May 22, 2015]

§610.46 Human immunodeficiency virus (HIV) "lookback" requirements.

(a) If you are an establishment that collects Whole Blood or blood components, including Source Plasma and Source Leukocytes, you must establish, maintain, and follow an appropriate system for the following actions:

(1) Within 3 calendar days after a donor tests reactive for evidence of human immunodeficiency virus (HIV) infection when tested under §610.40(a) and (b) or when you are made aware of other reliable test results or information indicating evidence of HIV infection, you must review all records required under §606.160(d) of this chapter, to identify blood and blood components previously donated by such a donor. For those identified blood and blood components collected:

(i) Twelve months and less before the donor's most recent nonreactive screening tests, or

(ii) Twelve months and less before the donor's reactive direct viral detection test, e.g., nucleic acid test or HIV p24 antigen test, and nonreactive antibody screening test, whichever is the lesser period, you must:

(A) Quarantine all previously collected in-date blood and blood components identified under paragraph (a)(1) of this section if intended for use in another person or for further manufacture into injectable products, except pooled blood components intended solely for further manufacturing into products that are manufactured using validated viral clearance procedures; and

(B) Notify consignees to quarantine all previously collected in-date blood and blood components identified under paragraph (a)(1) of this section if intended for use in another person or for further manufacture into injectable products, except pooled blood components intended solely for further manufacturing into products that are manufactured using validated viral clearance procedures;

(2) You must perform further testing for HIV as required under §610.40(e) of this chapter on the reactive donation.

(3) You must notify consignees of the results of further testing for HIV, or the results of the reactive screening test if further testing under paragraph (a)(2) of this section is not available, or if under an investigational new drug application (IND) or investigational device exemption (IDE), is exempted for such use by FDA, within 45 calendar days after the donor tests reactive for evidence of HIV infection under §610.40(a) and (b) of this chapter. Notification of consignees must include the test results for blood and blood components identified under paragraph (a)(1) of this section that were previously collected from donors who later test reactive for evidence of HIV infection.

(4) You must release from quarantine, destroy, or relabel quarantined in-date blood and blood components, consistent with the results of the further testing performed under paragraph (a)(2) of this section or the results of the reactive screening test if further testing is not available, or if under an IND or IDE, exempted for such use by FDA.

(b) If you are a consignee of Whole Blood or blood components, including Source Plasma and Source Leukocytes, you must establish, maintain, and follow an appropriate system for the following actions:

(1) You must quarantine all previously collected in-date blood and blood components identified under paragraph (a)(1) of this section, except pooled blood components intended solely for further manufacturing into products that are manufactured using validated viral clearance procedures, when notified by the collecting establishment.

(2) You must release from quarantine, destroy, or relabel quarantined in-date blood and blood components consistent with the results of the further testing performed under paragraph (a)(2) of this section, or the results of the reactive screening test if further testing is not available, or if under an IND or IDE, is exempted for such use by FDA.

(3) When further testing for HIV is positive or when the screening test is reactive and further testing is not available, or if under an IND or IDE is exempted for such use by FDA, you must notify transfusion recipients of previous collections of blood and blood components at increased risk of transmitting HIV infection, or the recipient's physician of record, of the need for recipient HIV testing and counseling. You must notify the recipient's physician of record or a legal representative or relative if the recipient is a minor, deceased, adjudged incompetent by a State court, or, if the recipient is

competent but State law permits a legal representative or relative to receive information on behalf of the recipient. You must make reasonable attempts to perform the notification within 12 weeks after receiving the results of further testing for evidence of HIV infection from the collecting establishment, or after receiving the donor's reactive screening test result for HIV if further testing is not available, or if under an IND or IDE is exempted for such use by FDA.

(c) Actions under this section do not constitute a recall as defined in §7.3 of this chapter.

[72 FR 48799, Aug. 24, 2007, as amended at 80 FR 29897, May 22, 2015]

§610.47 Hepatitis C virus (HCV) "lookback" requirements.

(a) If you are an establishment that collects Whole Blood or blood components, including Source Plasma and Source Leukocytes, you must establish, maintain, and follow an appropriate system for the following actions:

(1) Within 3 calendar days after a donor tests reactive for evidence of hepatitis C virus (HCV) infection when tested under §610.40(a) and (b) of this chapter or when you are made aware of other reliable test results or information indicating evidence of HCV infection, you must review all records required under §606.160(d) of this chapter, to identify blood and blood components previously donated by such a donor. For those identified blood and blood components collected:

(i) Twelve months and less before the donor's most recent nonreactive screening tests, or

(ii) Twelve months and less before the donor's reactive direct viral detection test, e.g., nucleic acid test and nonreactive antibody screening test, whichever is the lesser period, you must:

(A) Quarantine all previously collected in-date blood and blood components identified under paragraph (a)(1) of this section if intended for use in another person or for further manufacture into injectable products, except pooled blood components intended solely for further manufacturing into products that are manufactured using validated viral clearance procedures; and

(B) Notify consignees to quarantine all previously collected in-date blood and blood components identified under paragraph (a)(1) of this section if intended for use in another person or for further manufacture into injectable products, except pooled blood components intended solely for further manufacturing into products that are manufactured using validated viral clearance procedures;

(2) You must perform further testing for HCV as required under §610.40(e) on the reactive donation.

(3) You must notify consignees of the results of further testing for HCV, or the results of the reactive screening test if further testing is not available, or if under an investigational new drug application (IND) or investigational device exemption (IDE), is exempted for such use by FDA, within 45 calendar days after the donor tests reactive for evidence of HCV infection under §610.40(a) and (b). Notification of consignees must include the test results for blood and blood components identified under paragraph (a)(1) of this section that were previously collected from donors who later test reactive for evidence of HCV infection.

(4) You must release from quarantine, destroy, or relabel quarantined in-date blood and blood components consistent with the results of the further testing performed under paragraph (a)(2) of this section, or the results of the reactive screening test if further testing is not available, or if under an IND or IDE, exempted for such use by FDA.

(b) If you are a consignee of Whole Blood or blood components, including Source Plasma or Source Leukocytes, you must establish, maintain, and follow an appropriate system for the following actions:

(1) You must quarantine all previously collected in-date blood and blood components identified under paragraph (a)(1) of this section, except pooled blood components intended solely for further

manufacturing into products that are manufactured using validated viral clearance procedures, when notified by the collecting establishment.

(2) You must release from quarantine, destroy, or relabel quarantined in-date blood and blood components, consistent with the results of the further testing performed under paragraph (a)(2) of this section, or the results of the reactive screening test if further testing is not available, or if under an IND or IDE, is exempted for such use by FDA.

(3) When the further testing for HCV is positive or when the screening test is reactive and further testing is not available, or if under an IND or IDE, is exempted for such use by FDA, you must notify transfusion recipients of previous collections of blood and blood components at increased risk of transmitting HCV infection, or the recipient's physician of record, of the need for recipient HCV testing and counseling. You must notify the recipient's physician of record or a legal representative or relative if the recipient is a minor, adjudged incompetent by a State court, or if the recipient is competent but State law permits a legal representative or relative to receive information on behalf of the recipient. You must make reasonable attempts to perform the notification within 12 weeks after receiving the results of further testing for evidence of HCV infection from the collecting establishment, or after receiving the donor's reactive screening test result for HCV if further testing is not available, or if under an IND or IDE, is exempted for such use by FDA.

(c) Actions under this section do not constitute a recall as defined in § 7.3 of this chapter.

[72 FR 48799, Aug. 24, 2007, as amended at 80 FR 29897, May 22, 2015]

§ 610.48 [Reserved]

Subpart F—Dating Period Limitations

§ 610.50 Date of manufacture for biological products.

(a) *When the dating period begins.* The dating period for a product must begin on the date of manufacture as described in paragraphs (b) and (c) of this section. The dating period for a combination of two or more products must be no longer than the dating period of the component with the shortest dating period.

(b) *Determining the date of manufacture for biological products other than Whole Blood and blood components.* The date of manufacture for biological products, other than Whole Blood and blood components, must be identified in the approved biologics license application as one of the following, whichever is applicable: The date of:

(1) Potency test or other specific test as described in a biologics license application or supplement to the application;

(2) Removal from animals or humans;

(3) Extraction;

(4) Solution;

(5) Cessation of growth;

(6) Final sterile filtration of a bulk solution;

(7) Manufacture as described in part 660 of this chapter; or

(8) Other specific manufacturing activity described in a biologics license application or supplement to the biologics license application.

(c) *Determining the date of manufacture for Whole Blood and blood components.* (1) The date of manufacture for Whole Blood and blood components must be one of the following, whichever is applicable:

(i) Collection date and/or time;

(ii) Irradiation date;

(iii) The time the red blood cell product was removed from frozen storage for deglycerolization;

(iv) The time the additive or rejuvenation solution was added;

(v) The time the product was entered for washing or removing plasma (if prepared in an open system);

(vi) As specified in the instructions for use by the blood collection, processing, and storage system approved or cleared for such use by FDA; or

(vii) As approved by the Director, Center for Biologics Evaluation and Research, in a biologics license application or supplement to the application.

(2) For licensed Whole Blood and blood components, the date of manufacture must be identified in the approved biologics license application or supplement to the application.

[81 FR 26691, May 4, 2016]

§ 610.53 Dating periods for Whole Blood and blood components.

(a) *General*. Dating periods for Whole Blood and blood components are specified in the table in paragraph (b) of this section.

(b) *Table of dating periods.* In using the table in this paragraph, when a product in column A is stored at the storage temperature prescribed in column B, storage of a product must not exceed the dating period specified in column C, unless a different dating period is specified in the instructions for use by the blood collection, processing and storage system approved or cleared for such use by FDA. Container labels for each product must include the recommended storage temperatures.

Whole Blood and Blood Components Storage Temperatures and Dating Periods

A	B	C
Product	**Storage temperature**	**Dating period**
Whole Blood		
ACD, CPD, CP2D	Between 1 and 6 °C	21 days from date of collection.
CPDA-1	do[1]	35 days from date of collection.
Red Blood Cells		
ACD, CPD, CP2D	Between 1 and 6 °C	21 days from date of collection.
CPDA-1	do	35 days from date of collection.
Additive solutions	do	42 days from date of collection.
Open system(e.g., deglycerolized, washed)	do	24 hours after entering bag.

Deglycerolized in closed system with additive solution added	do	14 days after entering bag.
Irradiated	do	28 days from date of irradiation or original dating, whichever is shorter.
Frozen	−65 °C or colder	10 years from date of collection.
Platelets		
Platelets	Between 20 and 24 °C	5 days from date of collection.
Platelets	Other temperatures according to storage bag instructions	As specified in the instructions for use by the blood collection, processing and storage system approved or cleared for such use by FDA.
Plasma		
Fresh Frozen Plasma	−18 °C or colder	1 year from date of collection.
Plasma Frozen Within 24 Hours After Phlebotomy	do	1 year from date of collection.
Plasma Frozen Within 24 Hours After Phlebotomy Held at Room Temperature Up To 24 Hours After Phlebotomy	do	1 year from date of collection.
Plasma Cryoprecipitate Reduced	do	1 year from date of collection.
Plasma	do	5 years from date of collection.
Liquid Plasma	Between 1 and 6 °C	5 days from end of Whole Blood dating period.
Source Plasma (frozen injectable)	−20 °C or colder	10 years from date of collection.
Source Plasma Liquid (injectable)	10 °C or colder	According to approved biologics license application.
Source Plasma (noninjectable)	Temperature appropriate for final product	10 years from date of collection.
Therapeutic Exchange Plasma	−20 °C or colder	10 years from date of collection.
Cryoprecipitated AHF		
Cryoprecipitated AHF	−18 °C or colder	1 year from date of collection of source blood or from date of collection of oldest source blood in pre-storage pool.
Source Leukocytes		

Source Leukocytes	Temperature appropriate for final product	In lieu of expiration date, the collection date must appear on the label.

1.The abbreviation "do." for ditto is used in the table to indicate that the previous line is being repeated.

[81 FR 26691, May 4, 2016]

Subpart G—Labeling Standards

§610.60 Container label.

(a) *Full label.* The following items shall appear on the label affixed to each container of a product capable of bearing a full label:

(1) The proper name of the product;

(2) The name, address, and license number of manufacturer;

(3) The lot number or other lot identification;

(4) The expiration date;

(5) The recommended individual dose, for multiple dose containers.

(6) The statement: "'Rx only'" for prescription biologicals.

(7) If a Medication Guide is required under part 208 of this chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label.

(b) *Package label information.* If the container is not enclosed in a package, all the items required for a package label shall appear on the container label.

(c) *Partial label.* If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label.

(d) No container label. If the container is incapable of bearing any label, the items required for a container label may be omitted, provided the container is placed in a package which bears all the items required for a package label.

(e) *Visual inspection.* When the label has been affixed to the container a sufficient area of the container shall remain uncovered for its full length or circumference to permit inspection of the contents.

[38 FR 32056, Nov. 20, 1973, as amended at 47 FR 22518, May 25, 1982; 63 FR 66400, Dec. 1, 1998; 67 FR 4907, Feb. 1, 2002]

§610.61 Package label.

The following items shall appear on the label affixed to each package containing a product:

(a) The proper name of the product;

(b) The name, address, and license number of manufacturer;

(c) The lot number or other lot identification;

(d) The expiration date;

(e) The preservative used and its concentration, or if no preservative is used and the absence of a preservative is a safety factor, the words "no preservative";

(f) The number of containers, if more than one;

(g) The amount of product in the container expressed as (1) the number of doses, (2) volume, (3) units of potency, (4) weight, (5) equivalent volume (for dried product to be reconstituted), or (6) such combination of the foregoing as needed for an accurate description of the contents, whichever is applicable;

(h) The recommended storage temperature;

(i) The words "Shake Well", "Do not Freeze" or the equivalent, as well as other instructions, when indicated by the character of the product;

(j) The recommended individual dose if the enclosed container(s) is a multiple-dose container;

(k) The route of administration recommended, or reference to such directions in an enclosed circular;

(l) Known sensitizing substances, or reference to an enclosed circular containing appropriate information;

(m) The type and calculated amount of antibiotics added during manufacture;

(n) The inactive ingredients when a safety factor, or reference to an enclosed circular containing appropriate information;

(o) The adjuvant, if present;

(p) The source of the product when a factor in safe administration;

(q) The identity of each microorganism used in manufacture, and, where applicable, the production medium and the method of inactivation, or reference to an enclosed circular containing appropriate information;

(r) Minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no U.S. standard of potency has been prescribed, the words "No U.S. standard of potency."

(s) The statement: "'Rx only'" for prescription biologicals.

[38 FR 32056, Nov. 20, 1973, as amended at 47 FR 22518, May 25, 1982; 55 FR 10423, Mar. 21, 1990; 67 FR 4907, Feb. 1, 2002]

§ 610.62 Proper name; package label; legible type.

(a) *Position*. The proper name of the product on the package label shall be placed above any trademark or trade name identifying the product and symmetrically arranged with respect to other printing on the label.

(b) *Prominence*. The point size and typeface of the proper name shall be at least as prominent as the point size and typeface used in designating the trademark and trade name. The contrast in color value between the proper name and the background shall be at least as great as the color value between the trademark and trade name and the background. Typography, layout, contrast, and other printing features shall not be used in a manner that will affect adversely the prominence of the proper name.

(c) *Legible type.* All items required to be on the container label and package label shall be in legible type. "Legible type" is type of a size and character which can be read with ease when held in a good light and with normal vision.

§610.63 Divided manufacturing responsibility to be shown.

If two or more licensed manufacturers participate in the manufacture of a biological product, the name, address, and license number of each must appear on the package label, and on the label of the container if capable of bearing a full label.

[64 FR 56453, Oct. 20, 1999]

§610.64 Name and address of distributor.

The name and address of the distributor of a product may appear on the label provided that the name, address, and license number of the manufacturer also appears on the label and the name of the distributor is qualified by one of the following phrases: "Manufactured for _____", "Distributed by _____", "Manufactured by _____ for _____", "Manufactured for _____ by _____", "Distributor: _____", or "Marketed by _____". The qualifying phrases may be abbreviated.

[61 FR 57330, Nov. 6, 1996]

§610.65 Products for export.

Labels on packages or containers of products for export may be adapted to meet specific requirements of the regulations of the country to which the product is to be exported provided that in all such cases the minimum label requirements prescribed in §610.60 are observed.

§610.67 Bar code label requirements.

Biological products must comply with the bar code requirements at §201.25 of this chapter. However, the bar code requirements do not apply to devices regulated by the Center for Biologics Evaluation and Research or to blood and blood components intended for transfusion. For blood and blood components intended for transfusion, the requirements at §606.121(c)(13) of this chapter apply instead.

[69 FR 9171, Feb. 26, 2004]

§610.68 Exceptions or alternatives to labeling requirements for biological products held by the Strategic National Stockpile.

(a) The appropriate FDA Center Director may grant an exception or alternative to any provision listed in paragraph (f) of this section and not explicitly required by statute, for specified lots, batches, or other units of a biological product, if the Center Director determines that compliance with such labeling requirement could adversely affect the safety, effectiveness, or availability of such product that is or will be included in the Strategic National Stockpile.

(b)(1)(i) A Strategic National Stockpile official or any entity that manufactures (including labeling, packing, relabeling, or repackaging), distributes, or stores a biological product that is or will be included in the Strategic National Stockpile may submit, with written concurrence from a Strategic National Stockpile official, a written request for an exception or alternative described in paragraph (a) of this section to the Center Director.

(ii) The Center Director may grant an exception or alternative described in paragraph (a) of this section on his or her own initiative.

(2) A written request for an exception or alternative described in paragraph (a) of this section must:

(i) Identify the specified lots, batches, or other units of the biological product that would be subject to the exception or alternative;

(ii) Identify the labeling provision(s) listed in paragraph (f) of this section that are the subject of the exception or alternative request;

(iii) Explain why compliance with such labeling provision(s) could adversely affect the safety, effectiveness, or availability of the specified lots, batches, or other units of the biological product that are or will be included in the Strategic National Stockpile;

(iv) Describe any proposed safeguards or conditions that will be implemented so that the labeling of the product includes appropriate information necessary for the safe and effective use of the product, given the anticipated circumstances of use of the product;

(v) Provide a draft of the proposed labeling of the specified lots, batches, or other units of the biological product subject to the exception or alternative; and

(vi) Provide any other information requested by the Center Director in support of the request.

(c) The Center Director must respond in writing to all requests under this section.

(d) A grant of an exception or alternative under this section will include any safeguards or conditions deemed appropriate by the Center Director so that the labeling of product subject to the exception or alternative includes the information necessary for the safe and effective use of the product, given the anticipated circumstances of use.

(e) If you are a sponsor receiving a grant of a request for an exception or alternative to the labeling requirements under this section:

(1) You need not submit a supplement under §601.12(f)(1) through (f)(2) of this chapter; however,

(2) You must report any grant of a request for an exception or alternative under this section as part of your annual report under §601.12(f)(3) of this chapter.

(f) The Center Director may grant an exception or alternative under this section to the following provisions of this chapter, to the extent that the requirements in these provisions are not explicitly required by statute:

(1) §610.60;

(2) §610.61(c) and (e) through (r);

(3) §610.62;

(4) §610.63;

(5) §610.64;

(6) §610.65; and

(7) §312.6.

[72 FR 73600, Dec. 28, 2007]

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SUBCHAPTER H—MEDICAL DEVICES

PART 812—INVESTIGATIONAL DEVICE EXEMPTIONS

Authority: 21 U.S.C. 331, 351, 352, 353, 355, 360, 360c-360f, 360h-360j, 360bbb-8b, 371, 372, 374, 379e, 381, 382, 383; 42 U.S.C. 216, 241, 262, 263b-263n.

