# 1

# US Regulations for the Pharmaceutical Industries

**CHAPTER MENU**





## 1.1 Introduction

In brief, the Food and Drug Administration (FDA) is tasked with protecting the public health of residents of the United States. It is not the only agency within the government that can identify with that goal, but it *is* the agency that is responsible for ensuring citizens safe, efficacious access to an array of products that include food, drugs, and medical devices. The scope of this chapter is to concentrate on the pharmaceutical aspects of the FDA's mission; however, it is important to understand the structure of the agency, its history, and its role in the regulatory arena.

In an ideal world, there would be no need for oversight, as all actions would be for the general good of society as a whole, as opposed to individual gain at the unfair expense, be it monetary, health, or some other metric, of others. That is not a political statement, but rather leads to an understanding that most regulations, and certainly the establishment of most of *regulatory agencies*, come about as the result of egregious acts that call for remedy. That is not to say that organizations have not been created as advisory advocates for industries, independent of scandal, as in the creation of the US Pharmacopeia (USP [1]) in 1820 and the Association of Official Agricultural Chemists (now AOAC International [2]) in 1897; however, the establishment of regulatory agencies historically has been reactive rather than proactive.

*Practical Pharmaceutical Engineering*, First Edition. Gary Prager.

It would be naïve, however, to suggest that regulatory agencies, including the FDA, are independent of political influence; they are not, nor can they be, given the structure of our legal system. The centerpiece of our legal system is the US Constitution, which establishes the structure of our country and also defines how we self-regulate. The legislative branch, working within the framework of the Constitution, establishes federal statutes (or legislations) that reinforce the principles of the Constitution and establish control of our society. The rules and proposed rules, as well as notices of federal agencies and organizations, executive orders, and documents are published daily in the Federal Register.

The Code of Federal Regulations (CFR) is the codification of the rules posted in the Federal Register. It is updated once each calendar year and issued quarterly. There are currently 50 titles in the CFR, with 21 CFR covering Food and Drugs. This codification is meant to clarify regulations, denoting the intent of the legislation passed. However, as might be expected, the regulations are subject to interpretation. Ultimately, disputes about the interpretation of legislation, as well as its constitutionality, are clarified by the Judicial Branch, which reviews specific complaints or disputes and can elect to apply its opinion narrowly to the specific dispute or as an overarching opinion having much broader impact. At the time of publication, the CFR can be accessed online at http://www.ecfr.gov/cgi-bin/ECFR?page=browse. This, as well as any other online address in this text, is subject to change.

The crafting of statutes, the codification of the legislation, and the interpretation of both the intent and the scope of regulations are all subject to the vagaries of human judgment and influence; hence the previous statement that regulatory agencies are subject to political influence. Reviewing the timeline of the formation of the FDA as provided on its own website (http://www.fda.gov/AboutFDA/WhatWeDo/History/Milestones/ucm128305.htm) illustrates the difficulty of establishing regulation in the face of competing influences. Be that as it may, once the regulations and regulatory agencies are established, there has historically been remarkable resistance to the politicization of the agencies themselves. The "greater good" prevails.

## 1.2 The FDA: Formation of a Regulatory Agency

The seminal event that led to the formation of the precursor to the FDA was the discovery of adulterated antimalarial drugs (quinine) being imported into the United States at time when malaria was a major health concern. In 1848 Congress required US Customs Service inspectors to stop the importation of these drugs when it passed the Drug Importation Act, effectively sealing off the United States from unscrupulous overseas manufacturers. Almost 50 years later, it was again the US Customs Service that was tasked, at importers expense, with the inspection of all tea entering the United States when the Tea Importation Act of 1897 was implemented.

In 1862, President Abraham Lincoln appointed Charles M. Wetherill, a chemist, to serve in the newly created US Department of Agriculture (USDA). The USDA housed the Bureau of Chemistry, a precursor to the FDA, where Wetherill began investigating the adulteration of agricultural products. Succeeding USDA Chief Chemists Peter Collier (1880) and Dr. Harvey W. Wiley (1883) expanded the food adulteration studies and campaigned for a federal law regulating foods. For his efforts, Dr. Wiley is regarded as the "Father of the Pure Food and Drugs Act," having vigorously crusaded for its eventual passage.

In 1902 the Biologics Control Act was passed to ensure purity and safety of serums, vaccines, and similar products used to prevent or treat diseases in humans by licensing biologics manufacturers and regulating the interstate commerce of biologics.

The first major legislation was passed in response to growing outrage, fanned by muckraking writers, over the unsanitary conditions in meat-packing plants and the presence of poisonous

preservatives and dyes in foods. The original Food and Drug Act was passed in 1906 prohibiting interstate commerce of misbranded or adulterated foods, drinks, and drugs. The Federal Meat Inspection Act was passed the same day. The next year, the Certified Color Regulations listed seven color additives that were considered safe in food. Poisonous, colorful coal-tar dyes were banned from foods.

From 1912 to 1933, a series of minor back-and-forth legislative and judicial rulings effectively increased the regulations against misleading therapeutic statements, mislabeling of contents, and other deceptive practices. Also imposed were more stringent requirements for the dispensing of narcotic substances and the qualitative and quantitative labeling of package contents. Still under the auspices of the USDA, the precursor to the FDA began to be separated from nonregulatory research, which was placed under the aegis of the Bureau of Chemistry and Soils in 1927. The beginning of the separation of regulation of meat and dairy products from FDA control began in 1930, the same year the name was officially changed to the FDA.

This new agency recommended a complete revision of the obsolete 1906 Food and Drugs Act, launching a 5-year legislative battle. The second major regulatory revision, the 1938 Federal Food, Drug, and Cosmetic Act (FD&C) was largely passed as a result of a 1937 incident in which 107 persons were killed by consuming Elixir Sulfanilamide containing the poisonous solvent diethylene glycol. As a result, new provisions were added:

- Control was extended to cosmetics and therapeutic devices.
- New drugs were required to be shown to be safe *prior* to marketing.
- Eliminated the need to prove intent to defraud in misbranding cases.
- Provided safe levels of poisonous components that were unavoidable.
- Authorized standards of identity, quality, and fill weights for foods.
- Authorized inspections of manufacturing facilities.
- Added court injunctions to the previously authorized penalties of seizures and prosecutions.

That same year, however, regulation of advertising of all FDA-regulated products with the exception of prescription drugs was transferred to the Federal Trade Commission (FTC).

In 1940, the FDA was transferred from the USDA to the Federal Security Agency, precursor to the Department of Health, Education, and Welfare (HEW). In the 1940s a Supreme Court decision extended liability for violations by companies to officials responsible within the company regardless of their knowledge of the violations. Two particular amendments were passed requiring the FDA to test and certify the purity and potency of the drugs insulin and penicillin. Other legislation extended the reach of government and the maintenance of public health and confirmed the agency's regulatory control over interstate commerce. At the end of the decade, the FDA published for the first time guidance to the industry and procedures for appraisal toxicity of chemicals in food.

In the 1950s, there was an increased oversight of both food and drug products, including their labeling. Drugs that required medical supervision were restricted in their sale, requiring a licensed practitioner to authorize purchases. The purpose for which a drug is offered was required to be on the label as part of the directions for use of that product. The factory inspection was found to be too vague and therefore was reinforced by a further amendment in 1953. The FDA increased its oversight of the safety of foods with the Miller pesticide amendment, the food additives amendment, and the color additives amendment.

In the 1960s the United States was spared of the tragedy suffered by Western European families because the drug thalidomide was kept off the US market, preventing birth defects affecting potentially thousands of babies. This success, by the FDA medical officer Frances Kelsey, aroused strong public support for stronger drug regulation. As a result the Kefauver–Harris drug amendments were passed to ensure drug efficacy and greater drug safety. These amendments required that drug manufacturers prove to the FDA the effectiveness of their

products before placing them on the market. The FDA contracted with the National Academy of Sciences and National Research Council to evaluate the effectiveness of 4000 drugs that had been approved on the basis of safety alone between 1938 and 1962. Other legislation enacted in the 1960s included Drug Abuse Control Amendments, to combat abuse of stimulants, depressants, and hallucinogens, and a Consumer Bill of Rights.

In the 1970s further consumer protections were put into place with the first patient package insert for oral contraceptives that delineated the risks and benefits of taking the drug. The Comprehensive Drug Abuse Prevention and Control Act replaced previous laws and categorized drugs based on abuse and addiction potential versus their therapeutic value. Some responsibility shifted among government agencies with the Environmental Protection Agency (EPA) taking over the FDA program for setting pesticide tolerances. Regulation of biologics – including serums, vaccines, and blood products – was transferred from the National Institute of Health (NIH) to the FDA. Over-the-counter drug reviews began to enhance the safety, effectiveness, and labeling of drugs sold over-the-counter. The Bureau of Radiological Health was transferred to the FDA to protect humans against unnecessary exposure to radiation from products in the home, in industry, and in healthcare professions.

The 1980s saw the FDA revise regulations on drug testing, greatly increasing protections for subjects upon whom new drugs were tested. In reaction to deaths caused by cyanide placed in Tylenol bottles, packaging regulations requiring tamper-resistant closures was enacted. The FDA also promoted research and marketing of drugs needed for treating rare diseases with the Orphan Drug Act. To promote competition and lessen costs, the FDA allowed the marketing of generic versions of brand-name drugs without requiring repeating the research necessary to prove them to be safe and effective. At the same time, they gave brand-name companies the right to apply for up to 5 years of additional patent protection for the new medicines they had developed to make up for the time lost, while the products were going through the FDA's approval process.

Acquired immune deficiency syndrome (AIDS) tests for blood were approved by the FDA to prevent the transmission of the causative agent to recipients of blood donations. The marketing of prescription drugs was limited to legitimate commercial channels in order to prevent the distribution of mislabeled, adulterated, subpotent, and/or counterfeit drugs to the public.

Investigational drug regulations were revised, expanding access to investigational drugs for patients with serious diseases with no alternative therapies. This trend was continued in the early 1990s as regulations were established to accelerate a review of drugs for life-threatening diseases.

In 1994 the Dietary Supplement Health and Education Act established specific labeling requirements, a regulatory framework, and authorized the FDA to promulgate good manufacturing practice (GMP) regulations for dietary supplements. Dietary supplements and dietary ingredients were classified as food, and a commission was established to recommend how to regulate any claims appearing on the labels. As a result of this, 21 CFR part 111 Current Good Manufacturing Practice (cGMP) in manufacturing, packaging, labeling, or holding operations for dietary supplements was established.

Also in the 1990s was a relaxation of some regulations on pharmaceutical manufacturers including an expansion of allowable promotional material on the approved use of drugs. It was during this period that the FDA attempted to extend its reach to the tobacco industry, defining nicotine as a drug and smoking or smokeless tobacco products to be combination of drug delivery systems, restricting the sale of such materials to minors. The FDA was forced to rescind its rule in 2000 when the Supreme Court upheld a lower court ruling supporting a lawsuit by a tobacco company against the FDA.

In the 1990s there was increased focus on the effectiveness of drugs as influenced by gender and, in 2002, in children. This was a reaction to the discovery that drugs commonly tested on male subjects left unresolved the question of how female subjects responded to

exposure to these drugs. Similarly, the safety and efficacy of drugs prescribed for children was required.

In the 2000s there was again a response to the current events. The Public Health Security and Bioterrorism Preparedness and Response Act of 2002 was designed to improve the country's ability to prevent and to respond to public health emergencies. In response to questions about the jurisdiction of various departments within the FDA, the Office of Combination Products was formed to oversee products that fall into multiple jurisdictions, for example, medical devices that contain a drug component.

The cGMP initiative focused on the greatest risks to public health in manufacturing procedures applying a consistent approach across FDA. It also ensured that process and product quality standards did not impede innovation of new products.

In general, in this new century the FDA has continued to respond and grow in three main areas:

1) Responding to specific external forces, as in COX-2 selective agents and dietary supplements containing ephedrine alkaloids as health risks. The Drug Quality and Security Act (DQSA) of 2013 in response to an epidemic of fungal meningitis linked to a compounded steroid, among other provisions, outlined steps for an electronic and interoperable system to identify and trace certain drugs throughout the United States.
2) The FDA increased its influence on product development (for both human and nonhuman species) by encouraging specific remedies and also by expanding how the FDA can collaborate in the process of developing therapeutic products from laboratory to production to end use. Establishment of user fees for drugs, medical devices, and biosimilar biologic agents that are targeted to fund expedited reviews.
3) Has promoted a continuation of improved dissemination of information to both physicians and patients.

In summary, the FDA was created out of necessity in response to events that threatened the health and safety of citizens with regard to their food and medical supplies. It has continued to oversee our food and drug supply for both humans and animals as it has evolved. Perhaps the most influential pieces of legislation were the Food and Drugs Act of 1906, the Food Drug and Cosmetic Act of 1938, the Kefauver–Harris Amendments of 1962, and a Medical Device Amendments of 1976. Until 1990 all US laws and regulations relating to medical products were in reaction to medical catastrophes. A proactive stance, with new laws and regulations written to avoid medical calamities began in the 1990s.

There are corresponding agencies around the world that operate independently according to their individual mandates from their legislative bodies. In some cases the relations in the United States are more restrictive than those agencies of other countries; in other cases the United States is less restrictive in its oversight. Given the ever-increasing interrelationships of multinational companies and their markets, there is great impetus to align the regulatory requirements of individual countries into harmonized code. International agencies are working toward that end at this time. However, the trend in regulation, while vacillating, has been toward the more restrictive, including more detailed accountability and traceability of all products. This is likely to continue.

With the trend toward greater regulation, greater international harmonization and acceptance of the FDA as a partner in producing safe, efficacious, high-quality products, and learning to work with this development will be most beneficial not only for the consumers but also to the manufacturers. The FDA focuses on ensuring public safety within the scope of their mandate, and it is in the best interest of all. Rather than view the FDA as an adversary to be controlled, the FDA should be viewed as a partner in product development.

## 1.3 FDA's Seven Program Centers and Their Responsibility

### 1.3.1 Center for Biologics Evaluation and Research

This is the center within the FDA that regulates biological products for human use including blood, vaccines, tissues, allergenics, and cellular and gene therapies. Biologics are derived from living sources and many are manufactured using biotechnology. They often review cutting-edge biomedical research, evaluating scientific and clinical data submitted to determine whether or not the products meet the Center for Biologics Evaluation and Research (CBER)'s standards for approval. The approvals may be for newly submitted biologicals or for new indications for products already approved for a different purpose.

### 1.3.2 Center for Drug Evaluation and Research

The Center for Drug Evaluation and Research (CDER) oversees over-the-counter and prescription drugs including biological therapeutics and generic drugs. For regulatory purposes, products such as fluoride toothpaste, antiperspirants and dandruff shampoos, and sunscreens are all considered to be drugs.