Source: 45 FR 3751, Jan. 18, 1980, unless otherwise noted.

Subpart A—General Provisions

§812.1 Scope.

(a) The purpose of this part is to encourage, to the extent consistent with the protection of public health and safety and with ethical standards, the discovery and development of useful devices intended for human use, and to that end to maintain optimum freedom for scientific investigators in their pursuit of this purpose. This part provides procedures for the conduct of clinical investigations of devices. An approved investigational device exemption (IDE) permits a device that otherwise would be required to comply with a performance standard or to have premarket approval to be shipped lawfully for the purpose of conducting investigations of that device. An IDE approved under §812.30 or considered approved under §812.2(b) exempts a device from the requirements of the following sections of the Federal Food, Drug, and Cosmetic Act (the act) and regulations issued thereunder: Misbranding under section 502 of the act, registration, listing, and premarket notification under section 510, performance standards under section 514, premarket approval under section 515, a banned device regulation under section 516, records and reports under section 519, restricted device requirements under section 520(e), good manufacturing practice requirements under section 520(f) except for the requirements found in §820.30, if applicable (unless the sponsor states an intention to comply with these requirements under §812.20(b)(3) or §812.140(b)(4)(v)) and color additive requirements under section 721.

(b) References in this part to regulatory sections of the Code of Federal Regulations are to chapter I of title 21, unless otherwise noted.

[45 FR 3751, Jan. 18, 1980, as amended at 59 FR 14366, Mar. 28, 1994; 61 FR 52654, Oct. 7, 1996]

§812.2 Applicability.

(a) *General*. This part applies to all clinical investigations of devices to determine safety and effectiveness, except as provided in paragraph (c) of this section.

(b) *Abbreviated requirements.* The following categories of investigations are considered to have approved applications for IDE's, unless FDA has notified a sponsor under §812.20(a) that approval of an application is required:

(1) An investigation of a device other than a significant risk device, if the device is not a banned device and the sponsor:

(i) Labels the device in accordance with §812.5;

(ii) Obtains IRB approval of the investigation after presenting the reviewing IRB with a brief explanation of why the device is not a significant risk device, and maintains such approval;

(iii) Ensures that each investigator participating in an investigation of the device obtains from each subject under the investigator's care, informed consent under part 50 and documents it, unless documentation is waived by an IRB under §56.109(c).

(iv) Complies with the requirements of §812.46 with respect to monitoring investigations;

(v) Maintains the records required under §812.140(b) (4) and (5) and makes the reports required under §812.150(b) (1) through (3) and (5) through (10);

(vi) Ensures that participating investigators maintain the records required by §812.140(a)(3)(i) and make the reports required under §812.150(a) (1), (2), (5), and (7); and

(vii) Complies with the prohibitions in §812.7 against promotion and other practices.

(2) An investigation of a device other than one subject to paragraph (e) of this section, if the investigation was begun on or before July 16, 1980, and to be completed, and is completed, on or before January 19, 1981.

(c) *Exempted investigations.* This part, with the exception of §812.119, does not apply to investigations of the following categories of devices:

(1) A device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time.

(2) A device, other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of part 807 in determining substantial equivalence.

(3) A diagnostic device, if the sponsor complies with applicable requirements in §809.10(c) and if the testing:

(i) Is noninvasive,

(ii) Does not require an invasive sampling procedure that presents significant risk,

(iii) Does not by design or intention introduce energy into a subject, and

(iv) Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.

(4) A device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk.

(5) A device intended solely for veterinary use.

(6) A device shipped solely for research on or with laboratory animals and labeled in accordance with §812.5(c).

(7) A custom device as defined in §812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution.

(d) *Limit on certain exemptions.* In the case of class II or class III device described in paragraph (c)(1) or (2) of this section, this part applies beginning on the date stipulated in an FDA regulation or order that calls for the submission of premarket approval applications for an unapproved class III device, or establishes a performance standard for a class II device.

(e) *Investigations subject to IND's.* A sponsor that, on July 16, 1980, has an effective investigational new drug application (IND) for an investigation of a device shall continue to comply with the requirements of part 312 until 90 days after that date. To continue the investigation after that date, a sponsor shall comply with paragraph (b)(1) of this section, if the device is not a significant risk device, or shall have obtained FDA approval under §812.30 of an IDE application for the investigation of the device.

[45 FR 3751, Jan. 18, 1980, as amended at 46 FR 8956, Jan. 27, 1981; 46 FR 14340, Feb. 27, 1981; 53 FR 11252, Apr. 6, 1988; 62 FR 4165, Jan. 29, 1997; 62 FR 12096, Mar. 14, 1997]

§812.3 Definitions.

(a) *Act* means the Federal Food, Drug, and Cosmetic Act (sections 201-901, 52 Stat. 1040 et seq., as amended (21 U.S.C. 301-392)).

(b) A custom device means a device within the meaning of section 520(b) of the Federal Food, Drug, and Cosmetic Act.

(c) *FDA* means the Food and Drug Administration.

(d) *Implant* means a device that is placed into a surgically or naturally formed cavity of the human body if it is intended to remain there for a period of 30 days or more. FDA may, in order to protect public health, determine that devices placed in subjects for shorter periods are also "implants" for purposes of this part.

(e) *Institution* means a person, other than an individual, who engages in the conduct of research on subjects or in the delivery of medical services to individuals as a primary activity or as an adjunct to providing residential or custodial care to humans. The term includes, for example, a hospital, retirement home, confinement facility, academic establishment, and device manufacturer. The term has the same meaning as "facility" in section 520(g) of the act.

(f) *Institutional review board* (IRB) means any board, committee, or other group formally designated by an institution to review biomedical research involving subjects and established, operated, and functioning in conformance with part 56. The term has the same meaning as "institutional review committee" in section 520(g) of the act.

(g) *Investigational device* means a device, including a transitional device, that is the object of an investigation.

(h) *Investigation* means a clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device.

(i) *Investigator* means an individual who actually conducts a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject, or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team.

(j) *Monitor*, when used as a noun, means an individual designated by a sponsor or contract research organization to oversee the progress of an investigation. The monitor may be an employee of a sponsor or a consultant to the sponsor, or an employee of or consultant to a contract research organization. Monitor, when used as a verb, means to oversee an investigation.

(k) *Noninvasive*, when applied to a diagnostic device or procedure, means one that does not by design or intention: (1) Penetrate or pierce the skin or mucous membranes of the body, the ocular cavity, or the urethra, or (2) enter the ear beyond the external auditory canal, the nose beyond the nares, the mouth beyond the pharynx, the anal canal beyond the rectum, or the vagina beyond the cervical os. For purposes of this part, blood sampling that involves simple venipuncture is considered noninvasive, and the use of surplus samples of body fluids or tissues that are left over from samples taken for noninvestigational purposes is also considered noninvasive.

(l) *Person* includes any individual, partnership, corporation, association, scientific or academic establishment, Government agency or organizational unit of a Government agency, and any other legal entity.

(m) *Significant risk device* means an investigational device that:

(1) Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;

(2) Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;

(3) Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or

(4) Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

(n) *Sponsor* means a person who initiates, but who does not actually conduct, the investigation, that is, the investigational device is administered, dispensed, or used under the immediate direction of another individual. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators.

(o) *Sponsor-investigator* means an individual who both initiates and actually conducts, alone or with others, an investigation, that is, under whose immediate direction the investigational device is administered, dispensed, or used. The term does not include any person other than an individual. The obligations of a sponsor-investigator under this part include those of an investigator and those of a sponsor.

(p) *Subject* means a human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control. A subject may be in normal health or may have a medical condition or disease.

(q) *Termination* means a discontinuance, by sponsor or by withdrawal of IRB or FDA approval, of an investigation before completion.

(r) *Transitional device* means a device subject to section 520(l) of the act, that is, a device that FDA considered to be a new drug or an antibiotic drug before May 28, 1976.

(s) *Unanticipated adverse device effect* means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

(t) *Independent ethics committee (IEC)* means an independent review panel that is responsible for ensuring the protection of the rights, safety, and well-being of subjects involved in a clinical investigation and is adequately constituted to ensure that protection. An institutional review board (IRB), as defined in paragraph (f) of this section and subject to the requirements of part 56 of this chapter, is one type of IEC.

[45 FR 3751, Jan. 18, 1980, as amended at 46 FR 8956, Jan. 27, 1981; 48 FR 15622, Apr. 12, 1983; 81 FR 70340, Oct. 12, 2016; 83 FR 7385, Feb. 21, 2018]

§812.5 Labeling of investigational devices.

(a) *Contents*. An investigational device or its immediate package shall bear a label with the following information: the name and place of business of the manufacturer, packer, or distributor (in accordance with §801.1), the quantity of contents, if appropriate, and the following statement: "CAUTION—Investigational device. Limited by Federal (or United States) law to investigational use." The label or other labeling shall describe all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions.

(b) *Prohibitions*. The labeling of an investigational device shall not bear any statement that is false or misleading in any particular and shall not represent that the device is safe or effective for the purposes for which it is being investigated.

(c) *Animal research.* An investigational device shipped solely for research on or with laboratory animals shall bear on its label the following statement: "CAUTION—Device for investigational use in laboratory animals or other tests that do not involve human subjects."

(d) The appropriate FDA Center Director, according to the procedures set forth in §801.128 or §809.11 of this chapter, may grant an exception or alternative to the provisions in paragraphs (a) and (c) of this section, to the extent that these provisions are not explicitly required by statute, for specified lots, batches, or other units of a device that are or will be included in the Strategic National Stockpile.

[45 FR 3751, Jan. 18, 1980, as amended at 45 FR 58842, Sept. 5, 1980; 72 FR 73602, Dec. 28, 2007]

§812.7 Prohibition of promotion and other practices.

A sponsor, investigator, or any person acting for or on behalf of a sponsor or investigator shall not:

(a) Promote or test market an investigational device, until after FDA has approved the device for commercial distribution.

(b) Commercialize an investigational device by charging the subjects or investigators for a device a price larger than that necessary to recover costs of manufacture, research, development, and handling.

(c) Unduly prolong an investigation. If data developed by the investigation indicate in the case of a class III device that premarket approval cannot be justified or in the case of a class II device that it will not comply with an applicable performance standard or an amendment to that standard, the sponsor shall promptly terminate the investigation.

(d) Represent that an investigational device is safe or effective for the purposes for which it is being investigated.

§812.10 Waivers.

(a) *Request*. A sponsor may request FDA to waive any requirement of this part. A waiver request, with supporting documentation, may be submitted separately or as part of an application to the address in §812.19.

(b) FDA action. FDA may by letter grant a waiver of any requirement that FDA finds is not required by the act and is unnecessary to protect the rights, safety, or welfare of human subjects.

(c) *Effect of request.* Any requirement shall continue to apply unless and until FDA waives it.

§812.18 Import and export requirements.

(a) *Imports*. In addition to complying with other requirements of this part, a person who imports or offers for importation an investigational device subject to this part shall be the agent of the foreign exporter with respect to investigations of the device and shall act as the sponsor of the clinical investigation, or ensure that another person acts as the agent of the foreign exporter and the sponsor of the investigation.

(b) *Exports*. A person exporting an investigational device subject to this part shall obtain FDA's prior approval, as required by section 801(e) of the act or comply with section 802 of the act.

[45 FR 3751, Jan. 18, 1980, as amended at 62 FR 26229, May 13, 1997]

§812.19 Address for IDE correspondence.

(a) If you are sending an application, supplemental application, report, request for waiver, request for import or export approval, or other correspondence relating to matters covered by this part, you must send the submission to the appropriate address as follows:

(1) For devices regulated by the Center for Devices and Radiological Health, send it to Food and Drug Administration, Center for Devices and Radiological Health, Document Mail Center, 10903 New Hampshire Ave., Bldg. 66, rm. G609, Silver Spring, MD 20993-0002.

(2) For devices regulated by the Center for Biologics Evaluation and Research, send it to the Food and Drug Administration, Center for Biologics Evaluation and Research, Document Control Center, 10903 New Hampshire Ave., Bldg. 71, Rm. G112, Silver Spring, MD 20993-0002.

(3) For devices regulated by the Center for Drug Evaluation and Research, send it to Central Document Control Room, Center for Drug Evaluation and Research, Food and Drug Administration, 5901-B Ammendale Rd., Beltsville, MD 20705-1266.

(b) You must state on the outside wrapper of each submission what the submission is, for example, an "IDE application," a "supplemental IDE application," or a "correspondence concerning an IDE (or an IDE application)."

[71 FR 42048, July 25, 2006, as amended at 75 FR 20915, Apr. 22, 2010; 80 FR 18094, Apr. 3, 2015]

Subpart B—Application and Administrative Action

§812.20 Application.

(a) *Submission*. (1) A sponsor shall submit an application to FDA if the sponsor intends to use a significant risk device in an investigation, intends to conduct an investigation that involves an exception from informed consent under §50.24 of this chapter, or if FDA notifies the sponsor that an application is required for an investigation.

(2) A sponsor shall not begin an investigation for which FDA's approval of an application is required until FDA has approved the application.

(3) A sponsor shall submit three copies of a signed "Application for an Investigational Device Exemption" (IDE application), together with accompanying materials, by registered mail or by hand to the address in §812.19. Subsequent correspondence concerning an application or a supplemental application shall be submitted by registered mail or by hand.

(4)(i) A sponsor shall submit a separate IDE for any clinical investigation involving an exception from informed consent under §50.24 of this chapter. Such a clinical investigation is not permitted to proceed without the prior written authorization of FDA. FDA shall provide a written determination 30 days after FDA receives the IDE or earlier.

(ii) If the investigation involves an exception from informed consent under §50.24 of this chapter, the sponsor shall prominently identify on the cover sheet that the investigation is subject to the requirements in §50.24 of this chapter.

(b) *Contents*. An IDE application shall include, in the following order:

(1) The name and address of the sponsor.

(2) A complete report of prior investigations of the device and an accurate summary of those sections of the investigational plan described in §812.25(a) through (e) or, in lieu of the summary, the complete plan. The sponsor shall submit to FDA a complete investigational plan and a complete report of prior investigations of the device if no IRB has reviewed them, if FDA has found an IRB's review inadequate, or if FDA requests them.

(3) A description of the methods, facilities, and controls used for the manufacture, processing, packing, storage, and, where appropriate, installation of the device, in sufficient detail so that a person generally familiar with good manufacturing practices can make a knowledgeable judgment about the quality control used in the manufacture of the device.

(4) An example of the agreements to be entered into by all investigators to comply with investigator obligations under this part, and a list of the names and addresses of all investigators who have signed the agreement.

(5) A certification that all investigators who will participate in the investigation have signed the agreement, that the list of investigators includes all the investigators participating in the investigation, and that no investigators will be added to the investigation until they have signed the agreement.

(6) A list of the name, address, and chairperson of each IRB that has been or will be asked to review the investigation and a certification of the action concerning the investigation taken by each such IRB.

(7) The name and address of any institution at which a part of the investigation may be conducted that has not been identified in accordance with paragraph (b)(6) of this section.

(8) If the device is to be sold, the amount to be charged and an explanation of why sale does not constitute commercialization of the device.

(9) A claim for categorical exclusion under § 25.30 or § 25.34 or an environmental assessment under § 25.40.

(10) Copies of all labeling for the device.

(11) Copies of all forms and informational materials to be provided to subjects to obtain informed consent.

(12) Any other relevant information FDA requests for review of the application.

(c) *Additional information*. FDA may request additional information concerning an investigation or revision in the investigational plan. The sponsor may treat such a request as a disapproval of the application for purposes of requesting a hearing under part 16.

(d) *Information previously submitted.* Information previously submitted to the Center for Devices and Radiological Health, the Center for Biologics Evaluation and Research, or the Center for Drug Evaluation and Research, as applicable, in accordance with this chapter ordinarily need not be resubmitted, but may be incorporated by reference.

[45 FR 3751, Jan. 18, 1980, as amended at 46 FR 8956, Jan. 27, 1981; 50 FR 16669, Apr. 26, 1985; 53 FR 11252, Apr. 6, 1988; 61 FR 51530, Oct. 2, 1996; 62 FR 40600, July 29, 1997; 64 FR 10942, Mar. 8, 1999; 73 FR 49942, Aug. 25, 2008]

§ 812.25 Investigational plan.

The investigational plan shall include, in the following order:

(a) *Purpose*. The name and intended use of the device and the objectives and duration of the investigation.

(b) *Protocol*. A written protocol describing the methodology to be used and an analysis of the protocol demonstrating that the investigation is scientifically sound.

(c) *Risk analysis.* A description and analysis of all increased risks to which subjects will be exposed by the investigation; the manner in which these risks will be minimized; a justification for the investigation; and a description of the patient population, including the number, age, sex, and condition.

(d) *Description of device.* A description of each important component, ingredient, property, and principle of operation of the device and of each anticipated change in the device during the course of the investigation.

(e) *Monitoring procedures*. The sponsor's written procedures for monitoring the investigation and the name and address of any monitor.

(f) *Labeling*. Copies of all labeling for the device.

(g) *Consent materials.* Copies of all forms and informational materials to be provided to subjects to obtain informed consent.

(h) *IRB information.* A list of the names, locations, and chairpersons of all IRB's that have been or will be asked to review the investigation, and a certification of any action taken by any of those IRB's with respect to the investigation.

(i) *Other institutions.* The name and address of each institution at which a part of the investigation may be conducted that has not been identified in paragraph (h) of this section.

(j) *Additional records and reports*. A description of records and reports that will be maintained on the investigation in addition to those prescribed in subpart G.

§ 812.27 Report of prior investigations.

(a) *General*. The report of prior investigations shall include reports of all prior clinical, animal, and laboratory testing of the device and shall be comprehensive and adequate to justify the proposed investigation.

(b) *Specific contents.* The report also shall include:

(1) A bibliography of all publications, whether adverse or supportive, that are relevant to an evaluation of the safety or effectiveness of the device, copies of all published and unpublished adverse information, and, if requested by an IRB or FDA, copies of other significant publications.

(2) A summary of all other unpublished information (whether adverse or supportive) in the possession of, or reasonably obtainable by, the sponsor that is relevant to an evaluation of the safety or effectiveness of the device.

(3) If information on nonclinical laboratory studies is provided, a statement that all such studies have been conducted in compliance with applicable requirements in the good laboratory practice regulations in part 58, or if any such study was not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance. Failure or inability to comply with this requirement does not justify failure to provide information on a relevant nonclinical test study.

(4)(i) If data from clinical investigations conducted in the United States are provided, a statement that each investigation was conducted in compliance with applicable requirements in the protection of human subjects regulations in part 50 of this chapter, the institutional review boards regulations in part 56 of this chapter, or was not subject to the regulations under § 56.104 or § 56.105, and the investigational device exemptions regulations in this part, or if any such investigation was not conducted in compliance with those regulations, a brief statement of the reason for the noncompliance. Failure or inability to comply with these requirements does not justify failure to provide information on a relevant clinical investigation.

(ii) If data from clinical investigations conducted outside the United States are provided to support the IDE, the requirements under § 812.28 apply. If any such investigation was not conducted in accordance with good clinical practice (GCP) as described in § 812.28(a), the report of prior investigations shall include either a waiver request in accordance with § 812.28(c) or a brief statement of the reason for not conducting the investigation in accordance with GCP and a description of steps taken to ensure that the data and results are credible and accurate and that the rights, safety, and well-being of subjects have been adequately protected. Failure or inability to comply with these requirements does not justify failure to provide information on a relevant clinical investigation.

[45 FR 3751, Jan. 18, 1980, as amended at 50 FR 7518, Feb. 22, 1985; 83 FR 7385, Feb. 21, 2018]

§ 812.28 Acceptance of data from clinical investigations conducted outside the United States.

(a) *Acceptance of data from clinical investigations conducted outside the United States to support an IDE or a device marketing application or submission (an application under section 515 or 520(m) of the Federal Food, Drug, and Cosmetic Act, a premarket notification submission under section 510(k) of the Federal Food, Drug, and Cosmetic Act, or a request for De Novo classification under section 513(f)(2) of the Federal Food, Drug, and Cosmetic Act).* FDA will accept information on a clinical investigation conducted outside the United States to support an IDE or a device marketing application or submission if the investigation is well-designed and well-conducted and the following conditions are met:

(1) A statement is provided that the investigation was conducted in accordance with good clinical practice (GCP). For the purposes of this section, GCP is defined as a standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical investigations in a way that provides assurance that the data and results are credible and accurate and that the rights, safety, and well-being of subjects are protected. GCP includes review and approval (or provision of a favorable opinion) by an independent ethics committee (IEC) before initiating an investigation, continuing review of an ongoing investigation by an IEC, and obtaining and documenting the freely given informed consent of the subject (or a subject's legally authorized representative, if the subject is unable to provide informed consent) before initiating an investigation. GCP does not

require informed consent in life-threatening situations when the IEC reviewing the investigation finds, before initiation of the investigation, that informed consent is not feasible and either that the conditions present are consistent with those described in § 50.23 or § 50.24(a) of this chapter, or that the measures described in the protocol or elsewhere will protect the rights, safety, and well-being of subjects.

(2) In addition to the information required elsewhere in parts 807, 812, and 814 of this chapter, as applicable, the information in paragraph (b) of this section is submitted, as follows:

(i) For an investigation of a significant risk device, as defined in § 812.3(m), the supporting information as described in paragraph (b) of this section is submitted.

(ii) For an investigation of a device, other than a significant risk device, the supporting information as described in paragraphs (b)(1), (4), (5), (7) through (9), and (11) of this section is submitted, and the supporting information as described in paragraph (b)(10) of this section and the rationale for determining the investigation is of a device other than a significant risk device are made available for agency review upon request by FDA.

(iii) For a device investigation that meets the exemption criteria in § 812.2(c), the supporting information as described in paragraphs (b)(1), (4), (5), (7) through (11) of this section and the rationale for determining the investigation meets the exemption criteria in § 812.2(c) are made available for agency review upon request by FDA.

(3) FDA is able to validate the data from the investigation through an onsite inspection, or through other appropriate means, if the agency deems it necessary.

(b) *Supporting information.* A sponsor or applicant who submits data from a clinical investigation conducted outside the United States to support an IDE or a device marketing application or submission, in addition to information required elsewhere in parts 807, 812, and 814 of this chapter, as applicable, shall provide a description of the actions the sponsor or applicant took to ensure that the research conformed to GCP as described in paragraph (a)(1) of this section. The description is not required to duplicate information already submitted in the application or submission. Instead, the description must provide either the following information, as specified in paragraph (a)(2) of this section, or a cross-reference to another section of the application or submission where the information is located:

(1) The names of the investigators and the names and addresses of the research facilities and sites where records relating to the investigation are maintained;

(2) The investigator's qualifications;

(3) A description of the research facility(ies);

(4) A detailed summary of the protocol and results of the investigation and, should FDA request, case records maintained by the investigator or additional background data such as hospital or other institutional records;

(5) Either a statement that the device used in the investigation conducted outside the United States is identical to the device that is the subject of the submission or application, or a detailed description of the device and each important component (including all materials and specifications), ingredient, property, and principle of operation of the device used in the investigation conducted outside the United States and a comparison to the device that is the subject of the submission or application that indicates how the device used in the investigation is similar to and/or different from the device that is the subject of the submission or application;

(6) If the investigation is intended to support the safety and effectiveness of a device, a discussion demonstrating that the data and information constitute valid scientific evidence within the meaning of § 860.7 of this chapter;

(7) The name and address of the IEC that reviewed the investigation and a statement that the IEC meets the definition in §812.3(t). The sponsor or applicant must maintain records supporting such statement, including records describing the qualifications of IEC members, and make these records available for agency review upon request;

(8) A summary of the IEC's decision to approve or modify and approve the investigation, or to provide a favorable opinion;

(9) A description of how informed consent was obtained;

(10) A description of what incentives, if any, were provided to subjects to participate in the investigation; (11) A description of how the sponsor(s) monitored the investigation and ensured that the investigation was carried out consistently with the protocol; and

(12) A description of how investigators were trained to comply with GCP (as described in paragraph (a)(1) of this section) and to conduct the investigation in accordance with the protocol, and a statement on whether written commitments by investigators to comply with GCP and the protocol were obtained. Any signed written commitments by investigators must be maintained by the sponsor or applicant and made available for agency review upon request.

(c) *Waivers*. (1) A sponsor or applicant may ask FDA to waive any applicable requirements under paragraphs (a)(1) and (b) of this section. A waiver request may be submitted in an IDE or in an amendment or supplement to an IDE, in a device marketing application or submission (an application under section 515 or 520(m) of the Federal Food, Drug, and Cosmetic Act, a premarket notification submission under section 510(k) of the Federal Food, Drug, and Cosmetic Act, or a request for De Novo classification under section 513(f)(2) of the Federal Food, Drug, and Cosmetic Act) or in an amendment or supplement to a device marketing application or submission, or in a pre-submission. A waiver request is required to contain at least one of the following:

(i) An explanation why the sponsor's or applicant's compliance with the requirement is unnecessary or cannot be achieved;

(ii) A description of an alternative submission or course of action that satisfies the purpose of the requirement; or

(iii) Other information justifying a waiver.

(2) FDA may grant a waiver if it finds that doing so would be in the interest of the public health.

(d) *Records*. A sponsor or applicant must retain the records required by this section for a clinical investigation conducted outside the United States as follows:

(1) If the investigation is submitted in support of an IDE, for 2 years after the termination or completion of the IDE; and

(2) If the investigation is submitted in support of a premarket approval application, a notice of completion of a product development protocol, a humanitarian device exemption application, a premarket notification submission, or a request for De Novo classification, for 2 years after an agency decision on that submission or application.

(e) *Clinical investigations conducted outside of the United States that do not meet conditions.* For clinical investigations conducted outside the United States that do not meet the conditions under paragraph (a) of this section, FDA may accept the information from such clinical investigations to support an IDE or a device marketing application or submission if FDA believes that the data and results from such clinical investigation are credible and accurate and that the rights, safety, and well-being of subjects have been adequately protected.

[83 FR 7386, Feb. 21, 2018]

§812.30 FDA action on applications.

(a) *Approval or disapproval.* FDA will notify the sponsor in writing of the date it receives an application. FDA may approve an investigation as proposed, approve it with modifications, or disapprove it. An investigation may not begin until:

(1) Thirty days after FDA receives the application at the address in §812.19 for the investigation of a device other than a banned device, unless FDA notifies the sponsor that the investigation may not begin; or

(2) FDA approves, by order, an IDE for the investigation.

(b) *Grounds for disapproval or withdrawal.* FDA may disapprove or withdraw approval of an application if FDA finds that:

(1) There has been a failure to comply with any requirement of this part or the act, any other applicable regulation or statute, or any condition of approval imposed by an IRB or FDA.

(2) The application or a report contains an untrue statement of a material fact, or omits material information required by this part.

(3) The sponsor fails to respond to a request for additional information within the time prescribed by FDA.

(4) There is reason to believe that the risks to the subjects are not outweighed by the anticipated benefits to the subjects and the importance of the knowledge to be gained, or informed consent is inadequate, or the investigation is scientifically unsound, or there is reason to believe that the device as used is ineffective.

(5) It is otherwise unreasonable to begin or to continue the investigation owing to the way in which the device is used or the inadequacy of:

(i) The report of prior investigations or the investigational plan;

(ii) The methods, facilities, and controls used for the manufacturing, processing, packaging, storage, and, where appropriate, installation of the device; or

(iii) Monitoring and review of the investigation.

(c) *Notice of disapproval or withdrawal.* If FDA disapproves an application or proposes to withdraw approval of an application, FDA will notify the sponsor in writing.

(1) A disapproval order will contain a complete statement of the reasons for disapproval and a statement that the sponsor has an opportunity to request a hearing under part 16.

(2) A notice of a proposed withdrawal of approval will contain a complete statement of the reasons for withdrawal and a statement that the sponsor has an opportunity to request a hearing under part 16. FDA will provide the opportunity for hearing before withdrawal of approval, unless FDA determines in the notice that continuation of testing under the exemption will result in an unreasonble risk to the public health and orders withdrawal of approval before any hearing.

[45 FR 3751, Jan. 18, 1980, as amended at 45 FR 58842, Sept. 5, 1980]

§812.35 Supplemental applications.

(a) *Changes in investigational plan*—(1) *Changes requiring prior approval.* Except as described in paragraphs (a)(2) through (a)(4) of this section, a sponsor must obtain approval of a supplemental application under §812.30(a), and IRB approval when appropriate (see §§56.110 and 56.111 of this chapter), prior to implementing a change to an investigational plan. If a sponsor intends to conduct an investigation that involves an exception to informed consent under §50.24 of this chapter, the sponsor shall submit a separate investigational device exemption (IDE) application in accordance with §812.20(a).

(2) *Changes effected for emergency use.* The requirements of paragraph (a)(1) of this section regarding FDA approval of a supplement do not apply in the case of a deviation from the investiga-

tional plan to protect the life or physical well-being of a subject in an emergency. Such deviation shall be reported to FDA within 5-working days after the sponsor learns of it (see §812.150(a)(4)).

(3) *Changes effected with notice to FDA within 5 days.* A sponsor may make certain changes without prior approval of a supplemental application under paragraph (a)(1) of this section if the sponsor determines that these changes meet the criteria described in paragraphs (a)(3)(i) and (a)(3)(ii) of this section, on the basis of credible information defined in paragraph (a)(3)(iii) of this section, and the sponsor provides notice to FDA within 5-working days of making these changes.

(i) *Developmental changes.* The requirements in paragraph (a)(1) of this section regarding FDA approval of a supplement do not apply to developmental changes in the device (including manufacturing changes) that do not constitute a significant change in design or basic principles of operation and that are made in response to information gathered during the course of an investigation.

(ii) *Changes to clinical protocol.* The requirements in paragraph (a)(1) of this section regarding FDA approval of a supplement do not apply to changes to clinical protocols that do not affect:

(A) The validity of the data or information resulting from the completion of the approved protocol, or the relationship of likely patient risk to benefit relied upon to approve the protocol;

(B) The scientific soundness of the investigational plan; or

(C) The rights, safety, or welfare of the human subjects involved in the investigation.

(iii) *Definition of credible information.* (A) Credible information to support developmental changes in the device (including manufacturing changes) includes data generated under the design control procedures of §820.30, preclinical/animal testing, peer reviewed published literature, or other reliable information such as clinical information gathered during a trial or marketing.

(B) Credible information to support changes to clinical protocols is defined as the sponsor's documentation supporting the conclusion that a change does not have a significant impact on the study design or planned statistical analysis, and that the change does not affect the rights, safety, or welfare of the subjects. Documentation shall include information such as peer reviewed published literature, the recommendation of the clinical investigator(s), and/or the data gathered during the clinical trial or marketing.

(iv) *Notice of IDE change.* Changes meeting the criteria in paragraphs (a)(3)(i) and (a)(3)(ii) of this section that are supported by credible information as defined in paragraph (a)(3)(iii) of this section may be made without prior FDA approval if the sponsor submits a notice of the change to the IDE not later than 5-working days after making the change. Changes to devices are deemed to occur on the date the device, manufactured incorporating the design or manufacturing change, is distributed to the investigator(s). Changes to a clinical protocol are deemed to occur when a clinical investigator is notified by the sponsor that the change should be implemented in the protocol or, for sponsor-investigator studies, when a sponsor-investigator incorporates the change in the protocol. Such notices shall be identified as a "notice of IDE change."

(A) For a developmental or manufacturing change to the device, the notice shall include a summary of the relevant information gathered during the course of the investigation upon which the change was based; a description of the change to the device or manufacturing process (cross-referenced to the appropriate sections of the original device description or manufacturing process); and, if design controls were used to assess the change, a statement that no new risks were identified by appropriate risk analysis and that the verification and validation testing, as appropriate, demonstrated that the design outputs met the design input requirements. If another method of assessment was used, the notice shall include a summary of the information which served as the credible information supporting the change.

(B) For a protocol change, the notice shall include a description of the change (cross-referenced to the appropriate sections of the original protocol); an assessment supporting the conclusion that

the change does not have a significant impact on the study design or planned statistical analysis; and a summary of the information that served as the credible information supporting the sponsor's determination that the change does not affect the rights, safety, or welfare of the subjects.

(4) *Changes submitted in annual report.* The requirements of paragraph (a)(1) of this section do not apply to minor changes to the purpose of the study, risk analysis, monitoring procedures, labeling, informed consent materials, and IRB information that do not affect:

(i) The validity of the data or information resulting from the completion of the approved protocol, or the relationship of likely patient risk to benefit relied upon to approve the protocol;

(ii) The scientific soundness of the investigational plan; or

(iii) The rights, safety, or welfare of the human subjects involved in the investigation. Such changes shall be reported in the annual progress report for the IDE, under §812.150(b)(5).

(b) *IRB approval for new facilities.* A sponsor shall submit to FDA a certification of any IRB approval of an investigation or a part of an investigation not included in the IDE application. If the investigation is otherwise unchanged, the supplemental application shall consist of an updating of the information required by §812.20(b) and (c) and a description of any modifications in the investigational plan required by the IRB as a condition of approval. A certification of IRB approval need not be included in the initial submission of the supplemental application, and such certification is not a precondition for agency consideration of the application. Nevertheless, a sponsor may not begin a part of an investigation at a facility until the IRB has approved the investigation, FDA has received the certification of IRB approval, and FDA, under §812.30(a), has approved the supplemental application relating to that part of the investigation (see §56.103(a)).

[50 FR 25909, June 24, 1985; 50 FR 28932, July 17, 1985, as amended at 61 FR 51531, Oct. 2, 1996; 63 FR 64625, Nov. 23, 1998]

§812.36 Treatment use of an investigational device.

(a) *General*. A device that is not approved for marketing may be under clinical investigation for a serious or immediately life-threatening disease or condition in patients for whom no comparable or satisfactory alternative device or other therapy is available. During the clinical trial or prior to final action on the marketing application, it may be appropriate to use the device in the treatment of patients not in the trial under the provisions of a treatment investigational device exemption (IDE). The purpose of this section is to facilitate the availability of promising new devices to desperately ill patients as early in the device development process as possible, before general marketing begins, and to obtain additional data on the device's safety and effectiveness. In the case of a serious disease, a device ordinarily may be made available for treatment use under this section after all clinical trials have been completed. In the case of an immediately life-threatening disease, a device may be made available for treatment use under this section prior to the completion of all clinical trials. For the purpose of this section, an "immediately life-threatening" disease means a stage of a disease in which there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment. For purposes of this section, "treatment use"of a device includes the use of a device for diagnostic purposes.

(b) *Criteria*. FDA shall consider the use of an investigational device under a treatment IDE if:

(1) The device is intended to treat or diagnose a serious or immediately life-threatening disease or condition;

(2) There is no comparable or satisfactory alternative device or other therapy available to treat or diagnose that stage of the disease or condition in the intended patient population;

(3) The device is under investigation in a controlled clinical trial for the same use under an approved IDE, or such clinical trials have been completed; and

(4) The sponsor of the investigation is actively pursuing marketing approval/clearance of the investigational device with due diligence.

(c) *Applications for treatment use.* (1) A treatment IDE application shall include, in the following order:

(i) The name, address, and telephone number of the sponsor of the treatment IDE;

(ii) The intended use of the device, the criteria for patient selection, and a written protocol describing the treatment use;

(iii) An explanation of the rationale for use of the device, including, as appropriate, either a list of the available regimens that ordinarily should be tried before using the investigational device or an explanation of why the use of the investigational device is preferable to the use of available marketed treatments;

(iv) A description of clinical procedures, laboratory tests, or other measures that will be used to evaluate the effects of the device and to minimize risk;

(v) Written procedures for monitoring the treatment use and the name and address of the monitor;

(vi) Instructions for use for the device and all other labeling as required under § 812.5(a) and (b);

(vii) Information that is relevant to the safety and effectiveness of the device for the intended treatment use. Information from other IDE's may be incorporated by reference to support the treatment use;

(viii) A statement of the sponsor's commitment to meet all applicable responsibilities under this part and part 56 of this chapter and to ensure compliance of all participating investigators with the informed consent requirements of part 50 of this chapter;

(ix) An example of the agreement to be signed by all investigators participating in the treatment IDE and certification that no investigator will be added to the treatment IDE before the agreement is signed; and

(x) If the device is to be sold, the price to be charged and a statement indicating that the price is based on manufacturing and handling costs only.

(2) A licensed practitioner who receives an investigational device for treatment use under a treatment IDE is an "investigator" under the IDE and is responsible for meeting all applicable investigator responsibilities under this part and parts 50 and 56 of this chapter.

(d) *FDA action on treatment IDE applications*—(1) *Approval of treatment IDE's.* Treatment use may begin 30 days after FDA receives the treatment IDE submission at the address specified in § 812.19, unless FDA notifies the sponsor in writing earlier than the 30 days that the treatment use may or may not begin. FDA may approve the treatment use as proposed or approve it with modifications.

(2) *Disapproval or withdrawal of approval of treatment IDE's.* FDA may disapprove or withdraw approval of a treatment IDE if:

(i) The criteria specified in § 812.36(b) are not met or the treatment IDE does not contain the information required in § 812.36(c);

(ii) FDA determines that any of the grounds for disapproval or withdrawal of approval listed in § 812.30(b)(1) through (b)(5) apply;

(iii) The device is intended for a serious disease or condition and there is insufficient evidence of safety and effectiveness to support such use;

(iv) The device is intended for an immediately life-threatening disease or condition and the available scientific evidence, taken as a whole, fails to provide a reasonable basis for concluding that the device:

(A) May be effective for its intended use in its intended population; or

(B) Would not expose the patients to whom the device is to be administered to an unreasonable and significant additional risk of illness or injury;

(v) There is reasonable evidence that the treatment use is impeding enrollment in, or otherwise interfering with the conduct or completion of, a controlled investigation of the same or another investigational device;

(vi) The device has received marketing approval/clearance or a comparable device or therapy becomes available to treat or diagnose the same indication in the same patient population for which the investigational device is being used;

(vii) The sponsor of the controlled clinical trial is not pursuing marketing approval/clearance with due diligence;

(viii) Approval of the IDE for the controlled clinical investigation of the device has been withdrawn; or

(ix) The clinical investigator(s) named in the treatment IDE are not qualified by reason of their scientific training and/or experience to use the investigational device for the intended treatment use.

(3) *Notice of disapproval or withdrawal.* If FDA disapproves or proposes to withdraw approval of a treatment IDE, FDA will follow the procedures set forth in §812.30(c).

(e) *Safeguards*. Treatment use of an investigational device is conditioned upon the sponsor and investigators complying with the safeguards of the IDE process and the regulations governing informed consent (part 50 of this chapter) and institutional review boards (part 56 of this chapter).