### 1.3.3 Center for Devices and Radiological Health

FDA's Center for Devices and Radiological Health (CDRH) is tasked with eliminating unnecessary human exposure to man-made radiation from medical, occupational, or consumer products in addition to ensuring the safety and effectiveness of devices containing radiological materials. The CDRH is particularly concerned about the lifecycle of the product from conception to ultimate disposal in a safe manner.

### 1.3.4 Center for Food Safety and Applied Nutrition

Center for Food Safety and Applied Nutrition (CFSAN) is responsible for ensuring a safe, sanitary, wholesome, and properly labeled food supply. It is also responsible for dietary supplements and safe, properly labeled cosmetic products. As needed, it may work in conjunction with other centers as, for example, with CDER or enforcement of the FD&C Act or products that purport to be cosmetics but meet the statutory definitions of a drug.

### 1.3.5 Center for Veterinary Medicine

The Center for Veterinary Medicine (CVM) regulates the manufacture and distribution of food additives, drugs, and medical devices that will be given to animals. The animals may be either for human consumption or companion animals. One growing area of interest is that of genetically modified or genetically engineered animals. The FDA has expressed an interest in regulating these animals; however, depending upon the animal species and its intended use, the FDA will regulate these animals in combination with other federal departments and agencies such as the USDA and the EPA.

### 1.3.6 Office of Combinational Products

Combination products are defined in 21 CFR 3.2(e) as:

1) A product composed of two or more regulated components, i.e. drug/device, biologic/device, drug/biologic, and drug/device/biologic, that are physically or chemically combined or mixed and produced as a single entity.

2) Two or more separate products packaged together in a single package or as a unit and composed of drug and device products, device and biological products, or biological and drug products.
3) A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g. to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose.
4) Any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect.

### 1.3.7 Office of Regulatory Affairs

The Office of Regulatory Affairs (ORA) oversees the field activities of local FDA field operations. It also provides FDA leadership on imports inspections and enforcement policy, inspects regulated products and manufacturers, conducts sample analyses of regulated products, and reviews imported products offered for entry into the United States. The ORA also advises the commissioner and other officials on regulations and compliance-oriented matters and develops FDA-wide policy on compliance and enforcement. The ORA develops and/or recommends policy programs and plans activities between the FDA and state and local agencies.

## 1.4 New Drug Development

While the overall focus of this book is on the manufacture of pharmaceuticals, it is useful to understand how drugs are developed. Every new formulation must undergo a series of tests to prove it is both safe and efficacious to the consumer. The FDA estimates that it takes over 8 years, from concept to approval for public consumption of a new drug. At any stage in the investigation, or during postmarket evaluations, the drug may be deemed unsafe and restricted from market. The FDA does not actually test the drug itself for safety and efficacy, but rather reviews data submitted by the drug company sponsor.

### 1.4.1 Discovery

A typical drug development pathway involves the generation of large numbers of molecules of similar structures with the intention of identifying the most promising candidates for further development. The rationale behind this is that slight variations on a known structure may attenuate the behavior of the known molecule in a desirable fashion. That is to say, substitution on a well-characterized structure may be expected to increase beneficial properties of the chemical or alternately decrease detrimental characteristics.

The discovery of a new drug involves more than formulation development. On the lab scale, research and development will determine the potential drug stability and active ingredients, as well as any other requirements. A formal protocol for nonclinical studies must be designed to establish exactly how the preclinical study will be performed, including the types of animals to be tested, the duration and frequency of the test, and how the data will be handled. Finally chemistry, manufacturing, and controls (CMC) will be established to allow larger scale production of the drug under GMP.

Scale up from bench to manufacture requires consideration of the following:

Active ingredients: identity, purity, and stability.
Raw materials specifications and identification.
Intermediate products.
Filtration and/or purification process.
Solubility, particulate size, disintegration, dissolution (for pills and capsules).
Sterility requirements.
Final drug specifications.
Dose uniformity.
Required QC tests.
Methodologies for QC assays.
Validations: QC assay method
  Equipment
  Cleaning
Record keeping and documentation

The pertinent area of the CFR regarding investigation into the potential of a new drug for human use is 21 CFR 312, Investigational New Drug Application (IND or INDA). In this part of the regulations, procedure requirements governing use of investigational new drugs including stipulations for the submission for review to the FDA are found.

### 1.4.2 Investigational New Drug Application

It is illegal to transport unapproved drugs across state lines for any purpose. Thus there exists the necessity to request an exemption from this federal statute in order to conduct clinical trials. In order to transport a new unapproved drug, an IND or INDA must be filed to get an exemption from the statute. Form 1571 can be obtained from the FDA website (http://www.fda.gov/opacom/morechoices/fdaforms/cder.html).

Required information for the submission includes the data collected from the preclinical animal pharmacology and toxicology studies, showing the safety of the proposed drug. It must be demonstrated that the manufacturer can reliably reproduce and supply consistent batches of the said drug, so information about the composition, manufacture stability, and controls for manufacture must be supplied. Finally the detailed protocols for the proposed clinical studies, including the qualifications of the clinical investigators, and commitments to obtain informed consent from the research subjects, commitments to review the study by an institutional review board (IRB), and a firm commitment to adhere to investigational new drug regulations must be submitted.

The investigation of a drug for potential human applications is initiated and overseen by a sponsor committed to properly conduct a study, be they an institution or organization, a company, or even an individual. They are responsible for the management, from start to finish, of a clinical trial. Alternately, they may provide financing for the study by investigators who will actually initiate and complete the study. The sponsor does not, however, relinquish responsibility simply by financing a project proposed by an individual investigator.

Once the required NDA is submitted to the FDA, it is assigned an IND number that is to be used in all correspondence with the FDA regarding the application. The FDA or more specifically the CDER will review the IND. The IND is reviewed on medical, chemistry, pharmacology/toxicology, and statistical bases to review the safety of the proposed study. If the review is complete and acceptable with no deficiencies, the study may proceed. If not, a clinical hold is placed on the study and the sponsor is notified, affording him the opportunity to submit new data.

INDs are not approved by the FDA. An IND becomes effective 30 days after receipt by the FDA unless a clinical hold is imposed. The clinical hold can be placed at any time and is an order by the FDA to suspend or delay a proposed or ongoing clinical investigation. The clinical hold is commonly placed upon the study for deficient study design, unreasonable risk to subjects, inclusion of an unqualified investigator, misleading investigator brochure submission, or insufficient information to assess the risk to test subjects.

Once the IND is in effect, it must be maintained so that current information is submitted to the FDA. Toward this end, amendments are made to the original protocol. These may be either protocol amendments or information amendments. Three types of protocol amendments may be submitted: for a new protocol, a change in protocol or a new investigator carrying out a previously submitted protocol. Informational amendments fall outside the scope of the protocol amendments. An information amendment is any amendment to an IND application with information essential to the investigational product that is not within the scope of protocol amendments, safety reports, or annual reports. This may include new technical information or discontinuation of the clinical trial.

A written safety report that transmits information about any adverse drug experience or adverse events associated with the use of the drug is to be submitted to the FDA and all participating investigators along with Form 3500A as soon as possible, but no more than 15 calendar days after initial notification to the sponsor. In the case of serious adverse events, the report must be submitted no later than 7 days after the receipt of information by the sponsor. The sponsor will follow up and investigate all safety and relevant information and report to the FDA as soon as possible.

An annual report is to be sent to the FDA to update the IND about the progress of the investigation and all changes not reported in amendments or other reports. It should be submitted within 60 days of the calendar date that the IND went into effect.

Additionally, meetings may be scheduled with the FDA at various stages of investigation. Meetings may be held pre-IND to discuss, for example, CMC issues. Meetings may also be held at the end of Phase I, Phase II, or pre-new drug application (NDA).

The IND can be withdrawn by the sponsor at any time without prejudice. The FDA and all pertinent IRBs will be notified. Any remaining drugs will be disposed of by the sponsor or returned to the sponsor.

An IND may go on inactive status at the request of the applicant or the FDA if, for example, no human subjects entered the study within a period of 2 years, or if the IND remains under a clinical hold for 1 year or more. An inactive application may be reactivated if activities under the IND have recommenced. An IND that remains on inactive status for 5 years or more may be terminated.

The IND may also be terminated for cause by the FDA. Such cause may be determination that test subjects may be exposed to significant or unreasonable risk or if methods, facilities, and controls used for the manufacturing are inadequate to maintain appropriate standards for quality and purity of the proposed drug as needed for subject safety. Additional grounds for termination may be found in 21 CFR 312.44.

### 1.4.3 Preclinical Studies (Animal)

Before a drug can be tested on a human being, it must be shown to be safe. This can be established by compiling data from previous nonclinical studies on the drug, by compiling data from previous clinical testing or data from markets in which the drug has previously been sold, if relevant, or new preclinical studies may be undertaken. Both in vivo and in vitro laboratory animal studies are used.

These preclinical studies must be able to show any potential toxic effects under the conditions of the proposed clinical trial. The toxicity studies should include single and repeated dose studies, reproductive studies, genotoxicity, local tolerance studies, and the potential for carcinogenicity or mutagenicity. Additionally pharmacology studies to establish safety and pharmacokinetic studies to determine how the drug reacts in the body (absorption, distribution, metabolism, or excretion) may be performed.

At this stage the FDA will generally ask for a pharmacological profile of the drug, a determination of the acute toxicity in at least two species of animals, and a short-term toxicity study. Under 21 CFR 312.23(a)(8) the basic safety tests are most often performed in rats and dogs. Selection of a safe starting dose for humans, suggestion of the target organs subject to toxic reactions, and a margin of safety between therapeutic doses of a toxic substance will be established.

Good laboratory practice (GLP) covers several different aspects of preclinical studies. An organizational chart delineating responsibilities and reporting relationships is essential. A quality assurance unit (QAU) is required to ensure that the study takes place under GLP standards. The testing facility must be of the proper size and condition to allow proper conduct of the studies. Feed, bedding supplies, and equipment must be stored separately and protected from contamination. A separate space must be maintained for the storage of test and control items. Laboratory space for routine and specialized procedures must be separated and data reports and specimens must have a separate, limited access area.

Any equipment used for data collection or assessment must be maintained, calibrated, and kept clean. Written standard operating procedures (SOPs) must be maintained for all aspects of specimen or data handling. All prepared solutions and reagents must be properly labeled with the name of the contents, the concentration, the preparer, the expiration date, the date of preparation, and the required storage conditions.

There must be a written protocol that clearly indicates the objectives and methods for the study. The study must be conducted in accordance with the approved study protocol. Proper forms will be used for the collection of data. If data is collected manually, the data must be recorded legibly and in ink, at the time it is observed or determined, with the dated signature of the person collecting the data.

### 1.4.4 Clinical Studies

Once the IND is in effect, clinical trials may begin. These are conducted in at least three phases under good clinical practices (GCP).

#### 1.4.4.1 Phase I Studies

Traditional Phase I studies are the first exposure of humans to the drug and are designed to evaluate how the drug acts in the body and how well it is tolerated. The human pharmacological studies evaluate the pharmacokinetic parameters, generally in healthy volunteers who are not the target market for the drugs, although some patients may be included in Phase I studies. These studies generally start out with single dose, followed by escalated dosage and short-term repeated dose studies. These trials are very closely monitored. Well-designed Phase I experiments will greatly aid the design of Phase II studies.

The FDA will periodically issue guidance to industry, outlining its then current thinking on pertinent topics. Such guidance does not establish legally enforceable responsibilities but rather should be viewed as recommendations. One such guidance was issued in June 2016, jointly by the CDER and the CBER providing information for industry, researchers, physicians, IRBs, and patients about the implementation of FDA's regulation on charging for investigational drugs under an IND for the purpose of either clinical trials or expanded access for treatment use (21 CFR 312.8), which went into effect on 13 October 2009.

Another guidance was developed by the Office of New Drugs in the CDER in 2006 was for exploratory IND studies. There exists a great deal of flexibility in existing regulations regarding the amount of data that needs to be submitted with an IND application. This guidance suggests that industry as a whole has been submitting more information for an IND than is required by regulations. The guidance sought to clarify the manufacturing controls preclinical testing and clinical approaches that should be considered when planning limited early exploratory IND studies in humans. Within the guidance the phrase "exploratory IND study" is

> "intended to describe the clinical trial that:
>
> is conducted early in Phase 1
> involves very limited human exposure, and
> has no therapeutic or diagnostic intent (e.g., screening studies, micro dose studies).

These exploratory IND studies precede traditional Phase I dose escalation, safety, and tolerance studies of investigational new drug and biological products.

In vitro testing models may examine binding sites, the effect on enzymatic activities, toxic effects, and other pharmacologic markers. These initial screening tests often require only small quantities of the drug of interest; any in vitro testing may eliminate unlikely candidates. Those candidates that provide the expected pharmacologic response will then be produced in larger quantities for in vivo testing in small animals to determine the efficacy and safety of the drug. In vitro testing is generally cheaper and less restrictive than in vivo testing, and the screening at this level is quite important.

The expense of conducting human trials is formidable; therefore the agency observed that "new tools are needed to distinguish earlier in the process those candidates that hold promise from those that do not." Traditionally, an IND is filed for one chemical entity that proved most promising during in vitro testing and subsequently showed promise in supporting toxicological data during studies of the investigational drug in animals.

The guidance suggests that exploratory IND studies having no therapeutic or diagnostic intent, be used in very limited population studies of short duration to limit human exposure, but further refine the efficacy and safety of the potential drug. For example, they can be used to determine if the method of action or response in humans is the same as that in the test animals (e.g. a binding property or enzyme inhibition). This further refinement can help select the most promising candidate from a group of products designed for a particular therapeutic effect in humans.

In-depth description of the exploratory filing as opposed to the traditional IND filing is beyond the scope of this chapter. Information for the candidate product in an exploratory IND application is similar to that of the traditional IND application including physical, chemical, and/or biological characteristics as well as the source (animal, plant, biotechnology, or synthetic derivation), the therapeutic class, doses, and administration routes intended for human trial.

Analytical characterization of the candidate product may be offered under two scenarios within the IND application. In the first case the chemicals used will be the same batch as those used in in vitro animal testing. Their use is to qualify the potential drug. It is recommended that the impurity profile of the drug be established to the extent possible; however at this stage in product development, not all impurities need be fully characterized. If issue arises during toxicological studies, it can be addressed at that time using appropriate agency guidance even when the sponsor files a traditional IND for further clinical investigation.

The second case is where the candidate drug to be used in clinical studies may not be from the same batch as that used in the preclinical studies. The focus in this situation is to demonstrate that the batch to be used is representative of the batch used in nonclinical toxicology studies, and this must be supported by relevant analytical comparisons.

Safety is, of course, paramount and the preclinical safety programs may be tailored to the exploratory study design, for example, micro-dose studies that are designed to evaluate pharmacokinetics or imaging of specific targets, such as binding affinity, and are not designed to induce pharmacologic effects. The single exposure to micro quantities is comparable with routine environmental exposures; therefore routine safety pharmacology studies are not needed. All preclinical safety studies supporting the application will be consistent with GLP.