(f) *Reporting requirements.* The sponsor of a treatment IDE shall submit progress reports on a semiannual basis to all reviewing IRB's and FDA until the filing of a marketing application. These reports shall be based on the period of time since initial approval of the treatment IDE and shall include the number of patients treated with the device under the treatment IDE, the names of the investigators participating in the treatment IDE, and a brief description of the sponsor's efforts to pursue marketing approval/clearance of the device. Upon filing of a marketing application, progress reports shall be submitted annually in accordance with §812.150(b)(5). The sponsor of a treatment IDE is responsible for submitting all other reports required under §812.150.

[62 FR 48947, Sept. 18, 1997]

§812.38 Confidentiality of data and information.

(a) *Existence of IDE*. FDA will not disclose the existence of an IDE unless its existence has previously been publicly disclosed or acknowledged, until FDA approves an application for premarket approval of the device subject to the IDE; or a notice of completion of a product development protocol for the device has become effective.

(b) *Availability of summaries or data.* (1) FDA will make publicly available, upon request, a detailed summary of information concerning the safety and effectiveness of the device that was the basis for an order approving, disapproving, or withdrawing approval of an application for an IDE for a banned device. The summary shall include information on any adverse effect on health caused by the device.

(2) If a device is a banned device or if the existence of an IDE has been publicly disclosed or acknowledged, data or information contained in the file is not available for public disclosure before approval of an application for premarket approval or the effective date of a notice of completion of a product development protocol except as provided in this section. FDA may, in its discretion, disclose a summary of selected portions of the safety and effectiveness data, that is, clinical, animal, or laboratory studies and tests of the device, for public consideration of a specific pending issue.

(3) If the existence of an IDE file has not been publicly disclosed or acknowledged, no data or information in the file are available for public disclosure except as provided in paragraphs (b)(1) and (c) of this section.

(4) Notwithstanding paragraph (b)(2) of this section, FDA will make available to the public, upon request, the information in the IDE that was required to be filed in Docket Number 95S-0158 in the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, for investigations involving an exception from informed consent under § 50.24 of this chapter. Persons wishing to request this information shall submit a request under the Freedom of Information Act.

(c) *Reports of adverse effects.* Upon request or on its own initiative, FDA shall disclose to an individual on whom an investigational device has been used a copy of a report of adverse device effects relating to that use.

(d) *Other rules.* Except as otherwise provided in this section, the availability for public disclosure of data and information in an IDE file shall be handled in accordance with § 814.9.

[45 FR 3751, Jan. 18, 1980, as amended at 53 FR 11253, Apr. 6, 1988; 61 FR 51531, Oct. 2, 1996]

Subpart C—Responsibilities of Sponsors

§ 812.40 General responsibilities of sponsors.

Sponsors are responsible for selecting qualified investigators and providing them with the information they need to conduct the investigation properly, ensuring proper monitoring of the investigation, ensuring that IRB review and approval are obtained, submitting an IDE application to FDA, and ensuring that any reviewing IRB and FDA are promptly informed of significant new information about an investigation. Additional responsibilities of sponsors are described in subparts B and G.

§ 812.42 FDA and IRB approval.

A sponsor shall not begin an investigation or part of an investigation until an IRB and FDA have both approved the application or supplemental application relating to the investigation or part of an investigation.

[46 FR 8957, Jan. 27, 1981]

§ 812.43 Selecting investigators and monitors.

(a) *Selecting investigators.* A sponsor shall select investigators qualified by training and experience to investigate the device.

(b) *Control of device.* A sponsor shall ship investigational devices only to qualified investigators participating in the investigation.

(c) *Obtaining agreements.* A sponsor shall obtain from each participating investigator a signed agreement that includes:

(1) The investigator's curriculum vitae.

(2) Where applicable, a statement of the investigator's relevant experience, including the dates, location, extent, and type of experience.

(3) If the investigator was involved in an investigation or other research that was terminated, an explanation of the circumstances that led to termination.

(4) A statement of the investigator's commitment to:

(i) Conduct the investigation in accordance with the agreement, the investigational plan, this part and other applicable FDA regulations, and conditions of approval imposed by the reviewing IRB or FDA;

(ii) Supervise all testing of the device involving human subjects; and

(iii) Ensure that the requirements for obtaining informed consent are met.

(5) Sufficient accurate financial disclosure information to allow the sponsor to submit a complete and accurate certification or disclosure statement as required under part 54 of this chapter. The sponsor shall obtain a commitment from the clinical investigator to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following completion of the study. This information shall not be submitted in an investigational device exemption application, but shall be submitted in any marketing application involving the device.

(d) *Selecting monitors.* A sponsor shall select monitors qualified by training and experience to monitor the investigational study in accordance with this part and other applicable FDA regulations.

[45 FR 3751, Jan. 18, 1980, as amended at 63 FR 5253, Feb. 2, 1998]

§ 812.45 Informing investigators.

A sponsor shall supply all investigators participating in the investigation with copies of the investigational plan and the report of prior investigations of the device.

§ 812.46 Monitoring investigations.

(a) *Securing compliance.* A sponsor who discovers that an investigator is not complying with the signed agreement, the investigational plan, the requirements of this part or other applicable FDA regulations, or any conditions of approval imposed by the reviewing IRB or FDA shall promptly either secure compliance, or discontinue shipments of the device to the investigator and terminate the investigator's participation in the investigation. A sponsor shall also require such an investigator to dispose of or return the device, unless this action would jeopardize the rights, safety, or welfare of a subject.

(b) *Unanticipated adverse device effects.* (1) A sponsor shall immediately conduct an evaluation of any unanticipated adverse device effect.

(2) A sponsor who determines that an unanticipated adverse device effect presents an unreasonable risk to subjects shall terminate all investigations or parts of investigations presenting that risk as soon as possible. Termination shall occur not later than 5 working days after the sponsor makes this determination and not later than 15 working days after the sponsor first received notice of the effect.

(c) *Resumption of terminated studies.* If the device is a significant risk device, a sponsor may not resume a terminated investigation without IRB and FDA approval. If the device is not a significant risk device, a sponsor may not resume a terminated investigation without IRB approval and, if the investigation was terminated under paragraph (b)(2) of this section, FDA approval.

§ 812.47 Emergency research under § 50.24 of this chapter.

(a) The sponsor shall monitor the progress of all investigations involving an exception from informed consent under § 50.24 of this chapter. When the sponsor receives from the IRB information concerning the public disclosures under § 50.24(a)(7)(ii) and (a)(7)(iii) of this chapter, the sponsor shall promptly submit to the IDE file and to Docket Number 95S-0158 in the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, copies of the information that was disclosed, identified by the IDE number.

(b) The sponsor also shall monitor such investigations to determine when an IRB determines that it cannot approve the research because it does not meet the criteria in the exception in § 50.24(a) of this chapter or because of other relevant ethical concerns. The sponsor promptly shall provide this information in writing to FDA, investigators who are asked to participate in this or a substantially equivalent clinical investigation, and other IRB's that are asked to review this or a substantially equivalent investigation.

[61 FR 51531, Oct. 2, 1996, as amended at 64 FR 10943, Mar. 8, 1999]

Subpart D—IRB Review and Approval

§ 812.60 IRB composition, duties, and functions.

An IRB reviewing and approving investigations under this part shall comply with the requirements of part 56 in all respects, including its composition, duties, and functions.

[46 FR 8957, Jan. 27, 1981]

§ 812.62 IRB approval.

(a) An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all investigations covered by this part.

(b) If no IRB exists or if FDA finds that an IRB's review is inadequate, a sponsor may submit an application to FDA.

[46 FR 8957, Jan. 27, 1981]

§ 812.64 IRB's continuing review.

The IRB shall conduct its continuing review of an investigation in accordance with part 56.

[46 FR 8957, Jan. 27, 1981]

§ 812.65 [Reserved]

§ 812.66 Significant risk device determinations.

If an IRB determines that an investigation, presented for approval under § 812.2(b)(1)(ii), involves a significant risk device, it shall so notify the investigator and, where appropriate, the sponsor. A sponsor may not begin the investigation except as provided in § 812.30(a).

[46 FR 8957, Jan. 27, 1981]

Subpart E—Responsibilities of Investigators

§ 812.100 General responsibilities of investigators.

An investigator is responsible for ensuring that an investigation is conducted according to the signed agreement, the investigational plan and applicable FDA regulations, for protecting the rights, safety, and welfare of subjects under the investigator's care, and for the control of devices under investigation. An investigator also is responsible for ensuring that informed consent is obtained in accordance with part 50 of this chapter. Additional responsibilities of investigators are described in subpart G.

[45 FR 3751, Jan. 18, 1980, as amended at 46 FR 8957, Jan. 27, 1981]

§ 812.110 Specific responsibilities of investigators.

(a) *Awaiting approval.* An investigator may determine whether potential subjects would be interested in participating in an investigation, but shall not request the written informed consent of any subject to participate, and shall not allow any subject to participate before obtaining IRB and FDA approval.

(b) *Compliance.* An investigator shall conduct an investigation in accordance with the signed agreement with the sponsor, the investigational plan, this part and other applicable FDA regulations, and any conditions of approval imposed by an IRB or FDA.

(c) *Supervising device use.* An investigator shall permit an investigational device to be used only with subjects under the investigator's supervision. An investigator shall not supply an investigational device to any person not authorized under this part to receive it.

(d) *Financial disclosure.* A clinical investigator shall disclose to the sponsor sufficient accurate financial information to allow the applicant to submit complete and accurate certification or disclosure statements required under part 54 of this chapter. The investigator shall promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following completion of the study.

(e) *Disposing of device.* Upon completion or termination of a clinical investigation or the investigator's part of an investigation, or at the sponsor's request, an investigator shall return to the sponsor any remaining supply of the device or otherwise dispose of the device as the sponsor directs.

[45 FR 3751, Jan. 18, 1980, as amended at 63 FR 5253, Feb. 2, 1998]

§812.119 Disqualification of a clinical investigator.

(a) If FDA has information indicating that an investigator (including a sponsor-investigator) has repeatedly or deliberately failed to comply with the requirements of this part, part 50, or part 56 of this chapter, or has repeatedly or deliberately submitted to FDA or to the sponsor false information in any required report, the Center for Devices and Radiological Health, the Center for Biologics Evaluation and Research, or the Center for Drug Evaluation and Research will furnish the investigator written notice of the matter complained of and offer the investigator an opportunity to explain the matter in writing, or, at the option of the investigator, in an informal conference. If an explanation is offered and accepted by the applicable Center, the Center will discontinue the disqualification proceeding. If an explanation is offered but not accepted by the applicable Center, the investigator will be given an opportunity for a regulatory hearing under part 16 of this chapter on the question of whether the investigator is eligible to receive test articles under this part and eligible to conduct any clinical investigation that supports an application for a research or marketing permit for products regulated by FDA.

(b) After evaluating all available information, including any explanation presented by the investigator, if the Commissioner determines that the investigator has repeatedly or deliberately failed to comply with the requirements of this part, part 50, or part 56 of this chapter, or has repeatedly or deliberately submitted to FDA or to the sponsor false information in any required report, the Commissioner will notify the investigator, the sponsor of any investigation in which the investigator has been named as a participant, and the reviewing investigational review boards (IRBs) that the investigator is not eligible to receive test articles under this part. The notification to the investigator, sponsor and IRBs will provide a statement of the basis for such determination. The notification also will explain that an investigator determined to be ineligible to receive test articles under this part will be ineligible to conduct any clinical investigation that supports an application for a research or marketing permit for products regulated by FDA, including drugs, biologics, devices, new animal drugs, foods, including dietary supplements, that bear a nutrient content claim or a health claim, infant formulas, food and color additives, and tobacco products.

(c) Each application or submission to FDA under the provisions of this chapter containing data reported by an investigator who has been determined to be ineligible to receive FDA-regulated test articles is subject to examination to determine whether the investigator has submitted unreliable data that are essential to the continuation of an investigation or essential to the clearance or approval of a marketing application, or essential to the continued marketing of an FDA-regulated product.

(d) If the Commissioner determines, after the unreliable data submitted by the investigator are eliminated from consideration, that the data remaining are inadequate to support a conclusion that it is reasonably safe to continue the investigation, the Commissioner will notify the sponsor, who shall have an opportunity for a regulatory hearing under part 16 of this chapter. If a danger to the public health exists, however, the Commissioner shall terminate the investigational device exemption (IDE) immediately and notify the sponsor and the reviewing IRBs of the termination. In such case, the sponsor shall have an opportunity for a regulatory hearing before FDA under part 16 of

this chapter on the question of whether the IDE should be reinstated. The determination that an investigation may not be considered in support of a research or marketing application or a notification or petition submission does not, however, relieve the sponsor of any obligation under any other applicable regulation to submit to FDA the results of the investigation.

(e) If the Commissioner determines, after the unreliable data submitted by the investigator are eliminated from consideration, that the continued clearance or approval of the product for which the data were submitted cannot be justified, the Commissioner will proceed to rescind clearance or withdraw approval of the product in accordance with the applicable provisions of the relevant statutes.

(f) An investigator who has been determined to be ineligible under paragraph (b) of this section may be reinstated as eligible when the Commissioner determines that the investigator has presented adequate assurances that the investigator will employ all test articles, and will conduct any clinical investigation that supports an application for a research or marketing permit for products regulated by FDA, solely in compliance with the applicable provisions of this chapter.

[77 FR 25360, Apr. 30, 2012]

Subpart F—[Reserved]

Subpart G—Records and Reports

§812.140 Records.

(a) *Investigator records.* A participating investigator shall maintain the following accurate, complete, and current records relating to the investigator's participation in an investigation:

(1) All correspondence with another investigator, an IRB, the sponsor, a monitor, or FDA, including required reports.

(2) Records of receipt, use or disposition of a device that relate to:

(i) The type and quantity of the device, the dates of its receipt, and the batch number or code mark.

(ii) The names of all persons who received, used, or disposed of each device.

(iii) Why and how many units of the device have been returned to the sponsor, repaired, or otherwise disposed of.

(3) Records of each subject's case history and exposure to the device. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. Such records shall include:

(i) Documents evidencing informed consent and, for any use of a device by the investigator without informed consent, any written concurrence of a licensed physician and a brief description of the circumstances justifying the failure to obtain informed consent. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

(ii) All relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated), information and data on the condition of each subject upon entering, and during the course of, the investigation, including information about relevant previous medical history and the results of all diagnostic tests.

(iii) A record of the exposure of each subject to the investigational device, including the date and time of each use, and any other therapy.

(4) The protocol, with documents showing the dates of and reasons for each deviation from the protocol.

(5) Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation.

(b) *Sponsor records.* A sponsor shall maintain the following accurate, complete, and current records relating to an investigation:

(1) All correspondence with another sponsor, a monitor, an investigator, an IRB, or FDA, including required reports.

(2) Records of shipment and disposition. Records of shipment shall include the name and address of the consignee, type and quantity of device, date of shipment, and batch number or code mark. Records of disposition shall describe the batch number or code marks of any devices returned to the sponsor, repaired, or disposed of in other ways by the investigator or another person, and the reasons for and method of disposal.

(3) Signed investigator agreements including the financial disclosure information required to be collected under §812.43(c)(5) in accordance with part 54 of this chapter.

(4) For each investigation subject to §812.2(b)(1) of a device other than a significant risk device, the records described in paragraph (b)(5) of this section and the following records, consolidated in one location and available for FDA inspection and copying:

(i) The name and intended use of the device and the objectives of the investigation;

(ii) A brief explanation of why the device is not a significant risk device:

(iii) The name and address of each investigator:

(iv) The name and address of each IRB that has reviewed the investigation:

(v) A statement of the extent to which the good manufacturing practice regulation in part 820 will be followed in manufacturing the device; and

(vi) Any other information required by FDA.

(5) Records concerning adverse device effects (whether anticipated or unanticipated) and complaints and

(6) Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigation or a particular investigation.

(c) *IRB records.* An IRB shall maintain records in accordance with part 56 of this chapter.

(d) *Retention period.* An investigator or sponsor shall maintain the records required by this subpart during the investigation and for a period of 2 years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application, a notice of completion of a product development protocol, a humanitarian device exemption application, a premarket notification submission, or a request for De Novo classification.

(e) *Records custody.* An investigator or sponsor may withdraw from the responsibility to maintain records for the period required in paragraph (d) of this section and transfer custody of the records to any other person who will accept responsibility for them under this part, including the requirements of §812.145. Notice of a transfer shall be given to FDA not later than 10 working days after transfer occurs.

[45 FR 3751, Jan. 18, 1980, as amended at 45 FR 58843, Sept. 5, 1980; 46 FR 8957, Jan. 27, 1981; 61 FR 57280, Nov. 5, 1996; 63 FR 5253, Feb. 2, 1998; 83 FR 7387, Feb. 21, 2018]

§812.145 Inspections.

(a) Entry and inspection. A sponsor or an investigator who has authority to grant access shall permit authorized FDA employees, at reasonable times and in a reasonable manner, to enter and inspect any establishment where devices are held (including any establishment where devices are

manufactured, processed, packed, installed, used, or implanted or where records of results from use of devices are kept).

(b) *Records inspection.* A sponsor, IRB, or investigator, or any other person acting on behalf of such a person with respect to an investigation, shall permit authorized FDA employees, at reasonable times and in a reasonable manner, to inspect and copy all records relating to an investigation.

(c) *Records identifying subjects.* An investigator shall permit authorized FDA employees to inspect and copy records that identify subjects, upon notice that FDA has reason to suspect that adequate informed consent was not obtained, or that reports required to be submitted by the investigator to the sponsor or IRB have not been submitted or are incomplete, inaccurate, false, or misleading.

§812.150 Reports.

(a) *Investigator reports.* An investigator shall prepare and submit the following complete, accurate, and timely reports:

(1) *Unanticipated adverse device effects.* An investigator shall submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.

(2) *Withdrawal of IRB approval.* An investigator shall report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the investigator's part of an investigation.

(3) *Progress*. An investigator shall submit progress reports on the investigation to the sponsor, the monitor, and the reviewing IRB at regular intervals, but in no event less often than yearly.

(4) *Deviations from the investigational plan.* An investigator shall notify the sponsor and the reviewing IRB (see §56.108(a) (3) and (4)) of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but in no event later than 5 working days after the emergency occurred. Except in such an emergency, prior approval by the sponsor is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, FDA and IRB in accordance with §812.35(a) also is required.

(5) *Informed consent.* If an investigator uses a device without obtaining informed consent, the investigator shall report such use to the sponsor and the reviewing IRB within 5 working days after the use occurs.

(6) *Final report.* An investigator shall, within 3 months after termination or completion of the investigation or the investigator's part of the investigation, submit a final report to the sponsor and the reviewing IRB.

(7) *Other*. An investigator shall, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.

(b) *Sponsor reports.* A sponsor shall prepare and submit the following complete, accurate, and timely reports:

(1) *Unanticipated adverse device effects.* A sponsor who conducts an evaluation of an unanticipated adverse device effect under §812.46(b) shall report the results of such evaluation to FDA and to all reviewing IRB's and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests.

(2) *Withdrawal of IRB approval.* A sponsor shall notify FDA and all reviewing IRB's and participating investigators of any withdrawal of approval of an investigation or a part of an investigation by a reviewing IRB within 5 working days after receipt of the withdrawal of approval.

(3) *Withdrawal of FDA approval.* A sponsor shall notify all reviewing IRB's and participating investigators of any withdrawal of FDA approval of the investigation, and shall do so within 5 working days after receipt of notice of the withdrawal of approval.

(4) *Current investigator list.* A sponsor shall submit to FDA, at 6-month intervals, a current list of the names and addresses of all investigators participating in the investigation. The sponsor shall submit the first such list 6 months after FDA approval.

(5) *Progress reports.* At regular intervals, and at least yearly, a sponsor shall submit progress reports to all reviewing IRB's. In the case of a significant risk device, a sponsor shall also submit progress reports to FDA. A sponsor of a treatment IDE shall submit semi-annual progress reports to all reviewing IRB's and FDA in accordance with §812.36(f) and annual reports in accordance with this section.

(6) *Recall and device disposition*. A sponsor shall notify FDA and all reviewing IRB's of any request that an investigator return, repair, or otherwise dispose of any units of a device. Such notice shall occur within 30 working days after the request is made and shall state why the request was made.

(7) *Final report.* In the case of a significant risk device, the sponsor shall notify FDA within 30 working days of the completion or termination of the investigation and shall submit a final report to FDA and all reviewing the IRB's and participating investigators within 6 months after completion or termination. In the case of a device that is not a significant risk device, the sponsor shall submit a final report to all reviewing IRB's within 6 months after termination or completion.

(8) *Informed consent.* A sponsor shall submit to FDA a copy of any report by an investigator under paragraph (a)(5) of this section of use of a device without obtaining informed consent, within 5 working days of receipt of notice of such use.

(9) *Significant risk device determinations.* If an IRB determines that a device is a significant risk device, and the sponsor had proposed that the IRB consider the device not to be a significant risk device, the sponsor shall submit to FDA a report of the IRB's determination within 5 working days after the sponsor first learns of the IRB's determination.

(10) *Other.* A sponsor shall, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.

[45 FR 3751, Jan. 18, 1980, as amended at 45 FR 58843, Sept. 5, 1980; 48 FR 15622, Apr. 12, 1983; 62 FR 48948, Sept. 18, 1997]

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PART 814—PREMARKET APPROVAL OF MEDICAL DEVICES

Authority: 21 U.S.C. 351, 352, 353, 360, 360c-360j, 360bbb-8b, 371, 372, 373, 374, 375, 379, 379e, 381.

Source: 51 FR 26364, July 22, 1986, unless otherwise noted.

Subpart A—General

§814.1 Scope.

(a) This section implements sections 515 and 515A of the act by providing procedures for the premarket approval of medical devices intended for human use.

(b) References in this part to regulatory sections of the Code of Federal Regulations are to chapter I of title 21, unless otherwise noted.

(c) This part applies to any class III medical device, unless exempt under section 520(g) of the act, that:

(1) Was not on the market (introduced or delivered for introduction into commerce for commercial distribution) before May 28, 1976, and is not substantially equivalent to a device on the market before May 28, 1976, or to a device first marketed on, or after that date, which has been classified into class I or class II; or

(2) Is required to have an approved premarket approval application (PMA) or a declared completed product development protocol under a regulation issued under section 515(b) of the act; or

(3) Was regulated by FDA as a new drug or antibiotic drug before May 28, 1976, and therefore is governed by section 520(1) of the act.

(d) This part amends the conditions to approval for any PMA approved before the effective date of this part. Any condition to approval for an approved PMA that is inconsistent with this part is revoked. Any condition to approval for an approved PMA that is consistent with this part remains in effect.

[51 FR 26364, July 22, 1986, as amended at 79 FR 1740, Jan. 10, 2014]

§814.2 Purpose.

The purpose of this part is to establish an efficient and thorough device review process—

(a) To facilitate the approval of PMA's for devices that have been shown to be safe and effective and that otherwise meet the statutory criteria for approval; and

(b) To ensure the disapproval of PMA's for devices that have not been shown to be safe and effective or that do not otherwise meet the statutory criteria for approval. This part shall be construed in light of these objectives.

§814.3 Definitions.

For the purposes of this part:

(a) *Act* means the Federal Food, Drug, and Cosmetic Act (sections 201-902, 52 Stat. 1040 et seq., as amended (21 U.S.C. 321-392)).

(b) *FDA* means the Food and Drug Administration.

(c) *IDE* means an approved or considered approved investigational device exemption under section 520(g) of the act and parts 812 and 813.

(d) *Master file* means a reference source that a person submits to FDA. A master file may contain detailed information on a specific manufacturing facility, process, methodology, or component used in the manufacture, processing, or packaging of a medical device.

(e) *PMA* means any premarket approval application for a class III medical device, including all information submitted with or incorporated by reference therein. "PMA" includes a new drug application for a device under section 520(1) of the act.

(f) *PMA amendment* means information an applicant submits to FDA to modify a pending PMA or a pending PMA supplement.

(g) *PMA supplement* means a supplemental application to an approved PMA for approval of a change or modification in a class III medical device, including all information submitted with or incorporated by reference therein.

(h) *Person* includes any individual, partnership, corporation, association, scientific or academic establishment, Government agency, or organizational unit thereof, or any other legal entity.

(i) *Statement of material fact* means a representation that tends to show that the safety or effectiveness of a device is more probable than it would be in the absence of such a representation. A

false affirmation or silence or an omission that would lead a reasonable person to draw a particular conclusion as to the safety or effectiveness of a device also may be a false statement of material fact, even if the statement was not intended by the person making it to be misleading or to have any probative effect.

(j) *30-day PMA supplement* means a supplemental application to an approved PMA in accordance with §814.39(e).

(k) *Reasonable probability* means that it is more likely than not that an event will occur.

(l) *Serious, adverse health consequences* means any significant adverse experience, including those which may be either life-threatening or involve permanent or long term injuries, but excluding injuries that are nonlife-threatening and that are temporary and reasonably reversible.

(m) *HDE* means a premarket approval application submitted pursuant to this subpart seeking a humanitarian device exemption from the effectiveness requirements of sections 514 and 515 of the act as authorized by section 520(m)(2) of the act.

(n) *HUD (humanitarian use device)* means a medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in not more than 8,000 individuals in the United States per year.

(o) *Newly acquired information* means data, analyses, or other information not previously submitted to the agency, which may include (but are not limited to) data derived from new clinical studies, reports of adverse events, or new analyses of previously submitted data (e.g., meta-analyses) if the studies, events or analyses reveal risks of a different type or greater severity or frequency than previously included in submissions to FDA.

(p) *Human cell, tissue, or cellular or tissue-based product (HCT/P) regulated as a device* means an HCT/P as defined in §1271.3(d) of this chapter that does not meet the criteria in §1271.10(a) and that is also regulated as a device.

(q) *Unique device identifier (UDI)* means an identifier that adequately identifies a device through its distribution and use by meeting the requirements of §830.20 of this chapter. A unique device identifier is composed of:

(1) *A device identifier*—a mandatory, fixed portion of a UDI that identifies the specific version or model of a device and the labeler of that device; and

(2) *A production identifier*—a conditional, variable portion of a UDI that identifies one or more of the following when included on the label of the device:

(i) The lot or batch within which a device was manufactured;

(ii) The serial number of a specific device;

(iii) The expiration date of a specific device;

(iv) The date a specific device was manufactured.

(v) For an HCT/P regulated as a device, the distinct identification code required by §1271.290(c) of this chapter.

(r) *Universal product code (UPC)* means the product identifier used to identify an item sold at retail in the United States.

(s) *Pediatric patients* means patients who are 21 years of age or younger (that is, from birth through the twenty-first year of life, up to but not including the twenty-second birthday) at the time of the diagnosis or treatment.

(t) *Readily available* means available in the public domain through commonly used public resources for conducting biomedical, regulatory, and medical product research.

[51 FR 26364, July 22, 1986, as amended at 61 FR 15190, Apr. 5, 1996; 61 FR 33244, June 26, 1996; 73 FR 49610, Aug. 22, 2008; 78 FR 55821, Sept. 24, 2013; 79 FR 1740, Jan. 10, 2014; 82 FR 26349, June 7, 2017]

§ 814.9 Confidentiality of data and information in a premarket approval application (PMA) file.

(a) A "PMA file" includes all data and information submitted with or incorporated by reference in the PMA, any IDE incorporated into the PMA, any PMA supplement, any report under § 814.82, any master file, or any other related submission. Any record in the PMA file will be available for public disclosure in accordance with the provisions of this section and part 20. The confidentiality of information in a color additive petition submitted as part of a PMA is governed by § 71.15.

(b) The existence of a PMA file may not be disclosed by FDA before an approval order is issued to the applicant unless it previously has been publicly disclosed or acknowledged.

(c) If the existence of a PMA file has not been publicly disclosed or acknowledged, data or information in the PMA file are not available for public disclosure.

(d)(1) If the existence of a PMA file has been publicly disclosed or acknowledged before an order approving, or an order denying approval of the PMA is issued, data or information contained in the file are not available for public disclosure before such order issues. FDA may, however, disclose a summary of portions of the safety and effectiveness data before an approval order or an order denying approval of the PMA issues if disclosure is relevant to public consideration of a specific pending issue.

(2) Notwithstanding paragraph (d)(1) of this section, FDA will make available to the public upon request the information in the IDE that was required to be filed in Docket Number 95S-0158 in the Division of Dockets Management (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857, for investigations involving an exception from informed consent under § 50.24 of this chapter. Persons wishing to request this information shall submit a request under the Freedom of Information Act.

(e) Upon issuance of an order approving, or an order denying approval of any PMA, FDA will make available to the public the fact of the existence of the PMA and a detailed summary of information submitted to FDA respecting the safety and effectiveness of the device that is the subject of the PMA and that is the basis for the order.

(f) After FDA issues an order approving, or an order denying approval of any PMA, the following data and information in the PMA file are immediately available for public disclosure:

(1) All safety and effectiveness data and information previously disclosed to the public, as such disclosure is defined in § 20.81.

(2) Any protocol for a test or study unless the protocol is shown to constitute trade secret or confidential commercial or financial information under § 20.61.

(3) Any adverse reaction report, product experience report, consumer complaint, and other similar data and information, after deletion of:

(i) Any information that constitutes trade secret or confidential commercial or financial information under § 20.61; and

(ii) Any personnel, medical, and similar information disclosure of which would constitute a clearly unwarranted invasion of personal privacy under § 20.63; provided, however, that except for the information that constitutes trade secret or confidential commercial or financial information under § 20.61, FDA will disclose to a patient who requests a report all the information in the report concerning that patient.

(4) A list of components previously disclosed to the public, as such disclosure is defined in § 20.81.

(5) An assay method or other analytical method, unless it does not serve any regulatory purpose and is shown to fall within the exemption in § 20.61 for trade secret or confidential commercial or financial information.

(6) All correspondence and written summaries of oral discussions relating to the PMA file, in accordance with the provisions of §§ 20.103 and 20.104.

(g) All safety and effectiveness data and other information not previously disclosed to the public are available for public disclosure if any one of the following events occurs and the data and information do not constitute trade secret or confidential commercial or financial information under § 20.61:

(1) The PMA has been abandoned. FDA will consider a PMA abandoned if:

(i)(A) The applicant fails to respond to a request for additional information within 180 days after the date FDA issues the request or

(B) Other circumstances indicate that further work is not being undertaken with respect to it, and

(ii) The applicant fails to communicate with FDA within 7 days after the date on which FDA notifies the applicant that the PMA appears to have been abandoned.

(2) An order denying approval of the PMA has issued, and all legal appeals have been exhausted.

(3) An order withdrawing approval of the PMA has issued, and all legal appeals have been exhausted.

(4) The device has been reclassified.

(5) The device has been found to be substantially equivalent to a class I or class II device.

(6) The PMA is considered voluntarily withdrawn under § 814.44(g).

(h) The following data and information in a PMA file are not available for public disclosure unless they have been previously disclosed to the public, as such disclosure is defined in § 20.81, or they relate to a device for which a PMA has been abandoned and they no longer represent a trade secret or confidential commercial or financial information as defined in § 20.61:

(1) Manufacturing methods or processes, including quality control procedures.

(2) Production, sales, distribution, and similar data and information, except that any compilation of such data and information aggregated and prepared in a way that does not reveal data or information which are not available for public disclosure under this provision is available for public disclosure.

(3) Quantitative or semiquantitative formulas.

[51 FR 26364, July 22, 1986, as amended at 61 FR 51531, Oct. 2, 1996]

§ 814.15 Research conducted outside the United States.

(a) *Data to support PMA.* If data from clinical investigations conducted outside the United States are submitted to support a PMA, the applicant shall comply with the provisions in § 812.28 of this chapter, as applicable.

(b) *As sole basis for marketing approval.* A PMA based solely on foreign clinical data and otherwise meeting the criteria for approval under this part may be approved if:

(1) The foreign data are applicable to the U.S. population and U.S. medical practice;

(2) The studies have been performed by clinical investigators of recognized competence; and

(3) The data may be considered valid without the need for an on-site inspection by FDA or, if FDA considers such an inspection to be necessary, FDA can validate the data through an on-site inspection or other appropriate means.

(c) *Consultation between FDA and applicants.* Applicants are encouraged to meet with FDA officials in a "presubmission" meeting when approval based solely on foreign data will be sought.

[51 FR 26364, July 22, 1986; 51 FR 40415, Nov. 7, 1986, as amended at 51 FR 43344, Dec. 2, 1986; 83 FR 7387, Feb. 21, 2018]

§814.17 Service of orders.

Orders issued under this part will be served in person by a designated officer or employee of FDA on, or by registered mail to, the applicant or the designated agent at the applicant's or designated agent's last known address in FDA's records.

§814.19 Product development protocol (PDP).

A class III device for which a product development protocol has been declared completed by FDA under this chapter will be considered to have an approved PMA.

Subpart B—Premarket Approval Application (PMA)

§814.20 Application.

(a) The applicant or an authorized representative shall sign the PMA. If the applicant does not reside or have a place of business within the United States, the PMA shall be countersigned by an authorized representative residing or maintaining a place of business in the United States and shall identify the representative's name and address.

(b) Unless the applicant justifies an omission in accordance with paragraph (d) of this section, a PMA shall include:

(1) The name and address of the applicant.

(2) A table of contents that specifies the volume and page number for each item referred to in the table. A PMA shall include separate sections on nonclinical laboratory studies and on clinical investigations involving human subjects. A PMA shall be submitted in six copies each bound in one or more numbered volumes of reasonable size. The applicant shall include information that it believes to be trade secret or confidential commercial or financial information in all copies of the PMA and identify in at least one copy the information that it believes to be trade secret or confidential commercial or financial information.

(3) A summary in sufficient detail that the reader may gain a general understanding of the data and information in the application. The summary shall contain the following information:

(i) *Indications for use.* A general description of the disease or condition the device will diagnose, treat, prevent, cure, or mitigate, including a description of the patient population for which the device is intended.

(ii) *Device description.* An explanation of how the device functions, the basic scientific concepts that form the basis for the device, and the significant physical and performance characteristics of the device. A brief description of the manufacturing process should be included if it will significantly enhance the reader's understanding of the device. The generic name of the device as well as any proprietary name or trade name should be included.

(iii) *Alternative practices and procedures.* A description of existing alternative practices or procedures for diagnosing, treating, preventing, curing, or mitigating the disease or condition for which the device is intended.

(iv) *Marketing history.* A brief description of the foreign and U.S. marketing history, if any, of the device, including a list of all countries in which the device has been marketed and a list of all countries in which the device has been withdrawn from marketing for any reason related to the safety or effectiveness of the device. The description shall include the history of the marketing of the device by the applicant and, if known, the history of the marketing of the device by any other person.

(v) *Summary of studies.* An abstract of any information or report described in the PMA under paragraph (b)(8)(ii) of this section and a summary of the results of technical data submitted under paragraph (b)(6) of this section. Such summary shall include a description of the objective of the study, a description of the experimental design of the study, a brief description of how the data were collected and analyzed, and a brief description of the results, whether positive, negative, or inconclusive. This section shall include the following:

(A) A summary of the nonclinical laboratory studies submitted in the application;

(B) A summary of the clinical investigations involving human subjects submitted in the application including a discussion of subject selection and exclusion criteria, study population, study period, safety and effectiveness data, adverse reactions and complications, patient discontinuation, patient complaints, device failures and replacements, results of statistical analyses of the clinical investigations, contraindications and precautions for use of the device, and other information from the clinical investigations as appropriate (any investigation conducted under an IDE shall be identified as such).

(vi) *Conclusions drawn from the studies.* A discussion demonstrating that the data and information in the application constitute valid scientific evidence within the meaning of §860.7 and provide reasonable assurance that the device is safe and effective for its intended use. A concluding discussion shall present benefit and risk considerations related to the device including a discussion of any adverse effects of the device on health and any proposed additional studies or surveillance the applicant intends to conduct following approval of the PMA.

(4) A complete description of:

(i) The device, including pictorial representations;

(ii) Each of the functional components or ingredients of the device if the device consists of more than one physical component or ingredient;

(iii) The properties of the device relevant to the diagnosis, treatment, prevention, cure, or mitigation of a disease or condition;

(iv) The principles of operation of the device; and

(v) The methods used in, and the facilities and controls used for, the manufacture, processing, packing, storage, and, where appropriate, installation of the device, in sufficient detail so that a person generally familiar with current good manufacturing practice can make a knowledgeable judgment about the quality control used in the manufacture of the device.

(5) Reference to any performance standard under section 514 of the act or under section 534 of Subchapter C—Electronic Product Radiation Control of the Federal Food, Drug, and Cosmetic Act (formerly the Radiation Control for Health and Safety Act of 1968) in effect or proposed at the time of the submission and to any voluntary standard that is relevant to any aspect of the safety or effectiveness of the device and that is known to or that should reasonably be known to the applicant. The applicant shall—

(i) Provide adequate information to demonstrate how the device meets, or justify any deviation from, any performance standard established under section 514 of the act or under section 534 of Subchapter C—Electronic Product Radiation Control of the Federal Food, Drug, and Cosmetic Act (formerly the Radiation Control for Health and Safety Act of 1968), and

(ii) Explain any deviation from a voluntary standard.

(6) The following technical sections which shall contain data and information in sufficient detail to permit FDA to determine whether to approve or deny approval of the application:

(i) A section containing results of the nonclinical laboratory studies with the device including microbiological, toxicological, immunological, biocompatibility, stress, wear, shelf life, and other labo-

ratory or animal tests as appropriate. Information on nonclinical laboratory studies shall include a statement that each such study was conducted in compliance with part 58, or, if the study was not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance.

(ii) A section containing results of the clinical investigations involving human subjects with the device including clinical protocols, number of investigators and subjects per investigator, subject selection and exclusion criteria, study population, study period, safety and effectiveness data, adverse reactions and complications, patient discontinuation, patient complaints, device failures and replacements, tabulations of data from all individual subject report forms and copies of such forms for each subject who died during a clinical investigation or who did not complete the investigation, results of statistical analyses of the clinical investigations, device failures and replacements, contraindications and precautions for use of the device, and any other appropriate information from the clinical investigations. Any investigation conducted under an IDE shall be identified as such. Information on clinical investigations involving human subjects shall include the following:

(A) For clinical investigations conducted in the United States, a statement with respect to each investigation that it either was conducted in compliance with the institutional review board regulations in part 56 of this chapter, or was not subject to the regulations under § 56.104 or § 56.105, and that it was conducted in compliance with the informed consent regulations in part 50 of this chapter; or if the investigation was not conducted in compliance with those regulations, a brief statement of the reason for the noncompliance. Failure or inability to comply with these requirements does not justify failure to provide information on a relevant clinical investigation.

(B) For clinical investigations conducted in the United States, a statement that each investigation was conducted in compliance with part 812 of this chapter concerning sponsors of clinical investigations and clinical investigators, or if the investigation was not conducted in compliance with those regulations, a brief statement of the reason for the noncompliance. Failure or inability to comply with these requirements does not justify failure to provide information on a relevant clinical investigation.