#### 1.4.4.2 Phase II Studies

Phase II studies are exploratory to determine the safety and efficacy of the drugs. These are generally referred to as therapeutic exploratory studies. The population is larger than that of Phase I. These studies are designed to demonstrate the therapeutic activity of the treatment and to assess the short-term safety of exposure to the drug. Dose response studies of this Phase will help to refine the appropriate dose ranges or regimens, thereby optimizing the design of the extensive Phase III studies.

#### 1.4.4.3 Phase III Studies

Phase III studies are done in larger populations of patients to confirm the results of the Phase II studies. These are generally called confirmatory clinical trials. The purpose of this study is to determine the short- and long-term risk–benefit balance of the active ingredient and to assess its overall therapeutic value. The data gathered from Phase III trials can be extrapolated to the general population. At the completion of Phase III studies, the data are submitted to the FDA as part of an NDA, with the intention of marketing of introducing the drug to market.

#### 1.4.4.4 Phase IV Studies

Phase IV studies are generally referred to as postmarketing studies, with the attendant implication that the drug has proven safe. It is, however, important to realize that critical information can be gained from postmarket studies. The finest designed Phase I, II, and III studies can have only a finite number of subjects taking part in the studies. The population that comprises the studies may not be large enough to statistically show an adverse effect that is limited in occurrence to a small segment of the general population. Once the drug is introduced to the marketplace, a much larger, more diverse population will, essentially, become test subjects in a Phase IV study. Careful analysis of the data may reveal adverse reactions that were not apparent in prior Phase studies.

#### 1.4.4.5 Institutional Review Board

The studies should be conducted under GCP, ensuring that the reports from the clinical trials in the data gathered are credible and accurate and that the rights, integrity, and confidentiality of trial subjects are protected. These principles are in accordance with the Declaration of Helsinki regarding participation in medical experiments. One key provision of that declaration is the right to self-determination and informed consent by any participants in a study.

Informed consent forms should be obtained from the IRB and provided to the test subject along with any other written material that will explain exactly what his or her participation in the trial entails. The participant in this trial is being put at risk for the purpose of helping his fellow man and or financial gain. That money changes hands is insufficient reason to withhold information about the study. Informed consent is just that a full and complete disclosure of all

the risks known to the best knowledge of the sponsor or investigator to which the subject will be exposed. Each participating test subject must sign a consent form prior to any initiation of the clinical trial.

An IRB is composed of a minimum of five experts with different backgrounds including scientific and nonscientific areas and at least one who is independent of the institutional trial site. The IRB is designated to review and monitor medical and biomedical research using human subjects. It is their purview to review the protocols and to maintain the safety of the test subjects at all times.

The object of clinical trials is to demonstrate the safety and efficacy of drugs for use in the human population. Although the drugs have passed initial stages of testing in preclinical (animal) populations, demonstrating that their injection or ingestion will leave the animals unharmed, how the drug interacts with the human body is still an unknown quantity. The trial of any unknown drug must contain some unknown risk to the test subject that must be addressed prior to the commencement of any human testing. The welfare of the individual test subject cannot be overlooked when qualifying drugs that may be beneficial to the greater population. The risk/benefit ratio to the test subject must be determined, balancing any perceivable risks or discomforts to which the test subject may be exposed against the anticipated benefits the drug may provide. Clinical testing of the drug can only be performed if that ratio is justifiable. Paramount above all is the test subject safety.

The IRB is the ultimate arbiter and will determine if the clinical test will go forward. Any clinical trials will be performed in compliance with instructions and/or approvals provided by the IRB. Some of the factors that the IRB will consider include what types of people may join a population of test subjects, the scheduled treatments, medications and dosages, procedures and tests, and the overall length of the designed study.

The IRB will also determine that the investigators and all support staff are qualified by training, education, and experience to perform the studies. Staffing should be adequate to perform all of the necessary duties as outlined in the protocol. Any medical decisions concerning treatment of the patient must be made by a physician or other qualified medical person.

#### 1.4.4.6 Clinical Data Monitoring Committees

The collection and handling of data is of critical importance during these trials. A properly designed trial will yield much information about the effects of the drug in the human body. It is imperative that the data is properly collected and is reviewed in a timely fashion, and the evaluation of the data is acted upon as necessary. Proper handling of the data will allow the sponsor to assess the progress of the clinical trial to determine whether to continue the study, modify, or terminate it if the safety of the subjects becomes an issue when the expected efficacy of the drug is not presented.

Sponsors of studies evaluating new drugs or devices are required to monitor these studies (21 CFR 312.50 and 312.56 for drugs and biologics) on an ongoing basis and may find it advisable to establish data monitoring committees (DMCs) to evaluate the accumulating data in clinical trials. The DMC may advise the sponsor of discovered adverse effects that may compromise the safety of the trial subjects as well as the continuing evaluation of the validity and scientific merit of the trial.

#### 1.4.4.7 Quality Assurance

The materials to be studied must be produced under GMPs (alternately called cGMPs: current good manufacturing practices); that is to say, they must be produced in accordance with all the standard practices and procedures normally associated with producing pharmaceutical materials. The manufacture, handling, storage, dispensation, and ultimate dissemination of the

investigational drug must be performed in adherence to the procedures outlined in the investigational protocol. If the clinical investigations conducted under the IND are terminated prior to the completion of the experiments as outlined in the investigational protocol, all stocks of the investigational drug should be returned to the sponsor or otherwise disposed of as a sponsor dictates.

There must be in place adequate quality assurance systems not only to ensure proper collection, tabulation, and reporting of data but also to maintain conformance with the procedures outlined in the investigation of protocol. Quality assurance must extend from the manufacture of the investigational drug, through the selection of both the individual and the collective test subjects, and through the administration of investigational drug to the subjects as well as the subsequent analytical procedures used to gather data and the ultimate compilation of that data into a report. Any laboratory analyses must use validated procedures and be appropriate for the data that they are intended to provide.

The clinical trial protocol is a formal document that is submitted and accepted as a template for the study. Information provided in the protocol include descriptors of the study, the date, name, and address of the sponsor and or investigators authorized to initiate the protocol, the medical expert, trial sites, and clinical laboratories where the investigation will take place.

#### 1.4.4.8 Investigator's Brochure

The drug to be investigated will be described in detail including its manufacture and a summary of the procedures and results of the nonclinical (animal) studies that serve as a basis for determining the dosage and application schedule of the investigational drug to the human subjects. The vector for conveying this information is in the investigator's brochure (IB). This is a compilation of all data, clinical and nonclinical, relevant to the study of the investigational drug and human test subjects. IB should begin with a summary, highlighting pharmaceutical, pharmacological, pharmacokinetic, toxicological, physical, and chemical information that has been gathered and is relevant to the development of a clinical study. Included in more detail is that the summary will be the physical, chemical, and pharmaceutical properties and formulation of the drug. The result includes any nonclinical studies including pharmacokinetics, drug metabolism in preclinical subjects including toxicology, the effects of any studies that were conducted on humans including safety and efficacy, and the drug's interaction with the human body. For studies researching new indications for existing drug, results of previous investigational studies should be included here, including postmarket investigations if any were conducted.

Here clearly defined description of the objective of the study as well as the experimental design of the study will be detailed.

The basis for the selection of the individuals that will partake in the study as test subjects as well as any reasons for exclusion of potential test subjects will be defined. For example, test subjects may be required to have a particular condition that is potentially responsive to the investigational drug. The inclusion of "normal" subjects may be sufficient to demonstrate the safety of the drug, but may be unable to support any findings of efficacy of the drug, as they would not have the physiological condition targeted by the proposed drug. Alternately, it may have been determined in the preclinical studies that the investigational drug is potentially dangerous to a limited number of people with specific indications and that risk may be minimized by excluding the defined subset from the investigational group. As described earlier, the risk–benefit analysis may be such that the potential therapeutic value of the investigational drug is outweighed by the overall risk to these potential test subjects, excluding this subset of the human population. The risk cannot be ignored, and the only safe way to proceed with a study of this type is to exclude from the potential test population those who would be harmed by the drug.

The treatment of the test subjects must be described in detail including how the drug will be administered and how the health of the subjects will subsequently be monitored, as well as the methods used to determine the safety and efficacy of the drug in human usage. Any methodologies for obtaining samples for analyses from the subjects must be detailed, and the handling of the data (recording, analyzing, etc.) included in the ultimate reports must be detailed in the protocol.

#### 1.4.4.9 Informed Consent

Second only to the safety of the test subject is the maintenance and respect of the privacy of the individual. It is important to acknowledge that abuse of research patients by investigators has occurred in relatively recent times, perhaps most egregiously in the infamous Tuskegee syphilis study in 1928. Initially started with the best of intentions, the Great Depression caused the financial sponsor of the study to withdraw funding to the US Public Health Service (PHS). The study sought to treat the occurrence of syphilis in black men living in various counties in Mississippi, Virginia, Georgia, Alabama, North Carolina, and Tennessee, in a test population of over 2000 men, 25% of whom had tested positive for syphilis. With restricted finances the PHS was unable to treat the infected men and the focus of the project changed.

There was a question at the time, of whether or not the progress of the disease within the black population was different from that in the white population. It was therefore decided to track the progression of the disease in the infected men without informing them that they were infected. The subjects received routine examinations but with either no treatment or substandard ineffectual treatment for their underlying condition, syphilis. Not only did the PHS not treat the subject for their disease, but also they prevented other government agencies from treating the "patients." When, in 1943, the PHS routinely began to use penicillin to treat patients under its purview, it specifically excluded those subjects of the Tuskegee syphilis study. Further it tracked the test subjects through the end of the study in the early 1970s, preventing them from receiving treatment. Even then the study was not ended by the PHS voluntarily, but rather only after being exposed by a reporter.

While we would like to think that nothing this outrageous could occur again, safeguards have been put in place to ensure that it does not. Indeed, the safeguards, including investigational protocol, endeavor to prevent any harm from occurring to any patient, mentally, physically, or as a violation of their rights to privacy. It should also be noted that while animal test subjects may be harmed and, indeed, sacrificed, the treatment and care of animals used in preclinical studies must be designed to minimize pain and suffering of the animals.

Informed consent granted by the research subject means that they or their legal representatives have been fully informed of all pertinent aspects of the proposed drug trial. This information is to be presented to the potential test subject so that they can decide whether or not to participate in the study, based upon their evaluation of the risks to which they themselves would be subjected. Neither the investigator nor any of his representatives is to exert any influence upon the potential subject, nor may any unreasonable time constraints to be placed upon the decision-making process. The information required for consent must be presented in a clear, unambiguous manner and understood by the potential test subject. Any and all questions about the trial must be answered completely to the satisfaction of the potential subject or his legal representative. Transmission of this information should be written as well as oral, and the explanations should be made in the presence of a witness who is uninvolved with the study. The witness will sign the informed consent confirming that information was properly transmitted to the potential subject or their legal representative and that all questions were properly asked and answered. Once all of these conditions have been met, the subject is to sign and personally date the informed consent form, attesting that he has been presented with complete information

about the test to which he is committing himself and that he willingly agrees to partake in the investigation. Any new information discovered during the trial that affects the informed consent will be transmitted to the subject or the legal representative, and a modified informed consent will be signed at that time. A copy of the original informed consent and copies of any amendments or changes to the informed consent should be provided to the subject and/or his legal representative as such changes are made.

The participation of a test subject in a research trial is completely voluntary, and the subject may decide to end his or her participation in the research trial at any time, without penalty. As part of informed consent, the subject will be informed of trial treatments and procedures including invasive procedures and be made aware that he or she may not receive the experimental treatment but rather be part of a control group. The subject will be fully informed of his responsibilities, as a member of the research population, of any expectations required of him during the study period. He must be informed of any anticipated risks or inconveniences as well as any expected benefits of the treatment that he may receive.

The duration, as well as the scope of the trial, is to be made known to the potential subject for his or her information. The potential research subject must also be informed of any foreseeable reasons for termination of his or her participation in the trial by the research team. The subject must be informed of any payment or expenses accruable to him or her as a result of participation in the trial.

Access to any data that may identify the subject, such as original medical records, shall be limited; however the subject must be made aware of that access to the said records by authorized researchers, and monitors or the IRB will be made. The subject also must be aware that records enabling the identification of individual research participants will not be released to the general public and that every effort will be made to conform to the legal requirements that the test subject's identity remain confidential.

As mentioned earlier, the handling of the data is critical. Therefore, the methods of statistical analysis to be used on experimental data, including the structure of the design, shall be provided. Further, the limitations placed upon access to the data must be specified in the investigational protocol. This is important for maintaining the privacy of individuals as well as assuring the integrity of the data used to form the reports, thereby enabling independent assessment of the study's results by third parties. It is axiomatic in any regulatory industry that if data is not recorded, it did not occur. The data must be properly acquired and recorded and the records maintained in an accessible and safe location for reasonable period of time.

## 1.5 Commercializing the New Drug

The ultimate goal for a new drug is commercialization. The IND is simply an investigational permit allowing transportation of an unapproved drug to a test site where it can undergo testing in human subjects to determine if it should be approved for sale to human populations. Application must be made to the FDA to market a new drug, assuming that the pharmaceutical company, after evaluation of the clinical studies, decides to proceed to market. At this point the pharmaceutical company needs to submit to the FDA an NDA seeking permission to market the new drug. The applicable Regulations are found under 21 CFR 314.

As noted earlier, the US FDA is the primary regulatory body for the dissemination and sale of drug products within the United States, with corresponding agencies serving a similar function in their respective countries. Clearance by the US FDA to introduce a new drug into the domestic market does not guarantee access to foreign markets. It is therefore in the best interest

of domestic drug manufacturers to fulfill international requirements simultaneously with domestic requirements, thereby gaining entrance to markets worldwide. Harmonization of worldwide requirements is an ongoing process with which the US FDA is committed.

The FDA has standardized the format for submission of NDAs. There exists a structure for the submission of INDs and evolving harmonized standards; however outlining only one such standardized format in depth is sufficient to illustrate the level of detail required. For illustrative purposes, the US application process and forms, as extracted from the applicable CFRs, will be described basically as issued. Following that will be a description of harmonized submission format with notations of where corresponding sections of US submission requirements are applicable. Finally, a more descriptive explanation of the sections of the US submission requirements will expand the understanding of what is required to submit a new drug for market approval.

### 1.5.1 New Drug Application

An NDA has been required since the revision to the FD&C Act of 1938. The initial NDA required by the 1938 Act required only the establishment of the safety of the drug under study. The 1962 Kefauver–Harris amendment to the FD&C Act additionally required demonstration of the efficacy of the drug for its intended use. Further in addressing the safety aspects of the potential drug, it must be shown that the benefits of the drug outweigh the risks associated with the drug.

Three copies of the NDA are submitted, providing an archival copy, a review copy, and a field copy.

An NDA for a new chemical entity will generally contain, under 21 CFR 314.5, the information as follows, although different groupings have been submitted. The description of each section below is not comprehensive.