(C) For clinical investigations conducted outside the United States that are intended to support the PMA, the requirements under § 812.28 of this chapter apply. If any such investigation was not conducted in accordance with good clinical practice (GCP) as described in § 812.28(a), include either a waiver request in accordance with § 812.28(c) or a brief statement of the reason for not conducting the investigation in accordance with GCP and a description of steps taken to ensure that the data and results are credible and accurate and that the rights, safety, and well-being of subjects have been adequately protected. Failure or inability to comply with these requirements does not justify failure to provide information on a relevant clinical investigation.

(7) For a PMA supported solely by data from one investigation, a justification showing that data and other information from a single investigator are sufficient to demonstrate the safety and effectiveness of the device and to ensure reproducibility of test results.

(8)(i) A bibliography of all published reports not submitted under paragraph (b)(6) of this section, whether adverse or supportive, known to or that should reasonably be known to the applicant and that concern the safety or effectiveness of the device.

(ii) An identification, discussion, and analysis of any other data, information, or report relevant to an evaluation of the safety and effectiveness of the device known to or that should reasonably be known to the applicant from any source, foreign or domestic, including information derived from investigations other than those proposed in the application and from commercial marketing experience.

(iii) Copies of such published reports or unpublished information in the possession of or reasonably obtainable by the applicant if an FDA advisory committee or FDA requests.

(9) One or more samples of the device and its components, if requested by FDA. If it is impractical to submit a requested sample of the device, the applicant shall name the location at which FDA may examine and test one or more devices.

(10) Copies of all proposed labeling for the device. Such labeling may include, e.g., instructions for installation and any information, literature, or advertising that constitutes labeling under section 201(m) of the act.

(11) An environmental assessment under § 25.20(n) prepared in the applicable format in § 25.40, unless the action qualifies for exclusion under § 25.30 or § 25.34. If the applicant believes that the action qualifies for exclusion, the PMA shall under § 25.15(a) and (d) provide information that establishes to FDA's satisfaction that the action requested is included within the excluded category and meets the criteria for the applicable exclusion.

(12) A financial certification or disclosure statement or both as required by part 54 of this chapter.

(13) *Information concerning uses in pediatric patients.* The application must include the following information, if readily available:

(i) A description of any pediatric subpopulations (neonates, infants, children, adolescents) that suffer from the disease or condition that the device is intended to treat, diagnose, or cure; and

(ii) The number of affected pediatric patients.

(14) Such other information as FDA may request. If necessary, FDA will obtain the concurrence of the appropriate FDA advisory committee before requesting additional information.

(c) Pertinent information in FDA files specifically referred to by an applicant may be incorporated into a PMA by reference. Information in a master file or other information submitted to FDA by a person other than the applicant will not be considered part of a PMA unless such reference is authorized in writing by the person who submitted the information or the master file. If a master file is not referenced within 5 years after the date that it is submitted to FDA, FDA will return the master file to the person who submitted it.

(d) If the applicant believes that certain information required under paragraph (b) of this section to be in a PMA is not applicable to the device that is the subject of the PMA, and omits any such information from its PMA, the applicant shall submit a statement that identifies the omitted information and justifies the omission. The statement shall be submitted as a separate section in the PMA and identified in the table of contents. If the justification for the omission is not accepted by the agency, FDA will so notify the applicant.

(e) The applicant shall periodically update its pending application with new safety and effectiveness information learned about the device from ongoing or completed studies that may reasonably affect an evaluation of the safety or effectiveness of the device or that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling. The update report shall be consistent with the data reporting provisions of the protocol. The applicant shall submit three copies of any update report and shall include in the report the number assigned by FDA to the PMA. These updates are considered to be amendments to the PMA. The time frame for review of a PMA will not be extended due to the submission of an update report unless the update is a major amendment under § 814.37(c)(1). The applicant shall submit these reports—

(1) 3 months after the filing date,

(2) Following receipt of an approvable letter, and

(3) At any other time as requested by FDA.

(f) If a color additive subject to section 721 of the act is used in or on the device and has not previously been listed for such use, then, in lieu of submitting a color additive petition under part 71, at the option of the applicant, the information required to be submitted under part 71 may be submit-

ted as part of the PMA. When submitted as part of the PMA, the information shall be submitted in three copies each bound in one or more numbered volumes of reasonable size. A PMA for a device that contains a color additive that is subject to section 721 of the act will not be approved until the color additive is listed for use in or on the device.

(g) Additional information on FDA policies and procedures, as well as links to PMA guidance documents, is available on the Internet at *http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/default.htm*.

(h) If you are sending a PMA, PMA amendment, PMA supplement, or correspondence with respect to a PMA, you must send the submission to the appropriate address as follows:

(1) For devices regulated by the Center for Devices and Radiological Health, Food and Drug Administration, Center for Devices and Radiological Health, Document Mail Center, 10903 New Hampshire Ave., Bldg. 66, rm. G609, Silver Spring, MD 20993-0002.

(2) For devices regulated by the Center for Biologics Evaluation and Research, send it to: Food and Drug Administration, Center for Biologics Evaluation and Research, Document Control Center, 10903 New Hampshire Ave., Bldg. 71, Rm. G112, Silver Spring, MD 20993-0002.

(3) For devices regulated by the Center for Drug Evaluation and Research, send it to: Central Document Control Room, Center for Drug Evaluation and Research, Food and Drug Administration, 5901-B Ammendale Rd., Beltsville, MD 20705-1266.

[51 FR 26364, July 22, 1986; 51 FR 40415, Nov. 7, 1986, as amended at 51 FR 43344, Dec. 2, 1986; 55 FR 11169, Mar. 27, 1990; 62 FR 40600, July 29, 1997; 63 FR 5253, Feb. 2, 1998; 65 FR 17137, Mar. 31, 2000; 65 FR 56480, Sept. 19, 2000; 67 FR 9587, Mar. 4, 2002; 71 FR 42048, July 25, 2006; 72 FR 17399, Apr. 9, 2007; 73 FR 34859, June 19, 2008; 74 FR 14478, Mar. 31, 2009; 75 FR 20915, Apr. 22, 2010; 78 FR 18233, Mar. 26, 2013; 79 FR 1740, Jan. 10, 2014; 80 FR 18094, Apr. 3, 2015; 83 FR 7387, Feb. 21, 2018]

§814.37 PMA amendments and resubmitted PMAs.

(a) An applicant may amend a pending PMA or PMA supplement to revise existing information or provide additional information.

(b)(1) FDA may request the applicant to amend a PMA or PMA supplement with any information regarding the device that is necessary for FDA or the appropriate advisory committee to complete the review of the PMA or PMA supplement.

(2) FDA may request the applicant to amend a PMA or PMA supplement with information concerning pediatric uses as required under §§ 814.20(b)(13) and 814.39(c)(2).

(c) A PMA amendment submitted to FDA shall include the PMA or PMA supplement number assigned to the original submission and, if submitted on the applicant's own initiative, the reason for submitting the amendment. FDA may extend the time required for its review of the PMA, or PMA supplement, as follows:

(1) If the applicant on its own initiative or at FDA's request submits a major PMA amendment (e.g., an amendment that contains significant new data from a previously unreported study, significant updated data from a previously reported study, detailed new analyses of previously submitted data, or significant required information previously omitted), the review period may be extended up to 180 days.

(2) If an applicant declines to submit a major amendment requested by FDA, the review period may be extended for the number of days that elapse between the date of such request and the date that FDA receives the written response declining to submit the requested amendment.

(d) An applicant may on its own initiative withdraw a PMA or PMA supplement. If FDA requests an applicant to submit a PMA amendment and a written response to FDA's request is not received

within 180 days of the date of the request, FDA will consider the pending PMA or PMA supplement to be withdrawn voluntarily by the applicant.

(e) An applicant may resubmit a PMA or PMA supplement after withdrawing it or after it is considered withdrawn under paragraph (d) of this section, or after FDA has refused to accept it for filing, or has denied approval of the PMA or PMA supplement. A resubmitted PMA or PMA supplement shall comply with the requirements of §814.20 or §814.39, respectively, and shall include the PMA number assigned to the original submission and the applicant's reasons for resubmission of the PMA or PMA supplement.

[51 FR 26364, July 22, 1986, as amended at 79 FR 1740, Jan. 10, 2014]

§814.39 PMA supplements.

(a) After FDA's approval of a PMA, an applicant shall submit a PMA supplement for review and approval by FDA before making a change affecting the safety or effectiveness of the device for which the applicant has an approved PMA, unless the change is of a type for which FDA, under paragraph (e) of this section, has advised that an alternate submission is permitted or is of a type which, under section 515(d)(6)(A) of the act and paragraph (f) of this section, does not require a PMA supplement under this paragraph. While the burden for determining whether a supplement is required is primarily on the PMA holder, changes for which an applicant shall submit a PMA supplement include, but are not limited to, the following types of changes if they affect the safety or effectiveness of the device:

(1) New indications for use of the device.

(2) Labeling changes.

(3) The use of a different facility or establishment to manufacture, process, or package the device.

(4) Changes in sterilization procedures.

(5) Changes in packaging.

(6) Changes in the performance or design specifications, circuits, components, ingredients, principle of operation, or physical layout of the device.

(7) Extension of the expiration date of the device based on data obtained under a new or revised stability or sterility testing protocol that has not been approved by FDA. If the protocol has been approved, the change shall be reported to FDA under paragraph (b) of this section.

(b) An applicant may make a change in a device after FDA's approval of a PMA for the device without submitting a PMA supplement if the change does not affect the device's safety or effectiveness and the change is reported to FDA in postapproval periodic reports required as a condition to approval of the device, e.g., an editorial change in labeling which does not affect the safety or effectiveness of the device.

(c)(1) All procedures and actions that apply to an application under §814.20 also apply to PMA supplements except that the information required in a supplement is limited to that needed to support the change. A summary under §814.20(b)(3) is required for only a supplement submitted for new indications for use of the device, significant changes in the performance or design specifications, circuits, components, ingredients, principles of operation, or physical layout of the device, or when otherwise required by FDA. The applicant shall submit three copies of a PMA supplement and shall include information relevant to the proposed changes in the device. A PMA supplement shall include a separate section that identifies each change for which approval is being requested and explains the reason for each such change. The applicant shall submit additional copies and additional information if requested by FDA. The time frames for review of, and FDA action on, a PMA supplement are the same as those provided in §814.40 for a PMA.

(2) The supplement must include the following information:

(i) Information concerning pediatric uses as required under §814.20(b)(13).

(ii) If information concerning the device that is the subject of the supplement was previously submitted under §814.20(b)(13) or under this section in a previous supplement, that information may be included by referencing a previous application or submission that contains the information. However, if additional information required under §814.20(b)(13) has become readily available to the applicant since the previous submission, the applicant must submit that information as part of the supplement.

(d)(1) After FDA approves a PMA, any change described in paragraph (d)(2) of this section to reflect newly acquired information that enhances the safety of the device or the safety in the use of the device may be placed into effect by the applicant prior to the receipt under §814.17 of a written FDA order approving the PMA supplement provided that:

(i) The PMA supplement and its mailing cover are plainly marked "Special PMA Supplement—Changes Being Effected";

(ii) The PMA supplement provides a full explanation of the basis for the changes;

(iii) The applicant has received acknowledgement from FDA of receipt of the supplement; and

(iv) The PMA supplement specifically identifies the date that such changes are being effected.

(2) The following changes are permitted by paragraph (d)(1) of this section:

(i) Labeling changes that add or strengthen a contraindication, warning, precaution, or information about an adverse reaction for which there is reasonable evidence of a causal association.

(ii) Labeling changes that add or strengthen an instruction that is intended to enhance the safe use of the device.

(iii) Labeling changes that delete misleading, false, or unsupported indications.

(iv) Changes in quality controls or manufacturing process that add a new specification or test method, or otherwise provide additional assurance of purity, identity, strength, or reliability of the device.

(e)(1) FDA will identify a change to a device for which an applicant has an approved PMA and for which a PMA supplement under paragraph (a) is not required. FDA will identify such a change in an advisory opinion under §10.85, if the change applies to a generic type of device, or in correspondence to the applicant, if the change applies only to the applicant's device. FDA will require that a change for which a PMA supplement under paragraph (a) is not required be reported to FDA in:

(i) A periodic report under §814.84 or

(ii) A 30-day PMA supplement under this paragraph.

(2) FDA will identify, in the advisory opinion or correspondence, the type of information that is to be included in the report or 30-day PMA supplement. If the change is required to be reported to FDA in a periodic report, the change may be made before it is reported to FDA. If the change is required to be reported in a 30-day PMA supplement, the change may be made 30 days after FDA files the 30-day PMA supplement unless FDA requires the PMA holder to provide additional information, informs the PMA holder that the supplement is not approvable, or disapproves the supplement. The 30-day PMA supplement shall follow the instructions in the correspondence or advisory opinion. Any 30-day PMA supplement that does not meet the requirements of the correspondence or advisory opinion will not be filed and, therefore, will not be deemed approved 30 days after receipt.

(f) Under section 515(d) of the act, modifications to manufacturing procedures or methods of manufacture that affect the safety and effectiveness of a device subject to an approved PMA do not require submission of a PMA supplement under paragraph (a) of this section and are eligible to be the subject of a 30-day notice. A 30-day notice shall describe in detail the change, summarize the data or information supporting the change, and state that the change has been made in ac-

cordance with the requirements of part 820 of this chapter. The manufacturer may distribute the device 30 days after the date on which FDA receives the 30-day notice, unless FDA notifies the applicant within 30 days from receipt of the notice that the notice is not adequate. If the notice is not adequate, FDA shall inform the applicant in writing that a 135-day PMA supplement is needed and shall describe what further information or action is required for acceptance of such change. The number of days under review as a 30-day notice shall be deducted from the 135-day PMA supplement review period if the notice meets appropriate content requirements for a PMA supplement.

(g) The submission and grant of a written request for an exception or alternative under § 801.128 or § 809.11 of this chapter satisfies the requirement in paragraph (a) of this section.

[51 FR 26364, July 22, 1986, as amended at 51 FR 43344, Dec. 2, 1986; 63 FR 54044, Oct. 8, 1998; 67 FR 9587, Mar. 4, 2002; 69 FR 11313, Mar. 10, 2004; 72 FR 73602, Dec. 28, 2007; 73 FR 49610, Aug. 22, 2008; 79 FR 1740, Jan. 10, 2014]

Subpart C—FDA Action on a PMA

§ 814.40 Time frames for reviewing a PMA.

Within 180 days after receipt of an application that is accepted for filing and to which the applicant does not submit a major amendment, FDA will review the PMA and, after receiving the report and recommendation of the appropriate FDA advisory committee, send the applicant an approval order under § 814.44(d), an approvable letter under § 814.44(e), a not approvable letter under § 814.44(f), or an order denying approval under § 814.45. The approvable letter and the not approvable letter will provide an opportunity for the applicant to amend or withdraw the application, or to consider the letter to be a denial of approval of the PMA under § 814.45 and to request administrative review under section 515 (d)(3) and (g) of the act.

§ 814.42 Filing a PMA.

(a) The filing of an application means that FDA has made a threshold determination that the application is sufficiently complete to permit a substantive review. Within 45 days after a PMA is received by FDA, the agency will notify the applicant whether the application has been filed.

(b) If FDA does not find that any of the reasons in paragraph (e) of this section for refusing to file the PMA applies, the agency will file the PMA and will notify the applicant in writing of the filing. The notice will include the PMA reference number and the date FDA filed the PMA. The date of filing is the date that a PMA accepted for filing was received by the agency. The 180-day period for review of a PMA starts on the date of filing.

(c) If FDA refuses to file a PMA, the agency will notify the applicant of the reasons for the refusal. This notice will identify the deficiencies in the application that prevent filing and will include the PMA reference number.

(d) If FDA refuses to file the PMA, the applicant may:

(1) Resubmit the PMA with additional information necessary to comply with the requirements of section 515(c)(1) (A)-(G) of the act and § 814.20. A resubmitted PMA shall include the PMA reference number of the original submission. If the resubmitted PMA is accepted for filing, the date of filing is the date FDA receives the resubmission;

(2) Request in writing within 10 working days of the date of receipt of the notice refusing to file the PMA, an informal conference with the Director of the Office of Device Evaluation to review FDA's decision not to file the PMA. FDA will hold the informal conference within 10 working days of its receipt of the request and will render its decision on filing within 5 working days after the informal conference. If, after the informal conference, FDA accepts the PMA for filing, the date of filing will be the date of the decision to accept the PMA for filing. If FDA does not reverse its decision not to file the PMA, the applicant may request reconsideration of the decision from the Director of the Center

for Devices and Radiological Health, the Director of the Center for Biologics Evaluation and Research, or the Director of the Center for Drug Evaluation and Research, as applicable. The Director's decision will constitute final administrative action for the purpose of judicial review.

(e) FDA may refuse to file a PMA if any of the following applies:

(1) The application is incomplete because it does not on its face contain all the information required under section 515(c)(1) (A)-(G) of the act;

(2) The PMA does not contain each of the items required under § 814.20 and justification for omission of any item is inadequate;

(3) The applicant has a pending premarket notification under section 510(k) of the act with respect to the same device, and FDA has not determined whether the device falls within the scope of § 814.1(c).

(4) The PMA contains a false statement of material fact.

(5) The PMA is not accompanied by a statement of either certification or disclosure as required by part 54 of this chapter.

[51 FR 26364, July 22, 1986, as amended at 63 FR 5254, Feb. 2, 1998; 73 FR 49942, Aug. 25, 2008]

§ 814.44 Procedures for review of a PMA.

(a) FDA will begin substantive review of a PMA after the PMA is accepted for filing under § 814.42. FDA may refer the PMA to a panel on its own initiative, and will do so upon request of an applicant, unless FDA determines that the application substantially duplicates information previously reviewed by a panel. If FDA refers an application to a panel, FDA will forward the PMA, or relevant portions thereof, to each member of the appropriate FDA panel for review. During the review process, FDA may communicate with the applicant as set forth under § 814.37(b), or with a panel to respond to questions that may be posed by panel members or to provide additional information to the panel. FDA will maintain a record of all communications with the applicant and with the panel.

(b) The advisory committee shall submit a report to FDA which includes the committee's recommendation and the basis for such recommendation on the PMA. Before submission of this report, the committee shall hold a public meeting to review the PMA in accordance with part 14. This meeting may be held by a telephone conference under § 14.22(g). The advisory committee report and recommendation may be in the form of a meeting transcript signed by the chairperson of the committee.

(c) FDA will complete its review of the PMA and the advisory committee report and recommendation and, within the later of 180 days from the date of filing of the PMA under § 814.42 or the number of days after the date of filing as determined under § 814.37(c), issue an approval order under paragraph (d) of this section, an approvable letter under paragraph (e) of this section, a not approvable letter under paragraph (f) of this section, or an order denying approval of the application under § 814.45(a).

(d)(1) FDA will issue to the applicant an order approving a PMA if none of the reasons in § 814.45 for denying approval of the application applies. FDA will approve an application on the basis of draft final labeling if the only deficiencies in the application concern editorial or similar minor deficiencies in the draft final labeling. Such approval will be conditioned upon the applicant incorporating the specified labeling changes exactly as directed and upon the applicant submitting to FDA a copy of the final printed labeling before marketing. FDA will also give the public notice of the order, including notice of and opportunity for any interested persons to request review under section 515(d)(3) of the act. The notice of approval will be placed on FDA's home page on the Internet (*http://www.fda.gov*), and it will state that a detailed summary of information respecting the safety and effectiveness of the device, which was the basis for the order approving the PMA, including information about any adverse effects of the device on health, is available on the Internet and has been placed on

public display, and that copies are available upon request. FDA will publish in the Federal Register after each quarter a list of the approvals announced in that quarter. When a notice of approval is published, data and information in the PMA file will be available for public disclosure in accordance with §814.9.

(2) A request for copies of the current PMA approvals and denials document and for copies of summaries of safety and effectiveness shall be sent in writing to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

(e) FDA will send the applicant an approvable letter if the application substantially meets the requirements of this part and the agency believes it can approve the application if specific additional information is submitted or specific conditions are agreed to by the applicant.

(1) The approvable letter will describe the information FDA requires to be provided by the applicant or the conditions the applicant is required to meet to obtain approval. For example, FDA may require, as a condition to approval:

(i) The submission of certain information identified in the approvable letter, e.g., final labeling;

(ii) The submission of additional information concerning pediatric uses required by §814.20(b)(13);

(iii) An FDA inspection that finds the manufacturing facilities, methods, and controls in compliance with part 820 and, if applicable, that verifies records pertinent to the PMA;

(iv) Restrictions imposed on the device under section 515(d)(1)(B)(ii) or 520(e) of the act;

(v) Postapproval requirements as described in subpart E of this part.

(2) In response to an approvable letter the applicant may:

(i) Amend the PMA as requested in the approvable letter; or

(ii) Consider the approvable letter to be a denial of approval of the PMA under §814.45 and request administrative review under section 515(d)(3) of the act by filing a petition in the form of a petition for reconsideration under §10.33; or

(iii) Withdraw the PMA.

(f) FDA will send the applicant a not approvable letter if the agency believes that the application may not be approved for one or more of the reasons given in §814.45(a). The not approvable letter will describe the deficiencies in the application, including each applicable ground for denial under section 515(d)(2)(A)-(E) of the act, and, where practical, will identify measures required to place the PMA in approvable form. In response to a not approvable letter, the applicant may:

(1) Amend the PMA as requested in the not approvable letter (such an amendment will be considered a major amendment under §814.37(c)(1)); or

(2) Consider the not approvable letter to be a denial of approval of the PMA under §814.45 and request administrative review under section 515(d)(3) of the act by filing a petition in the form of a petition for reconsideration under §10.33; or

(3) Withdraw the PMA.

(g) FDA will consider a PMA to have been withdrawn voluntarily if:

(1) The applicant fails to respond in writing to a written request for an amendment within 180 days after the date FDA issues such request;

(2) The applicant fails to respond in writing to an approvable or not approvable letter within 180 days after the date FDA issues such letter; or

(3) The applicant submits a written notice to FDA that the PMA has been withdrawn.

[51 FR 26364, July 22, 1986, as amended at 57 FR 58403, Dec. 10, 1992; 63 FR 4572, Jan. 30, 1998; 79 FR 1740, Jan. 10, 2014]

§ 814.45 Denial of approval of a PMA.

(a) FDA may issue an order denying approval of a PMA if the applicant fails to follow the requirements of this part or if, upon the basis of the information submitted in the PMA or any other information before the agency, FDA determines that any of the grounds for denying approval of a PMA specified in section 515(d)(2) (A)-(E) of the act applies. In addition, FDA may deny approval of a PMA for any of the following reasons:

(1) The PMA contains a false statement of material fact;

(2) The device's proposed labeling does not comply with the requirements in part 801 or part 809;

(3) The applicant does not permit an authorized FDA employee an opportunity to inspect at a reasonable time and in a reasonable manner the facilities, controls, and to have access to and to copy and verify all records pertinent to the application;

(4) A nonclinical laboratory study that is described in the PMA and that is essential to show that the device is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling, was not conducted in compliance with the good laboratory practice regulations in part 58 and no reason for the noncompliance is provided or, if it is, the differences between the practices used in conducting the study and the good laboratory practice regulations do not support the validity of the study; or

(5) Any clinical investigation involving human subjects described in the PMA, subject to the institutional review board regulations in part 56 of this chapter or informed consent regulations in part 50 of this chapter or GCP referenced in § 814.15(a) and described in § 812.28(a) of this chapter, was not conducted in compliance with those regulations such that the rights or safety of human subjects were not adequately protected or the supporting data were determined to be otherwise unreliable.

(b) FDA will issue any order denying approval of the PMA in accordance with § 814.17. The order will inform the applicant of the deficiencies in the PMA, including each applicable ground for denial under section 515(d)(2) of the act and the regulations under this part, and, where practical, will identify measures required to place the PMA in approvable form. The order will include a notice of an opportunity to request review under section 515(d)(4) of the act.

(c) FDA will use the criteria specified in § 860.7 to determine the safety and effectiveness of a device in deciding whether to approve or deny approval of a PMA. FDA may use information other than that submitted by the applicant in making such determination.

(d)(1) FDA will give the public notice of an order denying approval of the PMA. The notice will be placed on the FDA's home page on the Internet (*http://www.fda.gov*), and it will state that a detailed summary of information respecting the safety and effectiveness of the device, including information about any adverse effects of the device on health, is available on the Internet and has been placed on public display and that copies are available upon request. FDA will publish in the Federal Register after each quarter a list of the denials announced in that quarter. When a notice of denial of approval is made publicly available, data and information in the PMA file will be available for public disclosure in accordance with § 814.9.

(2) A request for copies of the current PMA approvals and denials document and copies of summaries of safety and effectiveness shall be sent in writing to the Freedom of Information Staff's address listed on the Agency's Web site at *http://www.fda.gov*.

(e) FDA will issue an order denying approval of a PMA after an approvable or not approvable letter has been sent and the applicant:

(1) Submits a requested amendment but any ground for denying approval of the application under section 515(d)(2) of the act still applies; or

(2) Notifies FDA in writing that the requested amendment will not be submitted; or

(3) Petitions for review under section 515(d)(3) of the act by filing a petition in the form of a petition for reconsideration under § 10.33.

[51 FR 26364, July 22, 1986, as amended at 63 FR 4572, Jan. 30, 1998; 73 FR 34859, June 19, 2008; 76 FR 31470, June 1, 2011; 79 FR 68115, Nov. 14, 2014; 83 FR 7387, Feb. 21, 2018]

§ 814.46 Withdrawal of approval of a PMA.

(a) FDA may issue an order withdrawing approval of a PMA if, from any information available to the agency, FDA determines that:

(1) Any of the grounds under section 515(e)(1) (A)-(G) of the act applies.

(2) Any postapproval requirement imposed by the PMA approval order or by regulation has not been met.

(3) A nonclinical laboratory study that is described in the PMA and that is essential to show that the device is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling, was not conducted in compliance with the good laboratory practice regulations in part 58 and no reason for the noncompliance is provided or, if it is, the differences between the practices used in conducting the study and the good laboratory practice regulations do not support the validity of the study.

(4) Any clinical investigation involving human subjects described in the PMA, subject to the institutional review board regulations in part 56 of this chapter or informed consent regulations in part 50 of this chapter or GCP referenced in § 814.15(a) and described in § 812.28(a) of this chapter, was not conducted in compliance with those regulations such that the rights or safety of human subjects were not adequately protected or the supporting data were determined to be otherwise unreliable.

(b)(1) FDA may seek advice on scientific matters from any appropriate FDA advisory committee in deciding whether to withdraw approval of a PMA.

(2) FDA may use information other than that submitted by the applicant in deciding whether to withdraw approval of a PMA.

(c) Before issuing an order withdrawing approval of a PMA, FDA will issue the holder of the approved application a notice of opportunity for an informal hearing under part 16.

(d) If the applicant does not request a hearing or if after the part 16 hearing is held the agency decides to proceed with the withdrawal, FDA will issue to the holder of the approved application an order withdrawing approval of the application. The order will be issued under § 814.17, will state each ground for withdrawing approval, and will include a notice of an opportunity for administrative review under section 515(e)(2) of the act.

(e) FDA will give the public notice of an order withdrawing approval of a PMA. The notice will be published in the Federal Register and will state that a detailed summary of information respecting the safety and effectiveness of the device, including information about any adverse effects of the device on health, has been placed on public display and that copies are available upon request. When a notice of withdrawal of approval is published, data and information in the PMA file will be available for public disclosure in accordance with § 814.9.

[51 FR 26364, July 22, 1986, as amended at 83 FR 7387, Feb. 21, 2018]

§ 814.47 Temporary suspension of approval of a PMA.

(a) *Scope*. (1) This section describes the procedures that FDA will follow in exercising its authority under section 515(e)(3) of the act (21 U.S.C. 360e(e)(3)). This authority applies to the original PMA, as well as any PMA supplement(s), for a medical device.

(2) FDA will issue an order temporarily suspending approval of a PMA if FDA determines that there is a reasonable probability that continued distribution of the device would cause serious, adverse health consequences or death.

(b) *Regulatory hearing.* (1) If FDA believes that there is a reasonable probability that the continued distribution of a device subject to an approved PMA would cause serious, adverse health consequences or death, FDA may initiate and conduct a regulatory hearing to determine whether to issue an order temporarily suspending approval of the PMA.

(2) Any regulatory hearing to determine whether to issue an order temporarily suspending approval of a PMA shall be initiated and conducted by FDA pursuant to part 16 of this chapter. If FDA believes that immediate action to remove a dangerous device from the market is necessary to protect the public health, the agency may, in accordance with § 16.60(h) of this chapter, waive, suspend, or modify any part 16 procedure pursuant to § 10.19 of this chapter.

(3) FDA shall deem the PMA holder's failure to request a hearing within the timeframe specified by FDA in the notice of opportunity for hearing to be a waiver.

(c) *Temporary suspension order*. If the PMA holder does not request a regulatory hearing or if, after the hearing, and after consideration of the administrative record of the hearing, FDA determines that there is a reasonable probability that the continued distribution of a device under an approved PMA would cause serious, adverse health consequences or death, the agency shall, under the authority of section 515(e)(3) of the act, issue an order to the PMA holder temporarily suspending approval of the PMA.

(d) *Permanent withdrawal of approval of the PMA.* If FDA issues an order temporarily suspending approval of a PMA, the agency shall proceed expeditiously, but within 60 days, to hold a hearing on whether to permanently withdraw approval of the PMA in accordance with section 515(e)(1) of the act and the procedures set out in § 814.46.

[61 FR 15190, Apr. 5, 1996]

Subpart D—Administrative Review [Reserved]

Subpart E—Postapproval Requirements

§ 814.80 General.

A device may not be manufactured, packaged, stored, labeled, distributed, or advertised in a manner that is inconsistent with any conditions to approval specified in the PMA approval order for the device.

§ 814.82 Postapproval requirements.

(a) FDA may impose postapproval requirements in a PMA approval order or by regulation at the time of approval of the PMA or by regulation subsequent to approval. Postapproval requirements may include as a condition to approval of the device:

(1) Restriction of the sale, distribution, or use of the device as provided by section 515(d)(1)(B)(ii) or 520(e) of the act.

(2) Continuing evaluation and periodic reporting on the safety, effectiveness, and reliability of the device for its intended use. FDA will state in the PMA approval order the reason or purpose for such requirement and the number of patients to be evaluated and the reports required to be submitted.

(3) Prominent display in the labeling of a device and in the advertising of any restricted device of warnings, hazards, or precautions important for the device's safe and effective use, including patient

information, e.g., information provided to the patient on alternative modes of therapy and on risks and benefits associated with the use of the device.

(4) Inclusion of identification codes on the device or its labeling, or in the case of an implant, on cards given to patients if necessary to protect the public health.

(5) Maintenance of records that will enable the applicant to submit to FDA information needed to trace patients if such information is necessary to protect the public health. Under section 519(a)(4) of the act, FDA will require that the identity of any patient be disclosed in records maintained under this paragraph only to the extent required for the medical welfare of the individual, to determine the safety or effectiveness of the device, or to verify a record, report, or information submitted to the agency.

(6) Maintenance of records for specified periods of time and organization and indexing of records into identifiable files to enable FDA to determine whether there is reasonable assurance of the continued safety and effectiveness of the device.

(7) Submission to FDA at intervals specified in the approval order of periodic reports containing the information required by §814.84(b).

(8) Batch testing of the device.

(9) Such other requirements as FDA determines are necessary to provide reasonable assurance, or continued reasonable assurance, of the safety and effectiveness of the device.

(b) An applicant shall grant to FDA access to any records and reports required under the provisions of this part, and shall permit authorized FDA employees to copy and verify such records and reports and to inspect at a reasonable time and in a reasonable manner all manufacturing facilities to verify that the device is being manufactured, stored, labeled, and shipped under approved conditions.

(c) Failure to comply with any postapproval requirement constitutes a ground for withdrawal of approval of a PMA.

(Approved by the Office of Management and Budget under control number 0910-0231)

[51 FR 26364, July 22, 1986, as amended at 51 FR 43344, Dec. 2, 1986]

§814.84 Reports.

(a) The holder of an approved PMA shall comply with the requirements of part 803 and with any other requirements applicable to the device by other regulations in this subchapter or by order approving the device.

(b) Unless FDA specifies otherwise, any periodic report shall:

(1) Identify changes described in §814.39(a) and changes required to be reported to FDA under §814.39(b).

(2) Contain a summary and bibliography of the following information not previously submitted as part of the PMA:

(i) Unpublished reports of data from any clinical investigations or nonclinical laboratory studies involving the device or related devices and known to or that reasonably should be known to the applicant.

(ii) Reports in the scientific literature concerning the device and known to or that reasonably should be known to the applicant. If, after reviewing the summary and bibliography, FDA concludes that the agency needs a copy of the unpublished or published reports, FDA will notify the applicant that copies of such reports shall be submitted.

(3) Identify changes made pursuant to an exception or alternative granted under §801.128 or §809.11 of this chapter.

(4) Identify each device identifier currently in use for the device, and each device identifier for the device that has been discontinued since the previous periodic report. It is not necessary to identify any device identifier discontinued prior to December 23, 2013.

[51 FR 26364, July 22, 1986, as amended at 51 FR 43344, Dec. 2, 1986; 67 FR 9587, Mar. 4, 2002; 72 FR 73602, Dec. 28, 2007; 78 FR 58822, Sept. 24, 2013]

Subparts F-G [Reserved]

Subpart H—Humanitarian Use Devices

Source: 61 FR 33244, June 26, 1996, unless otherwise noted.

(a) This subpart H implements sections 515A and 520(m) of the act.

(b) The purpose of section 520(m) is, to the extent consistent with the protection of the public health and safety and with ethical standards, to encourage the discovery and use of devices intended to benefit patients in the treatment or diagnosis of diseases or conditions that affect or are manifested in not more than 8,000 individuals in the United States per year. This subpart provides procedures for obtaining:

(1) HUD designation of a medical device; and

(2) Marketing approval for the HUD notwithstanding the absence of reasonable assurance of effectiveness that would otherwise be required under sections 514 and 515 of the act.

(c) Section 515A of the act is intended to ensure the submission of readily available information concerning:

(1) Any pediatric subpopulations (neonates, infants, children, adolescents) that suffer from the disease or condition that the device is intended to treat, diagnose, or cure; and

(2) The number of affected pediatric patients.

(d) Although a HUD may also have uses that differ from the humanitarian use, applicants seeking approval of any non-HUD use shall submit a PMA as required under § 814.20, or a premarket notification as required under part 807 of this chapter.

(e) Obtaining marketing approval for a HUD involves two steps:

(1) Obtaining designation of the device as a HUD from FDA's Office of Orphan Products Development, and

(2) Submitting an HDE to the Office of Device Evaluation (ODE), Center for Devices and Radiological Health (CDRH), the Center for Biologics Evaluation and Research (CBER), or the Center for Drug Evaluation and Research (CDER), as applicable.

(f) A person granted an exemption under section 520(m) of the act shall submit periodic reports as described in § 814.126(b).

(g) FDA may suspend or withdraw approval of an HDE after providing notice and an opportunity for an informal hearing.

[61 FR 33244, June 26, 1996, as amended at 63 FR 59220, Nov. 3, 1998; 73 FR 49942, Aug. 25, 2008; 79 FR 1740, Jan. 10, 2014; 82 FR 26349, June 7, 2017]

§814.102 Designation of HUD status.

(a) *Request for designation.* Prior to submitting an HDE application, the applicant shall submit a request for HUD designation to FDA's Office of Orphan Products Development. The request shall contain the following:

(1) A statement that the applicant requests HUD designation for a rare disease or condition or a valid subset of a disease or condition which shall be identified with specificity;

(2) The name and address of the applicant, the name of the applicant's primary contact person and/or resident agent, including title, address, and telephone number;

(3) A description of the rare disease or condition for which the device is to be used, the proposed indication or indications for use of the device, and the reasons why such therapy is needed. If the device is proposed for an indication that represents a subset of a common disease or condition, a demonstration that the subset is medically plausible should be included;

(4) A description of the device and a discussion of the scientific rationale for the use of the device for the rare disease or condition; and

(5) Documentation, with appended authoritative references, to demonstrate that the device is designed to treat or diagnose a disease or condition that affects or is manifested in not more than 8,000 people in the United States per year. If the device is for diagnostic purposes, the documentation must demonstrate that not more than 8,000 patients per year would be subjected to diagnosis by the device in the United States. Authoritative references include literature citations in specialized medical journals, textbooks, specialized medical society proceedings, or governmental statistics publications. When no such studies or literature citations exist, the applicant may be able to demonstrate the prevalence of the disease or condition in the United States by providing credible conclusions from appropriate research or surveys.

(b) *FDA action.* Within 45 days of receipt of a request for HUD designation, FDA will take one of the following actions:

(1) Approve the request and notify the applicant that the device has been designated as a HUD based on the information submitted;

(2) Return the request to the applicant pending further review upon submission of additional information. This action will ensue if the request is incomplete because it does not on its face contain all of the information required under §814.102(a). Upon receipt of this additional information, the review period may be extended up to 45 days; or

(3) Disapprove the request for HUD designation based on a substantive review of the information submitted. FDA may disapprove a request for HUD designation if:

(i) There is insufficient evidence to support the estimate that the disease or condition for which the device is designed to treat or diagnose affects or is manifested in not more than 8,000 people in the United States per year;

(ii) FDA determines that, for a diagnostic device, more than 8,000 patients in the United States would be subjected to diagnosis using the device per year; or

(iii) FDA determines that the patient population defined in the request is not a medically plausible subset of a larger population.

(c) *Revocation of designation.* FDA may revoke a HUD designation if the agency finds that:

(1) The request for designation contained an untrue statement of material fact or omitted material information; or

(2) Based on the evidence available, the device is not eligible for HUD designation.

(d) *Submission*. The applicant shall submit two copies of a completed, dated, and signed request for HUD designation to: Office of Orphan Products Development (HF-35), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

[61 FR 33244, June 26, 1996, as amended at 82 FR 26349, June 7, 2017]

§814.104 Original applications.

(a) *United States applicant or representative.* The applicant or an authorized representative shall sign the HDE. If the applicant does not reside or have a place of business within the United States, the HDE shall be countersigned by an authorized representative residing or maintaining a place of business in the United States and shall identify the representative's name and address.