#### 1.5.1.1 NDA Application Form 356h

Each NDA or supplement to approved NDAs must have an application form (Form 356h): Application to Market a New or Abbreviated New Drug or Biologic for Human Use (21 CFR 314 & 601) available online (www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM082348.pdf) signed and dated by an authorized agent or official of the applicant representing the submission to the FDA. It will have the name, address, telephone number, and e-mail address of the applicant; the date of the application; the application number if previously issued; the names (established, proprietary, code, and chemical) of the drug product; dosage form and strength; route of administration; identification numbers of all INDAs referenced; the identification numbers of all drug Master Files and other applications referenced in the application; and the potential drug product's proposed indications for use.

Also included will be a statement of the submission classification (new, resubmission, etc.), a statement of the potential market for the drug product as either prescription or over-the-counter product, and a checklist that will identify what enclosures are required under the section the applicant is submitting. This form will be used for contact by the FDA regarding the submission.

#### 1.5.1.2 Index

The NDA Application should include a comprehensive index by volume number and page number to the summary, the technical sections, and the supporting information for the archival copy of the NDA.

#### 1.5.1.3 Summary

Writing at the level of submission to a peer-reviewed journal, a summary of the various parts of the submission, using tabular or graphical data where possible, should contain enough detail to impart a good general understanding of data (including quantitative aspects) and information included in the NDA.

The summary must contain the following information:

Proposed labeling text (referring to support sections annotating inclusion of each statement in the labeling) including any medication guide required.
The pharmacologic class and rationale for intended use.
Any prior or pending foreign marketing history including any countries in which applications for marketing are pending or in which the drug has been withdrawn for safety or effectiveness issues.

A summary of the following sections of the NDA:

- Chemistry, manufacturing, and controls
- Nonclinical pharmacology and toxicology
- Human pharmacokinetics and bioavailability
- Microbiology section (if applicable)
- Clinical data, including statistical results

The summary will conclude with a discussion of the risk–benefit analysis and proposed additional studies or Phase IV.

#### 1.5.1.4 Technical Sections

##### *1.5.1.4.1 Chemistry, Manufacturing, and Controls*

A full description of the manufacturer(s), the components, and the specifications of the drug substance includes:

- A full description of the *drug substance* including its physical and chemical characteristics and stability; the manufacturer's name and address; the method of synthesis, isolation, and purification of the drug; and all process controls and specifications as well as analytical methods used to ensure identity, strength, quality, and purity of the drug substance and bioavailability of the drug product.
- A list of all components used in manufacture of the *drug product* and their specifications (regardless of whether they appear in the drug product) and a statement of the composition of the drug product and any manufacturer (including address) and stability data with proposed expiration dating.

  Any drug product batch history records of drug products used for bioavailability or bioequivalence studies, including manufacturer, specifications, and other criteria as above.

  Proposed or actual master production record including equipment and production process to be used for commercial manufacture of the drug product.
- Environmental impact claim or categorical exclusion under 21 CFR 25.30 or 25.31 or an environmental assessment under 21 CFR 25.40.
- The applicant may, at its option, submit a complete chemistry, manufacturing, and controls section 90–120 days before the anticipated submission of the remainder of the application.
- A statement certifying delivery of the field copy of the NDA to applicable FDA district office.

##### *1.5.1.4.2 Nonclinical Pharmacology and Toxicology*

Descriptions of the in vitro and in vivo studies, preferably presented in graphical or tabular format, includes:

- 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 any adverse effects.
- 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 and studies of toxicities related to the drug's mode of administration or conditions of use.
- As appropriate, studies of the effects of the drug on reproduction and fetal development.
- Also included should be any studies of the absorption, distribution, metabolism, and excretion of the drug in animals.
- For nonclinical laboratory study, a statement should also be made regarding GLP being used throughout the studies. Alternately, if the studies were not conducted under GLP, an explanation should be provided for each incident of noncompliance.

#### *1.5.1.4.3 Human Pharmacokinetics and Bioavailability*

Description of the human pharmacokinetic data and human bioavailability data or information supporting a waiver of the submission of in vivo bioavailability data includes:

- Description of each bioavailability and pharmacokinetic study of the drug in humans including analytical and statistical methods used.
- A statement about the rationale for establishing the tests, analytical procedures, and acceptance criteria including data and information supporting that rationale.
- A summarizing discussion and analysis of the pharmacokinetics and metabolism of the active ingredients and the bioavailability and/or bioequivalence of the drug product.

#### *1.5.1.4.4 Microbiology*

This section should detail, for anti-infective drugs only:

- This should include a description of the biochemical basis of the drug's action. Antimicrobial spectra of the drug, including preclinical studies, to establish effective use concentrations.
- Any known resistance factors or studies thereof.
- A description of clinical microbiological laboratory procedures.

#### *1.5.1.4.5 Clinical Data*

A description of the clinical investigations of the drug includes:

- Each clinical pharmacology study of the drug with a brief comparison of the results of the human studies with the animal pharmacology and toxicology data.
- A description of each controlled clinical study pertinent to the proposed use of the drug, including the protocol and a description of the statistical analyses used to evaluate the study.
- A description of each uncontrolled clinical study, a summary of the results, and a brief statement why the study is classified as uncontrolled.
- A description and analysis of any other data or information relevant to evaluation of the safety and efficacy of the drug product received by the applicant derived from any source, foreign or domestic, including controlled and uncontrolled studies of uses of the drug other than those proposed in the application.
- An integrated summary of the data demonstrating substantial evidence of effectiveness for the claimed indications. Included will be evidence required to support the dosage and administration section of the labeling.

- Safety summary and update including 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. The safety data shall be presented by gender, age, and racial subgroups. When appropriate, safety data from other subgroups of the population of patients treated also shall be presented.

  The applicant shall also update periodically its pending application 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 or medication guide.
- If the drug has the potential for abuse, a description and analysis of studies or information related to the abuse of the drug, including a proposal for scheduling under the Controlled Substances Act, is required. Studies related to overdosage including information on dialysis, antidotes, or other treatments if known shall be provided.
- A summary of the risks and benefits of the drug including a discussion of why the benefits exceed the risks under the conditions stated in the labeling.
- A statement with respect to each clinical study involving human subjects that either was conducted in compliance with the IRB regulations or were not subject to them and that it was conducted in compliance with the form consent regulations.
- If a sponsor transferred any obligations for the conduct of any clinical study to a contract research organization, the name and address of said organization, the clinical study transferred, and a listing of each obligation transferred or if all obligations transferred a general statement to that effect.
- Any audit or review by the sponsor of original records to verify the accuracy of case reports in the course of monitoring the study should be listed.

#### *1.5.1.4.6 Statistical*

This section describes the statistical evaluation of clinical data including:

- Description and analysis of each controlled clinical study with supporting documentation and statistical analysis.
- A summary of information about the safety of the drug product and documentation and supporting statistical analyses using evaluating the safety information.

#### *1.5.1.4.7 Pediatric Use*

This section will include a description of the investigation of the drug for use in pediatric populations, including an integrated summary of information that is relevant to the safety and effectiveness as well as the risk–benefit determinations in pediatric populations.

### 1.5.1.5 Samples and Labeling

The FDA may request samples be sent to, generally, two or more agency laboratories that will perform all necessary tests and validate the analytical procedures. Such samples will be:

- Four representative samples in quantities sufficient to perform the required tests in triplicate to determine if the drug substance and drug product meet the NDA specifications of the following:
  - The proposed drug product.
  - The drug substance used in the drug product above.
  - Reference standards and blanks (standards recognized by an official compendium excluded).
- Samples of the finished market package, if requested.

The following must be submitted in the archival copy of the NDA:

- Three copies of the analytical procedures and related descriptive information contained in the CMC section that are necessary for the FDA's laboratories to perform all tests on the drug substance and the drug product.
  This includes any supporting data for accuracy, specificity, precision, and ruggedness and complete results of the applicant's tests on each sample.
- Four copies of the draft or 12 copies of the final printed labeling for the drug product including, if applicable, any medical guide required.

#### 1.5.1.6 Case Report Forums and Tabulations

For the archival copy of the NDA:

- Case report tabulations for each adequate and well-controlled Phase I and Phase II studies, from the earliest Phase I studies and for safety data from other clinical studies. The tabulations must include the data on all patients in each study unless the FDA agrees in advance subject was not pertinent to a review of the drug's safety or efficacy.
- Case report forms for each patient who suffered an adverse event and had to leave the study or died must be included.
- Additional data to be provided by the applicant include additional case report forms and tabulations needed to conduct a proper review of the NDA.
- Prior to submitting an NDA to the FDA, applicants may meet with the agency to discuss the presentation and format of supporting information. Alternate formats must be agreed upon by both parties.

#### 1.5.1.7 Other

The following general requirements apply to the submission of information within the summaries and within the technical sections:

- Information previously submitted may be incorporated by reference to the file by name, reference number, volume, and page number in the agency's records where the information can be found. Resubmission is not required.
- A complete and accurate translation of each part of the NDA that is not in English and a copy of each original literature publication translated into English will be provided.
- If the NDA is submitted with an obtained "right of reference or use," a written statement signed by the owner of the data must be included, and access to the underlying data must be granted to the FDA.

#### 1.5.1.8 Patent Information

The information pertaining to the drug should be submitted for drug substance, drug product, and method of use. This section will include patent number and expiration date, type of patent, name of patent owner, name of US representative of a foreign patent owner, and declaration if patent covers the drug submitted. A more complete description of types of patents that must and must not be submitted is described in 21 CFR 314.53.

#### 1.5.1.9 Patent Certification

With regard to patents claiming drug, drug product, or method of use, a 505(b) submission, for each such patent the applicant shall provide the patent number and certify, in its opinion and to the best of its knowledge, one of the following circumstances:

1) Paragraph I Certification – that the patent information has not been submitted to the FDA.
2) Paragraph II Certification – that the patent has expired.

3) Paragraph III Certification – that the date on which the patent will expire.
4) Paragraph IV Certification – that the patent is invalid, unenforceable, will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

For more information regarding patents, refer to 21 CFR 314 as it goes into far greater detail about patents than above.

#### 1.5.1.10 Claimed Exclusivity

A new drug product, upon approval, may be entitled to a period of marketing exclusivity. To claim exclusivity, it must submit with the NDA prior to approval the following:

- A statement claiming exclusivity.
- A reference to the appropriate paragraph under 21 CFR 314.108 that supports the claim.
- Claims under 21 CFR 314.108(b)(2) must provide information to show that, to the best knowledge or belief, a drug has not previously been approved under Section 505(b) containing any active moiety in the drug for which approval is sought.
- An NDA claiming exclusivity under 21 CFR 314.108(b)(4) or (b)(5) must 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."
  - "New Clinical Investigations" requires a certification that to the best of the applicant's knowledge, each of the clinical investigations meet the definition set forth in 21 CFR 314.108(a).
  - "Essential to approval" is a list of all published studies or publicly available reports known to the applicant that to the best of the applicant's knowledge is complete and accurate and finds that the publications do not provide a sufficient basis for approval.
  - "Conducted or sponsored by" requires a certified accountant's statement that, if not the sponsor, the applicant provided 50% or more of the cost of the investigation.

#### 1.5.1.11 Financial Certification or Disclosure

The application shall contain a financial certification or disclosure statement or both as required. The applicable forms FDA 3454 (no financial interest) and FDA 3455 (disclosure of financial interest) shall be signed by the investigator and sponsor(s) CFO and submitted in this section.

#### 1.5.1.12 Format of an Original NDA

A complete archival copy of the NDA that will be maintained by the FDA 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.

A review copy of the NDA shall be provided with technical sections individually bound together with the application form and a copy of the summary.

A field copy contains the technical section, a copy of the application, a copy of the summary, and a certification that the field copy is a true copy of the technical section contained in the archival and review copies of the NDA.

Sufficient binding folders may be obtained from the FDA to bind the archival, the review, and the field copies of the NDA.

Electronic format submissions must be in a form that the FDA can process, review, and archive. Electronic submission is evolving, and the FDA periodically issues guidance as to file formats, media, and organization.

The above is the traditional format for submitting an NDA in the United States. The pharmaceutical business is, however, composed of worldwide enterprises. From a financial viewpoint, it makes sense for companies to move toward worldwide standardization of submission processes. From a government viewpoint standardization of submission and approval formats would allow faster access to worldwide markets for domestic companies and would also speed in the importation of new pharmaceuticals developed in other countries. Toward that end experts from around the world have been working to harmonize regulations.

## 1.6 Harmonization

For pharmaceutical products the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH [3]) is the organization whose unique mission is to reduce or eliminate redundant testing during the research and development phase of drug development. It brings together the regulatory authorities and experts from the pharmaceutical industries of the United States, Europe, and Japan to discuss scientific and technical aspects of data submission required for product registration (acceptance for sale).

### 1.6.1 Common Technical Document

One outcome of these meetings is called the "Common Technical Document" (CTD), a harmonized format for submitting new product applications. This format was agreed upon in November 2000, in San Diego, USA, with the agreed-upon implementation date in the three regions of July 2003. Currently the United States is accepting applications and submissions in both formats.

An FDA Draft Guidance for Industry Submitting Marketing Applications According to the ICH-CTD Format – General Considerations was issued August 2001.

The CTD is composed of five modules in the following format:

#### 1.6.1.1 Module 1. Administrative Information and Prescribing Information

1.1 FDA Form 356h
1.2 Comprehensive Table of Contents of the Submission including Module 1
The location of each document should be identified by referring to the volume numbers that contain the relevant documents and any tab identifiers.
1.3 Administrative Documents Specific to Each Region (for example, application forms, prescribing information)

This is a region-specific module containing, for example, application forms for use in the region. The content in the format can be adjusted for the particular regulatory agency to which the forms are being submitted. It is not technically a part of the CTD.

*The corresponding sections of the traditional submission to the FDA that should be included in Module 1 of the CTD are:*

*Index and FDA Form 356h*
*Labeling*
*Patent information on any patent that claims the drug*
*Patent certifications (not for Biologics License Application [BLA])*
*Debarment certification*
*Establishment description*
*Field copy certification (not for BLA)*
*Financial certification including User Fee cover sheet*
*Other information*

#### 1.6.1.2 Module 2. Common Technical Document Summaries

2.1 Overall Technical Document Table of Contents (Modules 2–5)
2.2 CTD Introduction to the Summary Documents
2.3 Overviews and Summaries
- Quality overall summary
- Nonclinical overview
- Clinical overview
- Nonclinical written and tabulated summaries
  - Pharmacology
  - Pharmacokinetics
  - Toxicology
- Clinical summary
  - Biopharmaceuticals studies and associated analytical methods
  - Clinical pharmacology studies
  - Clinical efficacy
  - Clinical safety
  - Literature references
  - Synopses of individual studies

This should be a single page and begin with a general introduction to the pharmaceutical, including its pharmacologic class, mode of action, and propose clinical use.