(b) *Contents*. Unless the applicant justifies an omission in accordance with paragraph (d) of this section, an HDE shall include:

(1) A copy of or reference to the determination made by FDA's Office of Orphan Products Development (in accordance with §814.102) that the device qualifies as a HUD;

(2) An explanation of why the device would not be available unless an HDE were granted and a statement that no comparable device (other than another HUD approved under this subpart or a device under an approved IDE) is available to treat or diagnose the disease or condition. The application also shall contain a discussion of the risks and benefits of currently available devices or alternative forms of treatment in the United States;

(3) An explanation of why the probable benefit to health from the use of the device outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment. Such explanation shall include a description, explanation, or theory of the underlying disease process or condition, and known or postulated mechanism(s) of action of the device in relation to the disease process or condition;

(4) All of the information required to be submitted under §814.20(b), except that:

(i) In lieu of the summaries, conclusions, and results from clinical investigations required under §814.20(b)(3)(v)(B), (b)(3)(vi), and the introductory text of (b)(6)(ii), the applicant shall include the summaries, conclusions, and results of all clinical experience or investigations (whether adverse or supportive) reasonably obtainable by the applicant that are relevant to an assessment of the risks and probable benefits of the device and to the extent the applicant includes data from clinical investigations, the applicant shall include the statements described in §814.20(b)(6)(ii)(A) and (B) with respect to clinical investigations conducted in the United States and the information described in §814.20(b)(6)(ii)(C) with respect to clinical investigations conducted outside the United States; and

(ii) In addition to the proposed labeling requirement set forth in §814.20(b)(10), the labeling shall bear the following statement: Humanitarian Device. Authorized by Federal law for use in the [treatment or diagnosis] of [specify disease or condition]. The effectiveness of this device for this use has not been demonstrated;

(5) The amount to be charged for the device and, if the amount is more than $250, a report by an independent certified public accountant, made in accordance with the Statement on Standards for Attestation established by the American Institute of Certified Public Accountants, or in lieu of such a report, an attestation by a responsible individual of the organization, verifying that the amount charged does not exceed the costs of the device's research, development, fabrication, and distribution. If the amount charged is $250 or less, the requirement for a report by an independent certified public accountant or an attestation by a responsible individual of the organization is waived; and

(6) Information concerning pediatric uses of the device, as required by §814.20(b)(13).

(c) *Omission of information.* If the applicant believes that certain information required under paragraph (b) of this section is not applicable to the device that is the subject of the HDE, and omits any

such information from its HDE, the applicant shall submit a statement that identifies and justifies the omission. The statement shall be submitted as a separate section in the HDE and identified in the table of contents. If the justification for the omission is not accepted by the agency, FDA will so notify the applicant.

(d) *Address for submissions and correspondence.* Copies of all original HDEs amendments and supplements, as well as any correspondence relating to an HDE, must be sent or delivered to the following:

(1) For devices regulated by the Center for Devices and Radiological Health, send to Document Mail Center, 10903 New Hampshire Ave., Bldg. 66, rm. G609, Silver Spring, MD 20993-0002.

(2) For devices regulated by the Center for Biologics Evaluation and Research, send this information to the Food and Drug Administration, Center for Biologics Evaluation and Research, Document Control Center, 10903 New Hampshire Ave., Bldg. 71, Rm. G112, Silver Spring, MD 20993-0002.

(3) For devices regulated by the Center for Drug Evaluation and Research, send this information to the Central Document Control Room, Center for Drug Evaluation and Research, Food and Drug Administration, 5901-B Ammendale Rd., Beltsville, MD 20705-1266.

[61 FR 33244, June 26, 1996, as amended at 63 FR 59220, Nov. 3, 1998; 73 FR 49942, Aug. 25, 2008; 75 FR 20915, Apr. 22, 2010; 79 FR 1740, Jan. 10, 2014; 80 FR 18094, Apr. 3, 2015; 83 FR 7388, Feb. 21, 2018]

§814.106 HDE amendments and resubmitted HDE's.

An HDE or HDE supplement may be amended or resubmitted upon an applicant's own initiative, or at the request of FDA, for the same reasons and in the same manner as prescribed for PMA's in §814.37, except that the timeframes set forth in §814.37(c)(1) and (d) do not apply. If FDA requests an HDE applicant to submit an HDE amendment, and a written response to FDA's request is not received within 75 days of the date of the request, FDA will consider the pending HDE or HDE supplement to be withdrawn voluntarily by the applicant. Furthermore, if the HDE applicant, on its own initiative or at FDA's request, submits a major amendment as described in §814.37(c)(1), the review period may be extended up to 75 days.

[63 FR 59220, Nov. 3, 1998]

§814.108 Supplemental applications.

After FDA approval of an original HDE, an applicant shall submit supplements in accordance with the requirements for PMA's under §814.39, except that a request for a new indication for use of a HUD shall comply with requirements set forth in §814.110. The timeframes for review of, and FDA action on, an HDE supplement are the same as those provided in §814.114 for an HDE.

[63 FR 59220, Nov. 3, 1998]

§814.110 New indications for use.

(a) An applicant seeking a new indication for use of a HUD approved under this subpart H shall obtain a new designation of HUD status in accordance with §814.102 and shall submit an original HDE in accordance with §814.104.

(b) An application for a new indication for use made under §814.104 may incorporate by reference any information or data previously submitted to the agency under an HDE.

§814.112 Filing an HDE.

(a) The filing of an HDE means that FDA has made a threshold determination that the application is sufficiently complete to permit substantive review. Within 30 days from the date an HDE is received by FDA, the agency will notify the applicant whether the application has been filed. FDA may refuse to file an HDE if any of the following applies:

(1) The application is incomplete because it does not on its face contain all the information required under §814.104(b);

(2) FDA determines that there is a comparable device available (other than another HUD approved under this subpart or a device under an approved IDE) to treat or diagnose the disease or condition for which approval of the HUD is being sought; or

(3) The application contains an untrue statement of material fact or omits material information.

(4) The HDE is not accompanied by a statement of either certification or disclosure, or both, as required by part 54 of this chapter.

(b) The provisions contained in §814.42(b), (c), and (d) regarding notification of filing decisions, filing dates, the start of the 75-day review period, and applicant's options in response to FDA refuse to file decisions shall apply to HDE's.

[61 FR 33244, June 26, 1996, as amended at 63 FR 5254, Feb. 2, 1998; 63 FR 59221, Nov. 3, 1998]

§814.114 Timeframes for reviewing an HDE.

Within 75 days after receipt of an HDE that is accepted for filing and to which the applicant does not submit a major amendment, FDA shall send the applicant an approval order, an approvable letter, a not approvable letter (under §814.116), or an order denying approval (under §814.118).

[63 FR 59221, Nov. 3, 1998]

§814.116 Procedures for review of an HDE.

(a) *Substantive review.* FDA will begin substantive review of an HDE after the HDE is accepted for filing under §814.112. FDA may refer an original HDE application to a panel on its own initiative, and shall do so upon the request of an applicant, unless FDA determines that the application substantially duplicates information previously reviewed by a panel. If the HDE is referred to a panel, the agency shall follow the procedures set forth under §814.44, with the exception that FDA will complete its review of the HDE and the advisory committee report and recommendations within 75 days from receipt of an HDE that is accepted for filing under §814.112 or the date of filing as determined under §814.106, whichever is later. Within the later of these two timeframes, FDA will issue an approval order under paragraph (b) of this section, an approvable letter under paragraph (c) of this section, a not approvable letter under paragraph (d) of this section, or an order denying approval of the application under §814.118(a).

(b) Approval order. FDA will issue to the applicant an order approving an HDE if none of the reasons in §814.118 for denying approval of the application applies. FDA will approve an application on the basis of draft final labeling if the only deficiencies in the application concern editorial or similar minor deficiencies in the draft final labeling. Such approval will be conditioned upon the applicant incorporating the specified labeling changes exactly as directed and upon the applicant submitting to FDA a copy of the final printed labeling before marketing. The notice of approval of an HDE will be published in the Federal Register in accordance with the rules and policies applicable to PMA's submitted under §814.20. Following the issuance of an approval order, data and information in the HDE file will be available for public disclosure in accordance with §814.9(b) through (h), as applicable.

(c) *Approvable letter.* FDA will send the applicant an approvable letter if the application substantially meets the requirements of this subpart and the agency believes it can approve the application if specific additional information is submitted or specific conditions are agreed to by the applicant. The approvable letter will describe the information FDA requires to be provided by the applicant or the conditions the applicant is required to meet to obtain approval. For example, FDA may require as a condition to approval:

(1) The submission of certain information identified in the approvable letter, e.g., final labeling;

(2) The submission of additional information concerning pediatric uses of the device, as required by §814.20(b)(13);

(3) Restrictions imposed on the device under section 520(e) of the act;

(4) Postapproval requirements as described in subpart E of this part; and

(5) An FDA inspection that finds the manufacturing facilities, methods, and controls in compliance with part 820 of this chapter and, if applicable, that verifies records pertinent to the HDE.

(d) *Not approvable letter.* FDA will send the applicant a not approvable letter if the agency believes that the application may not be approved for one or more of the reasons given in §814.118. The not approvable letter will describe the deficiencies in the application and, where practical, will identify measures required to place the HDE in approvable form. The applicant may respond to the not approvable letter in the same manner as permitted for not approvable letters for PMA's under §814.44(f), with the exception that if a major HDE amendment is submitted, the review period may be extended up to 75 days.

(e) FDA will consider an HDE to have been withdrawn voluntarily if:

(1) The applicant fails to respond in writing to a written request for an amendment within 75 days after the date FDA issues such request;

(2) The applicant fails to respond in writing to an approvable or not approvable letter within 75 days after the date FDA issues such letter; or

(3) The applicant submits a written notice to FDA that the HDE has been withdrawn.

[61 FR 33244, June 26, 1996, as amended at 63 FR 59221, Nov. 3, 1998; 79 FR 1741, Jan. 10, 2014]

§814.118 Denial of approval or withdrawal of approval of an HDE.

(a) FDA may deny approval or withdraw approval of an application if the applicant fails to meet the requirements of section 520(m) of the act or of this part, or of any condition of approval imposed by an IRB or by FDA, or any postapproval requirements imposed under §814.126. In addition, FDA may deny approval or withdraw approval of an application if, upon the basis of the information submitted in the HDE or any other information before the agency, FDA determines that:

(1) There is a lack of a showing of reasonable assurance that the device is safe under the conditions of use prescribed, recommended, or suggested in the labeling thereof;

(2) The device is ineffective under the conditions of use prescribed, recommended, or suggested in the labeling thereof;

(3) The applicant has not demonstrated that there is a reasonable basis from which to conclude that the probable benefit to health from the use of the device outweighs the risk of injury or illness, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment;

(4) The application or a report submitted by or on behalf of the applicant contains an untrue statement of material fact, or omits material information;

(5) The device's labeling does not comply with the requirements in part 801 or part 809 of this chapter;

(6) A nonclinical laboratory study that is described in the HDE and that is essential to show that the device is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling, was not conducted in compliance with the good laboratory practice regulations in part 58 of this chapter and no reason for the noncompliance is provided or, if it is, the differences between the practices used in conducting the study and the good laboratory practice regulations do not support the validity of the study;

(7) Any clinical investigation involving human subjects described in the HDE, subject to the institutional review board regulations in part 56 of this chapter or the informed consent regulations in part 50 of this chapter, was not conducted in compliance with those regulations such that the rights or safety of human subjects were not adequately protected;

(8) The applicant does not permit an authorized FDA employee an opportunity to inspect at a reasonable time and in a reasonable manner the facilities and controls, and to have access to and to copy and verify all records pertinent to the application; or

(9) The device's HUD designation should be revoked in accordance with §814.102(c).

(b) If FDA issues an order denying approval of an application, the agency will comply with the same notice and disclosure provisions required for PMA's under §814.45(b) and (d), as applicable.

(c) FDA will issue an order denying approval of an HDE after an approvable or not approvable letter has been sent and the applicant:

(1) Submits a requested amendment but any ground for denying approval of the application under §814.118(a) still applies;

(2) Notifies FDA in writing that the requested amendment will not be submitted; or

(3) Petitions for review under section 515(d)(3) of the act by filing a petition in the form of a petition for reconsideration under §10.33 of this chapter.

(d) Before issuing an order withdrawing approval of an HDE, FDA will provide the applicant with notice and an opportunity for a hearing as required for PMA's under §814.46(c) and (d), and will provide the public with notice in accordance with §814.46(e), as applicable.

[61 FR 33244, June 26, 1996, as amended at 63 FR 59221, Nov. 3, 1998]

§814.120 Temporary suspension of approval of an HDE.

An HDE or HDE supplement may be temporarily suspended for the same reasons and in the same manner as prescribed for PMA's in §814.47.

[63 FR 59221, Nov. 3, 1998]

§814.122 Confidentiality of data and information.

(a) *Requirement for disclosure.* The "HDE file" includes all data and information submitted with or referenced in the HDE, any IDE incorporated into the HDE, any HDE amendment or supplement, any report submitted under §814.126, any master file, or any other related submission. Any record in the HDE file will be available for public disclosure in accordance with the provisions of this section and part 20 of this chapter.

(b) Extent of disclosure. Disclosure by FDA of the existence and contents of an HDE file shall be subject to the same rules that pertain to PMA's under §814.9(b) through (h), as applicable.

§814.124 Institutional Review Board requirements.

(a) *IRB approval.* The HDE holder is responsible for ensuring that a HUD approved under this subpart is administered only in facilities having oversight by an Institutional Review Board (IRB) constituted and acting pursuant to part 56 of this chapter, including continuing review of use of the device. In addition, a HUD may be administered only if such use has been approved by an IRB. If, however, a physician in an emergency situation determines that approval from an IRB cannot be obtained in time to prevent serious harm or death to a patient, a HUD may be administered without prior approval by an IRB. In such an emergency situation, the physician shall, within 5 days after the use of the device, provide written notification to the chairman of the IRB of such use. Such written notification shall include the identification of the patient involved, the date on which the device was used, and the reason for the use.

(b) *Withdrawal of IRB approval.* A holder of an approved HDE shall notify FDA of any withdrawal of approval for the use of a HUD by a reviewing IRB within 5 working days after being notified of the withdrawal of approval.

[61 FR 33244, June 26, 1996, as amended at 63 FR 59221, Nov. 3, 1998; 82 FR 26349, June 7, 2017]

§814.126 Postapproval requirements and reports.

(a) An HDE approved under this subpart H shall be subject to the postapproval requirements and reports set forth under subpart E of this part, as applicable, with the exception of §814.82(a)(7). In addition, medical device reports submitted to FDA in compliance with the requirements of part 803 of this chapter shall also be submitted to the IRB of record.

(b) In addition to the reports identified in paragraph (a) of this section, the holder of an approved HDE shall prepare and submit the following complete, accurate, and timely reports:

(1) *Periodic reports.* An HDE applicant is required to submit reports in accordance with the approval order. Unless FDA specifies otherwise, any periodic report shall include:

(i) An update of the information required under §814.102(a) in a separately bound volume;

(ii) An update of the information required under §814.104(b)(2), (b)(3), and (b)(5);

(iii) The number of devices that have been shipped or sold since initial marketing approval under this subpart H and, if the number shipped or sold exceeds 8,000, an explanation and estimate of the number of devices used per patient. If a single device is used on multiple patients, the applicant shall submit an estimate of the number of patients treated or diagnosed using the device together with an explanation of the basis for the estimate;

(iv) Information describing the applicant's clinical experience with the device since the HDE was initially approved. This information shall include safety information that is known or reasonably should be known to the applicant, medical device reports made under part 803 of this chapter, any data generated from the postmarketing studies, and information (whether published or unpublished) that is known or reasonably expected to be known by the applicant that may affect an evaluation of the safety of the device or that may affect the statement of contraindications, warnings, precautions, and adverse reactions in the device's labeling; and

(v) A summary of any changes made to the device in accordance with supplements submitted under §814.108. If information provided in the periodic reports, or any other information in the possession of FDA, gives the agency reason to believe that a device raises public health concerns or that the criteria for exemption are no longer met, the agency may require the HDE holder to submit additional information to demonstrate continued compliance with the HDE requirements.

(2) *Other*. An HDE holder shall maintain records of the names and addresses of the facilities to which the HUD has been shipped, correspondence with reviewing IRB's, as well as any other information requested by a reviewing IRB or FDA. Such records shall be maintained in accordance with the HDE approval order.

[61 FR 33244, June 26, 1996, as amended at 63 FR 59221, Nov. 3, 1998; 71 FR 16228, Mar. 31, 2006; 82 FR 26349, June 7, 2017]

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Elizabeth Weeks-Rowe

Elizabeth Weeks-Rowe, LVN, CCRA, has spent over 18 years in a variety of clinical research roles including study coordinator, CRA, CRA trainer, CRA manager and clinical research writer. She has developed training content and presented clinical research topics for leading industry training and education organizations. She has created marketing content, website content and clinical operations newsletters for European and U.S.-based clinical research organizations. She is a contributing writer for several leading industry publications, including a recurring clinical research column for a leading clinical research news publication. She has authored a white paper on best industry practices for co-monitoring assessments, and unblinded pharmacy monitoring/monitoring practice. She is the author of a clinical research novella entitled, "Clinical Research Trials and Triumphs; a heart warming novel following a nurse's journey into clinical research." She is an instructor for a well known clinical research training company and speaks at global industry clinical research meetings. For the last 7 years, she has worked in a critical site selection and training role for a leading CRO.

Dr. Karen Woodin

Karen E. Woodin earned her M.S. in Applied Statistics at Western Michigan University and her Ph.D. in Epidemiology from the School of Public Health at the University of Massachusetts, Amherst.

Dr. Woodin has over 30 years of experience in the pharmaceutical industry, including more than 20 years at The Upjohn Company/Pharmacia (now part of Pfizer), where she worked in the areas of biostatistics, clinical trial operations and monitoring and drug safety. She currently works as an independent consultant specializing in clinical trial operations, good clinical practices (GCPs) and standard operating procedures (SOPs). She works with

investigative sites, sponsors and IRBs, and also develops and teaches courses in these areas. As well as co-authoring this book with JC Schneider, she is the author of *The CRC's Guide to Coordinating Clinical Research*, also published by CenterWatch.

Dr. Woodin is a long-time member of the Drug Information Association (DIA) and has served on the DIA board of directors and as chair of the Steering Committee for the Americas. She has also developed and taught courses for DIA. She is a recipient of the DIA Outstanding Service award.

John C. ("JC") Schneider

After receiving a B.S. in zoology form Michigan State University, JC Schneider joined the Upjohn Company. His tenure at Upjohn included seven years in the laboratory, 13 years as a Medical Research Associate and 12 years in management before "retiring" in 1994.

Upon his retirement from Upjohn, he was a senior clinical consultant for a large consulting company, at which he directed clinical consulting operations. He helped develop and taught a post-graduate course in clinical research administration at both Eastern Michigan University and Western Michigan University. Along with Dr. Woodin, he also developed and taught an investigator training course. He is now an independent consultant/trainer to the pharmaceutical industry in the areas of good clinical practices (GCPs), standard operating procedures (SOPs) and site monitoring.

JC Schneider had a 30-year career in the Army Reserve as a Medical Service Corps officer that included command of a 1,500-bed hospital and a seven-year assignment at the Clinical Investigation Division of the Army's Health Services Command at Brooke Army Medical Center in San Antonio, Texas. He was awarded the Army Commendation and Meritorious Service Medals and holds the rank of Colonel.

He is a long-time member of the Drug Information Association (DIA) and the Association of Clinical Research Professionals (ACRP). He helped revise DIA's entry-level CRA course, which he taught for several years, in addition to conducting numerous tutorials during DIA's Annual Meetings. He was a member of the Steering Committee of the Americas and is the recipient of the DIA's Outstanding Service Award.

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Falls Church, VA 22046
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