Information on quality should be presented in a structured format as described in FDA Guidelines M4Q, M4S, and M4E.

*Module 2 is equivalent of a summary of all technical sections of the traditional NDA.*

#### 1.6.1.3 Module 3. Quality

3.1 Module 3 Table of Contents
3.2 Body of Data
3.3 Literature References

Information on quality should be presented in a structured format as described in Guideline M4Q.

*The information here is similar to what is included in CMC in the traditional NDA.*

#### 1.6.1.4 Module 4. Nonclinical Study Reports

4.1 Module 4 Table of Contents
4.2 Study Reports and Related Information
4.3 Literature References

Nonclinical study reports should be presented in the order described in Guideline M4S.

*The information here is similar to what is included in Nonclinical Pharmacology and Toxicology in the traditional NDA.*

#### 1.6.1.5 Module 5. Clinical Study Reports

5.1 Module 5 Table of Contents
5.2 Tabular Listing of Clinical Studies
5.3 Clinical Study Reports
5.4 Literature References

The human study reports and related information are presented here in the order described in Guideline M4E.

*The corresponding sections of the traditional submission to the FDA that should be included in Module 5 of the CTD are:*

*Human Pharmacokinetics and Bioavailability*
*Clinical Microbiology*
*Clinical Data*
*Safety Updates*
*Statistical Information*
*Case Report Forms and Tabulations*

The Guidelines M4Q, M4S, and M4E give far greater detail about the exact order in which the data is presented. For example, M4S specifies that where multiple studies of the same type are summarized within pharmacokinetics and toxicology sections, the studies should be ordered by species, by route, and then by duration (shortest duration first).

What is important to note here is that, essentially, the information contained in the traditional FDA submission is the same as in the CTD. The difference is in how the presentation is organized. Standardized submissions will ensure that each area will receive the information that it requires to evaluate the new drug in the same format while still satisfying any particular area requirements of formats or forms. Obviously the advantage of harmonization is that once Modules 2–5 are prepared for one country, the same four modules can be submitted to other members of the harmonization project unchanged, with only the region-specific forms of Module 1 addressed to the country in who's market the drug company would like to enter.

## 1.7 Review Process of US NDA

Three copies of the application are required.

- Archival copy. The complete archival copy of the application contains all the sections in the application. FDA retains the archival copy to permit individual reviewers to refer to information that is not contained in their particular technical sections. The archival copy can be submitted in either electronic format in accordance with 21 CFR 11 or hard copy.
- Review copy. This copy contains the title sections. It is required to be separately bound to the top of the Application Form 356h and a copy of the summary section, Modules 1 and 2 in CTD.
  Review copies that may be necessary include:
  - Quality (Module 3)
  - Nonclinical (Module 4)
  - Clinical (Module 5) – safety and efficacy documents for clinical reviewer
  - Clinical (Module 5) – safety and efficacy documents for the statistical reviewer
  - Clinical (Module 5) – clinical pharmacology and pharmacokinetics documents (or bioequivalence documents) for Abbreviated New Drug Applications (ANDA's)
  - Clinical (Module 5) – clinical microbiology documents
- Field. Only the CMC section, or Module 4, Quality, in CTD format. The field copy should be submitted to the local district office of the FDA and a signed statement of submission attached.

The archival and a review copy of the drug marketing application are submitted to the CDER in Beltsville, Maryland. The first step is a review for completeness to ensure that sufficient data and information have been submitted in each area "filing" the application. Incomplete NDAs result in a formal "refuse-to-file" action, in which case the applicant receives a letter detailing the decision and the deficiencies noted. This decision must be made within 60 calendar days after CDER initially receives the NDA.

If the complete NDA is accepted, it undergoes technical reviews with each reviewer submitting a written evaluation of the NDA to the FDA division or office director who then evaluates the reviews and recommendations of the reviewers and decides the action to be taken on the application. A letter will be generated that provides either an approval, approvable, or non-approvable decision as well as a basis for that decision.

The technical reviewers each focus on a specific area of their expertise.

Medical reviewers evaluate the clinical sections of the application including the results of clinical trials and all toxicology and human pharmacology.

Biopharmaceutical review is performed by pharmacokineticists who evaluate the rate at which and the extent to which the drug's active ingredient is made available to the body as well as the ways it is metabolized, distributed, and eliminated from the human body.

Statistical reviewers are statisticians who validate the statistical relevance of the data in the NDA primarily by evaluating the methods used to conduct the studies and the methodology used to analyze the data.

Pharmacology/toxicology review team members evaluate the results of animal testing and the relationship of the animal drug effects to potential effects in humans.

Chemists perform the chemical review of the chemistry and manufacturing control sections of the NDA. The identification, manufacturing control, and analytical procedures are reviewed for suitability and accuracy. They confirm the ability to reproduce the drug reliably as well as its stability.

As part of the NDA review process, the FDA conducts preapproval inspections (PAIs) to verify the accuracy and completeness of the manufacturer-related information in the NDA. They will evaluate the manufacturing controls used to produce the pharmaceuticals that were studied in the preclinical and clinical trials. They will evaluate the manufacturers' compliance with cGMPs and collect a variety of drug samples for analysis to confirm methods validation, methods verification, and forensic screening for substitution. If the manufacturing facility is found wanting during the PAI process, approval of the NDA will be withheld until the deficiencies are addressed and corrected.

The timeframe for reviewing NDA is that within 180 days of receipt of application for new drug under Section 505(b) or an abbreviated application for new drug under Section 505(j). 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." The applicant may, anytime before the NDA is approved, withdraw an application or an abbreviated application, and it may later be submitted again for consideration. The initial review cycle may be adjusted by mutual agreement between FDA and applicant.

Repeated meetings may take place between the FDA and the applicant. A meeting prior to submission of the NDA is helpful to discuss the presentation of the data supporting the application. This pre-NDA meeting also helps reviewers become familiarized with the data to be submitted to facilitate its review. At this meeting a summary of the clinical studies would be discussed as well as a proposed format for organizing the submission.

About 90 days after the initial submission of the NDA, another meeting may be held in order to discuss any deficiencies or issues that are discovered on the initial review. Alternately the FDA may communicate with the applicant by telephone, letters, faxes, e-mails, or meetings.

"Correct the deficiencies" notifications are probably communicated by the FDA to the applicant. Major scientific issues are usually reserved for discussion and noted in a complete response letter after the initial review process is completed.

At the end of the review, a complete response letter will be sent if the FDA determines that the NDA submission will not be approved in its present form for one or more reasons. A complete response letter usually will describe all of the specific deficiencies that the agency has identified in an application.

An end of review conference provides an opportunity for the applicant to meet with the FDA to discuss the deficiencies. The purpose of this meeting is to address what further steps are necessary for the application to be approved.

Once the decision on action recommendation is made by the reviewers and their supervisors, the decision must ultimately be evaluated and agreed to by the division director. Once the director signs the approval action letter, the product can be legally marketed in the United States.

## 1.8 Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs

cGMP regulations for drug and biological products are geared toward commercial manufacturers for all types of pharmaceutical products for administration to humans or animals. 21 CFR 210 and 211 are the relevant regulations, with §210 being general applicability and definitions and §211 covering the 10 main categories addressed by the cGMPs.

### 1.8.1 Organization and Personnel

#### 1.8.1.1 Quality Control Unit

Quality is the responsibility of everybody in the pharmaceutical manufacturing organization. It is the responsibility of each manufacturer to establish, document, and implement a system for managing quality throughout the manufacturing operation.

The quality control unit shall have the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products, and the authority to review production records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated and corrective action taken if unexpected results occur during production.

The quality control unit shall be responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company. They shall have the responsibility for approving or rejecting all procedures or specifications impacting on the identity, strength, quality, and purity of the drug product. In order for the quality control unit to function properly, adequate laboratory facilities for testing and evaluation of all components of the pharmaceutical including raw materials and packaging materials as well as finished goods must be made available to the quality control unit.

The responsibilities and procedures of the quality control unit shall be in writing and the written procedures will be followed.

#### 1.8.1.2 Personnel

The pharmaceutical manufacturer is expected to employ personnel whose training and experience qualify them to perform their jobs. Additionally there should be an adequate number of people to perform all of the activities required and to supervise the production or processing of pharmaceutical products. The particular job functions should be specified in writing.

Training of operators should be conducted by qualified individuals on continuing basis. At a minimum, training should address the immediate responsibilities the employee performs. However, conveying an understanding of larger scope of the production process empowers the employees to recognize threats or concerns that may occur outside of their immediate prevue. The effectiveness of training should be assessed periodically and records of such training and assessment should be maintained.

#### 1.8.1.3 Personnel Hygiene

Maintenance of good personnel hygiene is required of all personnel, maintaining good sanitation and health habits. They should be provided with clean clothing and protective apparel such as head, face, and hand coverings, where appropriate to avoid contaminating drug products. Personnel with illnesses such as communicable diseases or open lesions should not be allowed potential contact with and subsequent contamination of the drug product.

#### 1.8.1.4 Consultants

Consultants who advise on the manufacture, processing, packing, or holding of pharmaceuticals should also have proper education, training, and experience to enable them to provide competent advice within their area of expertise. Records should be kept of all pertinent contact information for the consultant, their qualifications, and what services they provided to the company.

### 1.8.2 Building and Facilities

#### 1.8.2.1 Design and Construction Features

The design and construction features of the buildings wherein pharmaceutical manufacturing will occur should be such to suit the type of the drug manufactured, processed, packaged, and held in that facility. The building should be capable of being maintained as a clean environment wherein proper processing may occur.

There should be adequate room to receive, identify, and store and quarantine drug product containers, closures, labeling, process components, in-process intermediates, and drug products that securely safeguard against contamination or premature release pending quality control sampling, testing, and release for manufacture.

The facility should be designed so that workflow minimizes the chance for contamination or adulteration of product.

The building must have adequate lighting, ventilation, air filtration, air heating, and cooling. Plumbing must be such that water is available in sufficient quantities to supply all needs. Likewise source facilities and refuse containers must be sized accordingly.

Sewage, trash, and other refuse in and from the building and immediate surrounding area shall be disposed of in a safe and sanitary manner.

Adequate washing within the facilities must be made available for personnel to maintain personal hygiene and sanitary conditions on the factory floor. Maintenance of facilities must be an ongoing continuous process.

### 1.8.3 Equipment

The equipment used to manufacture pharmaceuticals must be designed to the proper size and in the proper location to produce the desired pharmaceutical. In general the construction equipment must be sturdy, easily cleanable, sanitizable, and easily maintained. The equipment should be regularly and reliably calibrated and there should be in place on location SOPs

explaining how to use the equipment as well as how to maintain, clean, and sanitize it. Records shall be maintained recording any and all calibrations, cleaning or sanitization, and/or maintenance operations for each piece of equipment used in the manufacture of drug products.

Automated systems, both mechanical and electronic, may be used provided that they are regularly and routinely inspected, checked, and calibrated according to established SOPs. Such systems will be put in place that prevent unauthorized alteration of computer controls, records, master batch records, or other records either intentionally or by error. Input and output checks of such systems shall be performed with sufficient frequency to assure the integrity of the records, calculations, and process controls.

#### 1.8.3.1 Filters

Filters that come in contact with liquids that are components of injectable drug products shall be of such construction as to not release fibers into said liquid.

### 1.8.4 Control of Components and Drug Product Containers and Closures

The containers and closures should be clean and kept under clean conditions and protected from contamination. Each individual lot of untested components, drug containers, and closures shall be received and isolated, pending quality control unit testing and release for use. The testing methodology shall be in accordance with SOPs specifying the appropriate test procedure and sampling size. The component should either be accepted and released for production or rejected and returned to the manufacturer. Rejected materials should be prevented from entering production stream while awaiting transport out of the facility.

### 1.8.5 Production and Process Controls

Each drug product shall have a written procedure describing in detail the manufacturing control process required to produce the pharmaceutical of the required identity, strength, quality, and purity. The components for the drug manufacturer should be weighed, measured, or subdivided as appropriate. Weighing, measuring, or subdividing operations for components shall be adequately supervised. Each component dispensed to manufacturing shall be examined by a second person to assure that the component was released by the quality control unit; the weight or measure is correct as stated in batch production records, and the container is properly identified. The components are then added to the batch by one person and their addition verified by a second person. If the weighing and measuring, subdividing, and/or adding to the batch is done by automated equipment, only one person is necessary to assure proper proportions.

All such containers shall be identified at all times to indicate their contents and phase of production, if applicable.

**Written records** must be kept as part of the master production records or master batch records, for all in-process and final drug product testing. The quality control unit will review all records. Any deviation from the written procedure must be recorded, investigated, and justified. The product produced is suspect until the review takes place. The final disposition of the suspect product must be recorded. The master production record in all production records will be maintained by document control. No products are released until a complete review of the entire production record by the corporate authorities.

**Retention samples** will be kept from each batch of finished product released for 1 year after the expiration date. These retention samples should be in their production packaging unless overly large, in which case smaller samples might be stored in appropriate containers with corresponding appropriate labeling.

**Actual yield and percentages of theoretical yield** shall be determined as appropriate at the conclusion of each phase of the manufacturing procedure.

When appropriate, time limits for each manufacturing phase shall be established to ensure product quality.

Appropriate SOPs to prevent contamination by objectionable microorganisms in both sterile and non-sterile drug products must be established and followed to eliminate microbial contamination of said products.

Written procedures shall be established and followed to reprocess, as appropriate, nonconforming batches of drug product or drug product intermediaries. Said reprocessing shall be supervised by the quality control unit.

### 1.8.6 Packaging and Labeling Control

Written procedures shall describe in sufficient detail the maintenance of strict control over labeling issued for use in drug packaging operations. Each batch of labels will be stringently examined for correctness and appropriate for each batch of pharmaceutical. The label reflects the proper identity and conformity to the labeling specified in the master or batch production records. All excess labeling bearing a lot with control number shall be destroyed. A methodology will be maintained to reconcile issues of labeling issued, use, and returned.

Written procedures for receiving and evaluating raw materials shall be in place including specific instructions for receiving, reviewing, releasing, and distributing all components. Any labeling or packaging materials meeting appropriate written specifications may be approved and released for use. Any labeling or packaging materials that do not meet appropriate written specifications will be rejected to prevent their use in operations for which they are unsuitable.

Records will be maintained for each shipment of its different labeling and packaging material indicating receipt, examination, and testing and whether accepted or rejected including quantities.

The labels for the final product shall be at minimum the name of the product, the active ingredients in quantities thereof, quantization of the contents, batch or control number, expiration date, storage and handling conditions, directions for use, warnings and precautions, and then the name and address of the manufacturer or marketer.

Obsolete and outdated labels and packaging will be destroyed and their disposition recorded.

Use of gang-printed labeling for different drug products or different strands or net contents of the same drug product is prohibited unless there is adequate differentiation by size, shape, or color to prevent misapplication.

If cut labeling is used packaging and labeling operation must include one of the following:

- Dedication of labeling and packaging lines for each different strength of each different drug product.
- 100% verification of correct labeling by use of appropriate electronic or electromechanical equipment.
- 100% visual inspection for correct labeling during or after completion of finishing operations for hand applied labeling. The examination will be conducted by one person and independently verified by second person.

On package printing the operation shall be confirmed to conform to the drug production record.

Issuance of labeling shall be under strict control. Labeling issued for a batch shall be inspected for conformity to the batch or master control record. Unused labels shall be returned to secured storage and any discrepancies among issued, used in production, and returned labels shall be resolved. All excess labeling bearing lot or control numbers shall be destroyed.

Unless specified by 21 CFR 211, over-the-counter drugs shall be produced in tamper-evident packaging, and all such features shall be prominently printed on the package and not obscured should any of the features be compromised.

Packaged and labeled drug shall be inspected during finishing operations to confirm that packages and containers have the proper labels. A representative sample shall be obtained at the conclusion of finishing operations and shall be visually inspected for correct labeling.

Appropriate expiration dating determined by stability testing shall be imprinted clearly on each package. The dating will be appropriate for the storage conditions the package may be exposed to. If the drug product is to be reconstituted, both the intact package and the reconstituted drug product expiration data shall be imprinted on the package.

### 1.8.7 Holding and Distribution

Each manufacturer will have written procedures describing the warehousing of drug products that will include the quarantine of drug products before release by the quality control unit. The drug products will be stored under appropriate conditions of temperature, humidity, and light assuring that the integrity of the drug product is not compromised by environmental conditions.

Similarly there shall be written procedures describing the distribution of drug product including a procedure whereby the oldest approved stock of drug product is distributed first. Temporary and appropriate deviations from this requirement are permitted.

There must exist a system in which each lot of drugs can be tracked, thereby facilitating the recall if necessary. The written instructions for implementing a recall must clearly define how the recalled lot(s) shall be implemented, including who will bear responsibility for each phase of the recall and how the recalled drug products shall be handled. A method to determine the effectiveness of the recall shall be established.

### 1.8.8 Laboratory Controls

The appropriate organizational unit shall determine any specification, standards, statistically based sampling plans, and test procedures to be used. These shall be reviewed and approved by the quality control unit for appropriate applicability and adequacy. Compliance with the written procedures used to assure the proper purity, identity, and strength of the final drug product, as well as proper labeling shall be documented at the time that the appropriate checks are made. Any deviation from established criteria is reason to quarantine and restrict from distribution any drug product pending review and release by the QAU, whose rationale for action will also be documented.

Scientifically sound and appropriate specifications, standards, sampling plans, and analytical procedures shall be established to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity. Testing procedures published by established independent organizations such as the Association of Analytical Communities (AOAC) may be cited, or independently derived testing procedures may be developed; however, in either case, the rationale and efficacy of specific methodology must be established and documented.

Written specifications for the receipt, quarantine, sampling, testing, and acceptance or rejection of raw materials will be followed. Instruments, apparatus, gauges, and recording devices shall be calibrated at suitable intervals in accordance with established written programs to maintain their appropriate levels of accuracy and precision. Instruments, apparatus, gauges, and recording devices that do not meet established specifications shall not be used. A record of

calibrations shall be maintained and instruments that do not meet established specifications shall be identified and securely isolated.

The satisfactory performance of each batch should be confirmed by established, written testing procedures, and no batch shall be released or distributed prior to confirmation by the QAU that it is in compliance with established criteria.

There should be written testing program designed to assess the stability characteristics of the drug products under various conditions. The results of such testing should be used to determine appropriate storage conditions expiration dates.

Reserves sample shall be maintained for periods appropriate relative to their expiration dates, typically 1 year past the expiration date of the last lot of the drug containing the active ingredient. The reserves sample shall consist of at least twice the quantity necessary for all tests required to determine whether the active ingredient meets its established specifications.

### 1.8.9 Records and Reports

If you don't write it down, you didn't do it. Good documentation ensures availability of data needed for validation, review, and statistical analysis. The data should be accessible in a format that lends itself to review and analysis such that the data may lead to modifications of established procedures.

Any record of production, control, or distribution is required to be maintained and that specifically associated with a batch of the drug product shall be retained for least 1 year after the expiration date of the batch or, in the case of certain OTC drug products lacking expiration dating, 3 years after the distribution of the batch.

All required records, or copies thereof, shall be readily available for authorized inspection during the retention period at the establishment where the activities occurred. The records may be photocopied or reproduced in other fashion as part of the inspection. Records can be immediately retrieved from an alternate location by computer or other electronic means should be deemed in compliance.

Written records shall be maintained such that the data can be used for evaluating, at least annually, the quality standards of each drug product to determine the need for any changes in the drug product specifications or of the manufacturing or the control procedures. Written procedures must be in place to review a representative number of batches either approved or rejected and, where applicable, all records associated with said batches. A review procedure of complaints, recalls, returned or salvage drug products, and investigations for each product shall be established. Procedures shall also be established to assure that responsible officials are notified in writing of any investigations, any recalls, reports of special observations issued by the FDA, or any regulatory actions relating to cGMPs brought by the FDA.

Records must show the capital equipment cleaning and use, except for routine maintenance such as lubrication and adjustments. The persons performing and checking the cleaning and maintenance performed shall date and initial the log, indicating that the work was performed at the time such observations are made. Entries in the log should be in chronological order.

Records shall be kept of all component, drug product container, closure, and labeling materials. These records shall include the results of a test or examination performed and the disposition of rejected components, drug product containers, closure, and labeling.

**Master production and control records** for each drug product including each batch size shall be prepared, dated, and signed (full signature) by one person and independently checked, dated, and signed by a second person. Written procedures shall be established, describing the preparation of master production and control records and said procedures shall be followed. Master batch control records shall include the name and strength of the product and a description

of the dosage form, the name and quantity of each active ingredient per unit of the drug product and a statement of the total weight or measure of any dosage unit, a complete list of components sufficiently specific to indicate any special quality characteristic, manufacturing statement weight or measure of each component, any calculated excess of component, theoretical weight, and a theoretical yield including the maximum and minimum percentages of theoretical yield beyond which investigation is required according to 21 CFR 211.192.

**Batch production and control records** shall be prepared for each batch of drug product produced and shall include complete information relating to the production and control of each batch, with an accurate representation of the appropriate master production or control record and recordings of lot identification for each component used. The records shall be checked for accuracy, dated, and signed. Documentation shall be maintained of each significant step in the manufacture, processing, packaging, or holding of the batch. The information recorded shall include dates, identity of major equipment and lines, weights, measures and lot numbers of components in process and laboratory control results.

It shall be recorded that the packaging and labeling area is inspected before and after use, including complete labeling control records and specimens of same identification of persons performing and directly supervising and checking each significant step in the packaging and labeling operation.

All production records shall be reviewed and approved by the quality control unit to determine compliance with all established approved written procedures before any batch is released or distributed.

Laboratory records shall include complete data derived from all tests necessary to ensure compliance with establish specifications and standards.

Distribution records shall contain the name and strength of the product and description of the dosage form, name and address of the consignee, date and quantity shipped, and lot or control number of the drug product.

**Complaint files** shall be maintained. There shall be written procedures describing the handling of all written and oral complaints regarding the drug product. The procedure will include provisions for review by the quality control unit and for review to determine whether the complaint represents a serious and unexpected adverse drug experience that is required to be reported to the FDA. A written record of each complaint shall be maintained in a file designated for drug product complaints. Access to this record will most likely be the first request of an FDA representative on a visit to the manufacturing facility.

### 1.8.10 Returned and Salvaged Drug Products

Drug products returned from the market shall be identified and quarantined pending determination of their disposition. If there is any doubt of their safety, identity, strength, quality, or purity, return drug product shall be destroyed unless subsequent testing proved the drug product meets appropriate standards of safety, identity, strength, quality, and purity. Records of returned drug product shall be maintained and shall include the name and labeled potency of the drug product dosage form, lot number, reason for the return, quantity return, date of disposition, and ultimate disposition of the returned drug product.

### 1.8.11 Other

While description of the cGMP in manufacturing, processing, packaging, and holding of drugs is generally limited to the 10 categories above, it is important to understand that the regulatory arena is a dynamic, changing environment. Toward that end, it is beneficial to adopt a broader

view to anticipate possible changes. Two categories are gaining wider attention in the processing world in areas of quality issues, and a brief description of change control and validation here is in order.

#### 1.8.11.1 Change Control

A formal change control system that evaluates and documents all changes that could impact the intermediate and final products should be established. The system shall include approval of changes in specifications, analytical methods, facilities, raw materials, support system, processing steps, labeling, and packaging. Any proposals for GMP relevant changes should be drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the quality unit(s).

#### 1.8.11.2 Validation

There are two ways to ensure the complete integrity of the final drug product: verify or validate. Verifying would involve the destructive testing of each and every unit. Validating a process ensures that by following the validated, written procedure, the ultimate drug product will meet all required specifications. The approach to validation, including the validation of production processes, cleaning procedures, analytical methods, in-process control test procedures, computerized systems, and persons responsible for design, review, approval, and documentation of each validation phase, should be documented.

The critical parameters/attributes should normally be identified during the development stage or from historical data, and the necessary ranges for the reproducible operation should be defined. This should include:

1) Process parameters that could affect the critical quality attributes must be identified.
2) The range for each critical process parameter expected to be used during routine manufacturing and process control must be determined.

Validation should extend to those operations determined to be critical to the quality and purity of the drug product.

## 1.9 Compliance

The FDA conducts regular inspections for a variety of reasons under the general authority granted by FD&C Act Sections 702 and 704, which allows it to conduct investigations and collect samples of suspected drugs. The goal of the FDA's inspections is to minimize consumer exposure to adulterated drug products. Inspections may be routine GMP reviews, in response to a specific complaint, re-inspection after a warning letter, a check of recall effectiveness, or PAI for an NDA.

FDA conducts inspections of establishments that manufacture drug products for use inside and outside the United States and foreign establishments that intend to conduct clinical studies on their new drug products or market their products inside the United States.

Some of the administrative tools available to the FDA to ensure compliance with cGMPs include notices of observations (Form 483), warning letters, recalls, product withdrawal, drug license suspension or revocation, debarment, penalties, and disqualifications.

The FDA can invoke both civil and criminal judicial enforcement. In general, criminal sanctions against persons are only used when a prior warning or other type of notice was issued and failure to take corrective action exists.

FDA enforcement options include seizure, wherein it may order a halt to production of a drug manufacturing facility when the product is held in an unacceptable environment. Quarantining

a warehouse is considered a "mass seizure" as it may include products that are not subject to contamination. A seizure may be specific for a product if, for example, labeling is noncompliant. At the same time a seizure is made, further injunctive action may be taken. These recommendations are made by the FDA compliance officer in district management. They are promptly acted upon by the Division of Compliance Management and Operations (DCMO).

An injunction is initiated to stop or prevent violation of the law; it is not necessary to show that the law has been violated, only to show that there is a likelihood that it may be violated if an injunction is not entered. An injunction does not preclude additional or concurrent action such as recall or seizure. Inspection warrants may be requested when inspection has been refused completely or when faced with refusals in limited areas.

Civil penalties are provided for and may be brought in any US District Court within whose jurisdiction, any act or omission constituting a violation, may have occurred. Such action may be taken for, among other infractions, failure to give notification or to take corrective action as required, the introduction or delivery of a noncompliant product into interstate commerce, the failure to properly maintain records or to permit inspections, nonresponse to prior warning/notice, failure to report, or failure ahead of obtaining product certification before distribution of the product.

The FDA is authorized to conduct inspections on factories, warehouses, establishments, vehicles, and all pertinent equipment, finished and unfinished materials, containers, and labeling where food, drugs, devices, or cosmetics are manufactured or held. The FDA authority extends to inspection of clinical laboratories and clinical study facilities as well as contract test laboratories, clinical study monitors, clinical study sponsors, and IRBs. The FDA is constrained to "reasonable" inspections, that is, inspection at reasonable times, within reasonable limits and in a reasonable manner.

Announced inspections are generally expected by the company and may include PAI requested by the company or international inspections. Notification is generally a few weeks before the inspection.

Unannounced inspections are conducted for specific reasons such as a product recall or a recall effectiveness check. It may be as a response to some complaint or as part of an FDA routine compliance inspection program.

During an inspection, the FDA inspector can review and inspect any and all documents related to the product under question. The inspector however cannot inspect and review financial or pricing data, personal data, sales data, and research data (unless related to the product safety).

At present the FDA uses a systems approach program for compliance inspections as opposed to the top-down approach and bottom-up approach previously employed. System inspections fall into six categories.

### 1.9.1 Quality System

The quality system is inspected to ensure compliance with cGMPs, internal procedures, and established specifications. The system includes the quality control unit, all product defect evaluations, and evaluation of return and salvaged drug products.

### 1.9.2 Facilities and Equipment System

Similarly the inspection activities of facilities and equipment systems and resources used in production of drugs or drug products are expected to ensure compliance with approved internal procedures and cGMP regulations.

Typical targets would be maintenance documents and records, equipment qualifications, calibration, preventative maintenance, cleaning validation records, and utility validations and calibrations.

### 1.9.3 Materials System

Review of material systems includes the control of finished products, incoming raw materials, containers, and closures.

### 1.9.4 Production System

When examining the manufacture of drugs and drug products, inspection of batch compounding, dosage form, production and process sampling and testing, and process validation may be performed.

### 1.9.5 Packaging and Labeling System

Records of the packaging and labeling process, printed labels and packaging materials, receiving examination, and uses of labels and packaging materials may be inspected.

### 1.9.6 Laboratory Control System

This inspection may include the examination of personnel to establish education and training qualifying them for their work assignments. Production, control, or distribution records that should be maintained by cGMP regulation should include inspection audit.

#### 1.9.6.1 Inspection Strategies

The FDA inspects drug manufacturers in three ways:

1) Full system inspection – includes a minimum of four of the six systems, one of which must be quality, to ensure that all systems are under control and comply with cGMP regulations.
2) Abbreviated inspection – includes the quality system and one other of the six systems.
3) Compliance inspections – conducted to evaluate or verify that corrective actions have been taken after regulatory action as a result of some aspect being found to be noncompliant. Specifically, areas that have been found deficient and subjected to corrective actions and systems are used to determine the overall compliance status of the firm after the corrective actions are taken. Manufacturers are expected to bring all deficiencies into compliance, not just those cited by FDA Form 483. The compliance inspection also includes cause inspections that investigate specific problems that come to the FDA's attention. The problems may be indicated in the Field Alert Report (FAR).

#### 1.9.6.2 Inspection Process

In any inspection, the inspector is required to present two pieces of picture ID to the firm. A responsible individual should be designated to meet with the inspector and he can examine and record the credential information but cannot make a copy of the credentials. The FDA expects senior management and responsible officials to attend the opening and closing (exit interview) meetings.

At the opening meeting the FDA inspectors will present Notice of Inspection, Form 482, and explain the reasons for their visit. The inspectors should be provided with a quiet space and all requested documents and records to review. Inspectors may request a tour of the facility, and the company should ensure that all required personnel are present to answer questions.

The FDA may also take photographs and obtain samples; if the company resists an inspection, warrant can be sought from FDA headquarters.

At the conclusion of the inspection Form 483, a Notice of Observations will be issued that include significant observations made during their visit. At this meeting the inspector will go through each observation in finding and giving the company the opportunity to respond. Corrections made during the FDA visit will be noted on Form 483; the observations will remain on the list. Findings are listed in order of their significance on Form 483. Upon completing the review, the inspector will issue a copy of the observations to the highest-ranking officer in the firm. The firm is not required to respond to the 483, but it is industry practice to send the FDA letter within 15 calendar days detailing corrections or correction plans.

#### 1.9.6.3 Warning Letters

A warning letter is a written communication from FDA to an individual or firm indicating that one or more products, practices, processes, or other activities are in violation of the FD&C Act. The FDA will issue a warning letter to the firm if the deficiencies are serious or if the product can cause a serious public health risk and if the firm continues violative conduct. The firm must respond to the warning letter as soon as possible.

#### 1.9.6.4 Establishment Inspection Report

The EIR is essentially a diary of the inspection and is prepared after the conclusion of the inspection. It will include the reason for the inspection, the date of inspection, the scope of the inspection, what type of inspection was performed as well as the findings and observations, and a brief description of the product and processes. The conclusion of the inspection is included in the EIR and will be one of three categories:

1) No Action Indicated (NAI): no significant or no cGMP deviations.
2) Voluntary Action Indicated (VAI): cGMP deviations the firm can correct that do not compromise public health or safety.
3) Official Action Indicated (OAI): this is requested by the FDA due to the serious nature of the findings indicating that deviations may affect safety.

Appropriate enforcement action for the recommended official action indicated will be assigned by the agency. Further violation of the law by the company may result in the FDA asking the court to hold company in civil or criminal action of the decree. Under consent decree conditions, the FDA may order the firm to cease operation if it is still not in compliance with cGMP regulations.

## 1.10 Electronic Records and Electronic Signatures

Under 21 CFR 11, 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 are established. This does not, however, apply to electronic transmissions of paper records.

### 1.10.1 Electronic Records

#### 1.10.1.1 Closed Systems

Closed systems used to create, modify, maintain, or transmit electronic records shall safeguard the system to ensure the authenticity, integrity, and the confidentiality of electronic records by

employing procedures and controls to ensure that the records cannot readily be altered. Such procedures and controls shall include the following:

- Validation of systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records.
- Generation and protection of records to enable their accurate retrieval throughout the records retention period.
- Limit system access to authorized individuals and use secure, computer-generated, time-stamped audit trails to document actions that create, modify, or delete electronic records.
- Verify that persons who develop, maintain, or use electronic record/electronic signature systems have the education, training, and experience to perform their assigned tasks. Establish controls over the access to and distribution of system operation and maintenance documentation. Implement change control procedures to maintain an audit trail that documents modification of systems documentation.

#### 1.10.1.2 Open Systems

Use of open systems to create, modify, maintain, or transmit electronic records shall employ procedures and controls designed to ensure the authenticity, the integrity, and the confidentiality of electronic records from the point of their creation to the point of their receipt. Such procedures may include document encryption and use of appropriate digital signature standards.

### 1.10.2 Electronic Signatures

A unique electronic signature shall be to one individual and shall not be reused by, or reassigned to, anyone else, and that individual's identity must be verified prior to sanction of its use. Biometrics such as fingerprint or scanned iris patterns may be used. Electronic signatures that are not based upon biometrics shall employ at least two separate components to establish identity, such as an identification code and a password. Such two component systems must be used only by their owners. The integrity of the generation of passwords or identification must be confirmed by periodic testing.

## 1.11 Employee Safety

While the FDA is the lead regulatory agency with regard to pharmaceuticals, its focus is on the safety and efficacy of the drug product, not on the hazardous conditions that employees in the industry may encounter. The agency primarily responsible for employee safety is the Occupational Safety and Health Administration (OSHA), housed within the US Department of Labor. The agency has overarching responsibility for employee safety in all industries, issuing regulations in response to diverse threats to health as varied as requiring respirators for manned entrance to confined chambers, hard hats and steel-toed shoes for construction sites, and ergonomic adjustments to prevent repetitive injuries in offices and assembly lines. While each of these (among many other conditions) may at some time apply to the pharmaceutical industry, we shall illustratively concentrate on one: process safety management of highly hazardous chemicals 29 CFR 1910.

Drug products and their in-process antecedents are chemicals to which the human body may react, not always in a favorable manner. While it may not be possible to eliminate exposure to known or potential hazardous chemicals in the workplace, it is in everyone's best interest to

limit exposure to levels below which the body can resist the deleterious effects, that is, below the threshold level.

The most obvious chemical hazards seem quite straight forward, if extreme exposure to a chemical results in near instantaneous death, acute toxicity. That may have sufficed in the not too distant past, but we have better understanding of how chemicals may affect our bodies and realize that the harmful effect may not appear long after exposure, like asbestosis, or cumulatively, like cigarette smoking, a chronic toxicity. Some chemicals, like aflatoxin, are both chronic and acute, killing at low dosages, but also carcinogenic. Death is not the only harmful outcome. Methanol may not kill at low doses, but neurologic manifestations including seizures, symptoms of amyotrophic lateral sclerosis, and blindness may present shortly after ingestion.

We now understand that there are chemicals whose damage may not present for a generation, or present without an obvious link to chemical exposure. Genotoxic chemicals are destructive to our genetic material, DNA (deoxyribonucleic acid) and RNA (ribonucleic acid), which may cause mutations. Fertility may be impaired. Teratogenic toxins may not affect those directly exposed, but cause birth defects. The human body has the ability to tolerate many of these chemicals at low levels so it is important to know the threshold levels above which harmful effects may be experienced.

For many, if not most, of the chemicals to which we are exposed in the workplace, critical data has been compiled in a safety data sheet (SDS). This technical document lists many of the chemical properties of the chemical and the known effects on human health. It provides detailed information about the health effects of exposure; a hazard evaluation relating to handling, storage, or use; measures to protect workers at risk of exposure to the chemical; and emergency procedures to follow in the event of exposure. An SDS may be considered the starting place when evaluating hazard risks of chemicals.

OSHA, through 29 CFR 1910.119, addresses risks to employees by catastrophic release of hazardous chemicals from:

- Concentrations of chemicals above the threshold levels.
- Flammable liquid or gas in excess of 10 000 lb in one location.
- Hydrocarbon fuels used for workplace consumption.
- Flammable liquids stored or transferred below their boiling points in atmospheric tanks without refrigeration.

### 1.11.1 Process Safety Information

The employer shall complete a compilation of written process safety information before conducting any process hazard analysis to facilitate, identify, and understand the hazards posed by those processes involving highly hazardous chemicals. This process safety information shall include information pertaining to:

- Hazards of chemicals (suitable SDSs may be used) used or produced by the process, which shall include:
  - Toxicity information.
  - Permissible exposure (threshold limits).
  - Physical data (boiling point, flash point, etc.).
  - Reactivity data.
  - Corrosivity data.
  - Thermal and chemical stability data.

  - Hazardous effects of inadvertent mixing of different materials that could foreseeably occur.
- Process technology information
  - Flow diagram of the process.
  - Process chemistry (reactions that take place).
  - Maximum intended inventory (bulk storage).
  - Safe upper/lower limits for temperatures, pressures, flows, or compositions.
  - An evaluation of the consequences of deviations, including those affecting the safety and health of employees.
- Process equipment information
  - Construction material.
  - Piping and instrument diagrams.
  - Electrical classification.
  - Relief system design and design basis.
  - Design codes and standards.
  - Material and energy balances for processes (built post 26 May 1992).
  - Safety systems (interlocks, detection, or suppression).

For existing equipment designed and constructed per superseded codes, standards or practices, the employer will certify that the equipment is designed, maintained, and operating in a safe manner.

### 1.11.2 Process Hazard Analysis

The employer shall perform an initial process hazard analysis (hazard evaluation) that is appropriate to the complexity of the process and shall identify, evaluate, and control the hazards involved in the process. The priority order for conducting process hazard analyses should be based on a rationale that includes such considerations as the extent of the process hazards, the number of potentially affected employees, and the operating history of the process.

One or more of the following methodologies shall be used: What-If, Checklist, What-If/Checklist, Hazard and Operability Study (HAZOP), Failure Mode and Effects Analysis (FMEA), Fault Tree Analysis, and/or an appropriate equivalent methodology.

The process hazard analysis shall address:

- The hazards of the process.
- The identification of any previous incident that had a likely potential for catastrophic consequences in the workplace.
- Engineering and administrative controls applicable to the hazards and their interrelationships (e.g. process monitoring and control instrumentation with alarms, hydrocarbon sensors).
- Failure of engineering and administrative controls consequences.
- Facility sitting.
- Human factors.
- A qualitative evaluation the possible safety and health effects of control failure on employees in the workplace.

A team with expertise in engineering and process operations, with at least one employee experienced and knowledgeable about the process being evaluated and one member knowledgeable in the specific process hazard analysis methodology used.

### 1.11.3 Operating Procedures

Written operating procedures will be developed and implemented by the employer to provide clear instructions for safely conducting processes that shall address:

- Steps for each operating phase:
  - Initial startup.
  - Normal operations.
  - Temporary operations.
  - Emergency shutdown including the conditions under which emergency shutdown is required, and the assignment of shutdown responsibility to qualified operators to ensure that emergency shutdown is executed in a safe and timely manner.
  - Emergency operations
  - Normal shutdown
  - Startup following a turnaround, or after an emergency shutdown
- Operating limits:
  - Consequences of deviation.
  - Steps required to correct or avoid deviation.
- Health and safety and considerations:
  - Properties of, and hazards presented by, the chemicals used in the process.
  - Precautions necessary to prevent exposure, including engineering controls, administrative controls, and personal protective equipment.
  - Control measures to be taken if physical contact or airborne exposure occurs.
  - Quality control for raw materials and control of hazardous chemical inventory levels.
  - Any special or unique hazards.
- Safety systems and their functions.

Operating procedures shall be readily accessible to employees. They shall be reviewed as needed to incorporate any changes to the operating processes.

The employer shall develop, document, and implement safe workplace practices for employees and contractors to control hazards during operations. These precautions may include lockout/tagout to prevent processes from proceeding while in an unsafe state or requiring a respirator and banning solo entry for confined space.

### 1.11.4 Training

Employees involved in or newly assigned to operate a process shall be trained in an overview of the process and in the operating procedures emphasizing the specific safety and health hazards, emergency operations, and applicable safe work practices. Refresher training shall be provided at least every 3 years. All training shall be documented stating the name of the employee, the date of training, and the means of verifying comprehension of the material.

### 1.11.5 New Facility Startup

#### 1.11.5.1 Pre-startup Safety Review

A safety review shall be performed when starting up a new facility or when modifications to an existing plant are extensive enough to require changes to the process safety information. It will ensure that prior to operation:

- Construction and equipment is in accordance with design specifications.
- Safety, operating, maintenance, and emergency procedures are adequate and in place.

- Process hazard analysis has been performed and recommendations have been resolved or implemented before startup.
- Training of each involved employee has been completed.

### 1.11.6 Mechanical Integrity

Mechanical integrity shall be checked for:

- Pressure vessels and storage tanks.
- Piping systems.
- Relief and vent systems.
- Emergency shutdown systems.
- Controls (including monitoring devices and sensors, alarms, and interlocks).
- Pumps.

Written Procedures

The employer shall establish and implement written procedures to maintain the ongoing integrity of process equipment.

Training for Process Maintenance Activities

The employer shall train each employee involved in maintaining the ongoing integrity of process equipment in an overview of that process and its hazards and in the procedures applicable to the employee's job tasks.

Inspection and Testing

Inspections and tests shall be performed on all process equipment and shall follow recognized and generally accepted good engineering practices. The frequency of inspections and process equipment tests shall be consistent with manufacturer's recommendations. Each inspection shall be documented.

Quality Assurance

Qualification that equipment is suitable for the process design specifications and is properly installed and consistent with manufacturer's instructions. Appropriate maintenance materials and spare parts are suitable for the process application.

### 1.11.7 Hot Work Permit

A permit shall be issued for hot work performed on or near a covered process. It shall document that prior to initiating work, proper fire prevention and protection procedures have been implemented, the dates the work is permitted, and the object upon which the hot work performed.

### 1.11.8 Management of Change

Written procedures shall be put in place to manage changes to all aspects of the covered process operation. Prior to any change the following considerations are to be addressed:

- Technical basis for change.
- Impact of change on safety and health.
- Modifications to the operating procedures.
- Time necessary for the change.
- Authorization requirements for the proposed change.

Employees affected by the change shall be informed and trained as necessary prior to startup of the process. If necessary, process safety information shall be updated.

### 1.11.9 Incident Investigation

Any incident that resulted in or could have resulted in a catastrophic release of highly hazardous chemicals in the workplace shall be investigated as promptly as possible but within 48 h of the incident. The incident investigation team shall contain at least one employee knowledgeable in the process involved and other persons with sufficient knowledge and experience to investigate and analyze the incident. An incident report shall include:

- Date of incident.
- Date investigation commenced.
- Description of the incident.
- Factors contributing to the incident.
- Recommendations resulting from the investigation.

The employer shall promptly address and resolve the incident report findings and recommendations documenting any corrective actions taken. The report shall be reviewed with all personnel whose tasks are relevant to the incident findings. The report shall be retained for 5 years.

### 1.11.10 Emergency Planning and Response

An emergency action plan shall be established for the entire plant. The plan shall include procedures for handling small releases. If applicable, hazardous waste and emergency response provisions shall apply 29 CFR 1910.120(a),(p), and (q).

### 1.11.11 Compliance Audits

Certification of compliance with regulatory provisions will be done at least every 3 years to verify that procedures and practices are adequate and implemented. The audit shall be conducted and reported by at least one person knowledgeable of the process. Any deficiencies in the report shall be corrected and documented.

## 1.12 US EPA

As manufacturing entities, pharmaceutical manufacturing facilities are subject to regulation by a variety of regulatory agencies not directly responsible for the production of safe, efficacious drug products. The EPA, specifically the Office of Compliance, Chemical Industry Branch, is tasked with enforcement of a number of statutes impacting drug manufacturing facilities. The EPA has, in the past, relied on a command and control approach to regulate industrial facilities, but now is combining its traditional method with innovative techniques such as self-assessments and facility management systems.

There is little correlation among the complex web of requirements that results from regulations originating independently that target the same medium or activity. Many industrial facilities have found that using a complete facility, the environmental management system (EMS) approach yields cost effective solutions for tackling all of the requirements as a complete facility solution instead of as individual components.

There are five major statutes that impact pharmaceutical manufacturing under the auspices of the EPA:

- Clean Air Act (CAA).
- Safe Drinking Water Act (SDWA).

- Resource Conservation and Recovery Act (RCRA).
- Emergency Planning and Community Right-to-Know Act (EPCRA).
- Clean Water Act (CWA).

A brief summary of the meaning and impact of these statutes will serve as an introduction to the understanding the scope of the Federal environmental regulations. State and local jurisdictions may also impact the facility, and all should be monitored to keep abreast of pending changes.

### 1.12.1 Clean Air Act

Clean Air Act Regulatory Requirements

- Title I: National Primary and Secondary Ambient Air Quality Standards (NAAQS)
  - The Air Quality Act of 1967 requires the designation of air quality control regions (AQCRs) based on "jurisdictional boundaries, urban-industrial concentrations, and other factors including atmospheric areas necessary to provide adequate implementation of air quality standards" [Section 107(a)(1967)].
  - Recognizing the deleterious effects of poor air quality on human health, NAAQS have been set for ozone, carbon monoxide, particulate matter <10 μm, sulfur dioxide, nitrogen dioxide, and lead. Of these, all but lead may have a significant impact on the pharmaceuticals industry.
  - Given the varying levels of pollutants among the regions, conformation to the regulations is site specific. Undergoing a new source review, permitting for "attainment areas" (where desirable air quality standards exist) would require installation of the best available control technology (BACT), whereas permitting for nonattainment areas (NAAQS are exceeded) would require installation of more stringent lowest achievable emission rate (LAER) technology.
  - Major pharmaceutical industry sources must, irrespective of location, comply with performance standards set by the EPA, referred to as new source performance standards (NSPS) applicable to new sources or modified facilities. Requirements include monitoring, recordkeeping, and reporting.
- Title III: National Emissions Standards for Hazardous Air Pollutants (NESHAP) and Maximum Achievable Control Technology (MACT) Standards
  - NESHAP refers to standards for a select group or hazardous air pollutants for which additional risk-based standards were developed prior to 1990s CAA amendments. Monitoring, recordkeeping, and reporting are required for these pollutants. 1990 CAA identified 189 hazardous air pollutants (HAPs) for which standards of performance were to be developed based upon maximum achievable technology, not risk.
  - Existing NESHAPs for HAPs on the 1990 list are still applicable, and the EPA set MACT standards applicable to specific industries for so-called hazardous organic NESHAPS (HON).
- Title V: Permitting Program
  - Defined the minimum standards and procedures for state-operating permit programs. This consolidates all of a source requirement into one permit. Any major source is required to obtain a permit.
  - Major sources emit or has potential to emit.
    - 10 tons per year (TPY) or more of any hazardous air pollutant.
    - 25 TPY or more of any combination of HAPs.
    - 100 TPY of any air pollutant.

  - Major sources in ozone nonattainment areas are defined as sources with the potential to emit.
    - 100 TPY or more of volatile organic compounds (VOCs), or nitrogen oxides ($NO_x$) in areas defined as moderate or marginal.
    - 50 TPY or more of VOCs or $NO_x$ in areas classified as serious.
    - 25 TPY or more of VOCs or $NO_x$ in areas classified as severe.
    - 10 TPY or more of VOCs or $NO_x$ in areas classified as extreme.
  - Other sources requiring permits regardless of source size include:
    - NSPS.
    - NESHAP.
    - PSD (Prevention of Significant Air Quality Deterioration)/NSR (New Source Review).
    - Acid rain.
- Title VI: Stratospheric Ozone Protection.
  - Provides for a phaseout of the production and consumption of chlorofluorocarbons (CFCs) and other chemicals that deteriorate the ozone layer.
- CAA Assessment Considerations
  - Many CAA requirements have been summarized into a comprehensive permit. The compliance assessor should review data derived from previous facility self-assessments.
- CAA regulatory requirements that may apply to the pharmaceutical industry.
  - 40 CFR Part 60
    - Subparts $D_a$, $D_b$, $D_c$, $K_b$, GG
  - 40 CFR Part 61
    - Subparts J, M, V, Y
  - 40 CFR Part 63
    - Subparts H, I, Q
  - 40 CFR Part 68
  - 40 CFR Part 82

### 1.12.2 Safe Drinking Water Act

Safe Drinking Water Act Regulatory Requirements

- SDWA mandated that EPA regulate to protect human health from contaminants in drinking water.
  - EPA developed drinking water standards.
    - Joint federal/state system to ensure compliance.
  - EPA to protect underground source of drinking water through control of underground injection of waste.
- Underground Injection Control Program
  - Permit program with five classes of injection wells.
    - Class I – Large volumes of hazardous and nonhazardous waste into deep, isolated rock formation separated from drinking water by impermeable clay.
    - Class II – Inject fluids, mostly brine, associated with oil and gas extraction. About 10 barrels of brine are required to yield 1 barrel of crude oil.
    - Class III – Inject super-hot steam or water into mineral formations that are then pumped to the surface and extracted. The fluid is treated and reinjected into the same formation. More than 50% of the salt and 80% of the uranium produced in the United States is obtained this way.

    - Class IV – hazardous or radioactive waste is injected into or above underground sources of drinking water. These wells are banned under UIC (Underground Injection Control) program.
    - Class V – other injection methods, some quite technologically advanced, but some low-tech holes in the ground. Generally shallow and dependent upon gravity to drain into the ground.
- Public Water System Program
  - Primary and secondary drinking water regulations.
    - Primary have adverse effects on human health.
    - Secondary affect aesthetic quality of water.
- Not EPA enforceable, but states may enforce.
  - Established testing procedures, monitoring requirements, notifications, and reporting.
- SDWA Assessment Considerations
  - If the facility has its own source of potable water and provides water to 25 unique individuals for 6 months, it is subject to national drinking water standards, in which case it must be monitored for required contaminants, is required frequency using an approved laboratory and tests, and is maintaining records.
- SDWA Regulatory Requirements
  - 40 CFR Part 141
    - Subparts B, G, F, C, H, I, D
  - 40 CFR Part 143
  - 40 CFR Part 144

### 1.12.3 Resource Conservation and Recovery Act

Resource Conservation and Recovery Act Regulatory Requirements:

- Amendment of the Waste Disposal Act of 1965 addresses hazardous and solid waste management. The Hazardous and Solid Waste Amendment (HSWA) of 1984 strengthened RCRA's provisions and added governance of Underground Storage Tanks. The objective is to protect human health and to conserve energy resources and valuable materials. A cradle-to-grave system was implemented, and some states are implementing more stringent regulations.
- Hazardous Waste Generation
  - Determination of what waste is hazardous is the initial step in determining compliance and is detailed in 40 CFR 261. A waste may not be on the federal list, but exist on a state list of hazardous materials.
  - Secondary materials generated by the drug industry may be classified as solid wastes or potentially hazardous waste. Potentially hazardous waste that is to be recycled is subject to rules about accumulation and disposal.
  - Generators are classified by the amount of waste generated.
    - Large quantity generator (LQG).
    - Small quantity generator (SQG).
    - Conditionally exempt small quantity generator (CESQG).
  - Generators may accumulate hazardous waste for up to 90 days (180 for small quantity generators).
- Hazardous Waste Transportation Regulations
  - Under 40 CFR 262, transporter must obtain an EPA identification number and specific manifesting and recordkeeping requirements.
- Hazardous Waste Treatment, Storage, and Disposal Regulations

  - Any facility that treats, stores, or disposes (TSDF) of hazardous waste is subject to requirements under 40 CFR 264 and 265.
  - Must obtain an operating permit and abide by TSD regulations, far more extensive than those for generators and transporters and include technical and administrative requirements.
- Land Disposal Restrictions (LDRs)
  - Hazardous waste is largely prohibited from land disposal.
    - Comply with a specified treatment standard.
    - Dispose in a "no migration unit."
- Underground Storage Tank (UST) Regulations
  - USTs containing hazardous materials and petroleum are regulated under 40 CFR 280. States have discretion to develop their own UST regulatory program.
  - In 1998 it was required that all existing USTs must add:
    - Spill, overfill, and corrosion protection
    - Close the existing UST
    - Replace with a new UST
- RCRA Assessment Considerations
  - Key Components
    - Knowledge of facility
    - Document review
      - Facility maps, organization charts, manuals, photos, etc.
    - Assessment plan
      - Trace Material Flow Through the Plant
- RCRA Regulatory Requirements
  - 40 CFR 261.5 and 262.34
  - 40 CFR 262
  - 40 CFR 263
  - 40 CFR 264 and 265
  - 40 CFR 268
  - 40 CFR 280

### 1.12.4 Emergency Planning and Community Right-to-Know Act

Emergency Planning and Community Right-to-Know Act Regulatory Requirements, also known as Superfund Amendments and Reauthorization Act (SARA) Title III, is intended to inform the general public emergency planning and emergency response personnel about potential hazards in the community.

- Hazardous Substance Notification
  - A release means any spilling, leaking, pumping, emitting, emptying, discharging, injecting, escaping, leaching dumping, or disposing of into the environment, excluding exposure only within a workplace.
  - Facilities releasing a hazardous substance equal to or exceeding the reportable quantity (RQ) must immediately notify the National Response Center at 800/424-8802 or 202/426-2675.
  - RQ ranges from 1 to 5000 lb.
- Emergency Planning and Notification
  - Release of a quantity equal to or exceeding its threshold planning quantity of an extremely hazardous substance shall notify the state emergency response commission (SERC) or governor (if no commission) and the local emergency planning commission (LEPC).

- Hazardous Chemical Reporting: Community Right-to-Know
  - Pharmaceutical facilities must submit a Safety Data Sheet (SDS) or a list of hazardous chemicals for which SDSs are required to the SERC, LEPC, and the fire department.
  - They must also submit a Tier I (Aggregate Information by Hazard Type) or Tier II (Specific Information by Chemical) form for all hazardous chemicals (above a threshold of 500 lb), indicating the aggregate amount at the facilities classified by hazard category.
  - If any agency requests a Tier II report, it must be submitted within 30 days of the request. A Tier II form may be submitted in lieu of a Tier I form.
- Toxic Chemical Release Inventory
  - A submission of the Toxic Chemical Release Inventory (TRI) reporting form (Form R) is required. This is a compilation of release information of toxic compounds into the community.
  - A complete Form R is required annually for each toxic chemical manufactured, processed, or otherwise used at each covered facility.
- EPCRA Assessment Considerations
  - Activities will focus primarily on reporting and recordkeeping.
  - Form R is highest profile reporting requirement.
- EPCRA Regulatory Requirements
  - 40 CFR 302
  - 40 CFR 355
  - 40 CFR 370
  - 40 CFR 372

### 1.12.5 Clean Water Act

#### 1.12.5.1 Clean Water Act Regulatory Requirements

The intent is to restore and maintain the physical and biological integrity of the nation's water. Both direct and indirect discharges of waters are regulated.

- Effluents Limitations Guidelines and Categorical Pretreatment Standards
  - Establishes limitations for direct and indirect discharges.
  - Biological oxygen demand (BOD).
  - Chemical oxygen demand (COD).
  - Total suspended solids (TSS).
  - pH.
  - Priority and nonconventional pollutants.
- National Pollutant Discharge Elimination System (NPDES)
  - Controls indirect discharges by permits.
    - Individual – specific facility.
    - General – category of similar discharges within an area.
- Pretreatment program.
  - Controls direct discharges.
  - Goals
    - Prevent damage to municipal wastewater treatment plants.
    - Prevent pollutants from passing through the treatment plant untreated.
    - Encourage reuse and recycling of municipal and industrial sludge.
- Policy on Effluent Trading in Watersheds
  - Water quality standards must be met and technology-based requirement remain in place.
  - Effluent trading potentially offers a number of economic, environmental, and social benefits.
- Spills of Oil and Hazardous Substances

  - Prohibits oil discharges
- Oil pollution prevention
  - Establishes procedures to prevent discharge of oil.
- Reportable Quantities for Hazardous Substances
  - Designates hazardous substances and reportable quantities.
- CWA Assessment Considerations
  - Verify facility's operations are properly regulated by the permit and that monitoring results are representative of the facility's operations.
- CWA Regulatory Requirements
  - 40 CFR 439
  - 40 CFR 110
  - 40 CFR 112
  - 40 CFR 116

## 1.13 Process Analytical Technology

Process Analytical Technology (PAT) is not strictly a regulatory issue. It is an FDA Guidance establishing a risk-based framework that is intended to support innovation and efficiency in pharmaceutical product development, manufacturing, and quality assurance, working within existing regulations. It is founded on process understanding to facilitate innovation and risk-based regulatory decisions by industry and the agency. The framework has two components:

1) A set of scientific principles and tools supporting innovation.
2) A strategy for regulatory implementation that will accommodate innovation.

The regulatory implementation strategy includes creation of a PAT Team approach to CMC review and cGMP inspections as well as joint training and certification of PAT review and inspection staff.

The FDA considers PAT to be a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e. during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality. A concise summation might be: know the product/process better and all will be well, that is, by better understanding the drug product and process, more effective tools can be brought to bear on the (newly discovered) critical control points with the ultimate result of delivering a better quality product more efficiently and at lower cost. The tighter controls would also (de facto) meet regulatory requirements.

This approach has not been widely adopted by the industry, not so much because of resistance, but rather because of the complexity, a lack of knowledgeable personnel, and uncertainty of regulatory implementation and acceptance. A broader view of reading the guidance may find intimations of the iterative quality approach of the International Organization for Standardization (ISO [4]). If so, that may ease the industry into broader implementation.

### 1.13.1 Process Understanding

By FDA definition, a process is generally considered well understood when

- All critical sources of variability are identified and explained.
- Variability is managed by the process.
- Product quality attributes can be accurately and reliably predicted.

In the FDA guidance, variability (e.g. in raw materials), caused by insufficiently understood chemical and mechanical attributes, is "adjusted" by experienced formulators and benchtop analyses. Better understanding of the unknowns would lead to real-time detection during production of these variations and allow instantaneous adjustments to process conditions, thus ensuring quality drug products that meet all specifications, thereby clearing regulatory hurdles.

By implementing during product development phase an experimental design to examine the effects of varied physical characteristics in real time on a small scale, transfer from bench to pilot plant and/or production would be optimized.

### 1.13.2 Principles and Tools

Currently, most unit operations are performed on a time basis that does not take into account physical, chemical, or biological variability. It is promulgated that proper implementation of PAT tools would lend greater understanding and therefore enable optimization. The PAT toolkit includes:

- Multivariate Tools for Design, Data Acquisition, and Analysis
  - Pharmaceutical processes and products are complex multi-factorial systems, therefore, to understand the impact of varied moieties (parts or functional groups of organic molecules), a multivariate mathematical analysis of the effect of variability on process/product characteristics would be key.
- Process Analyzers
  - Much advancement in the development of process analyzers, including the ability, in some analyzers, to nondestructively determine biological, chemical, and physical attributes of the materials being processed.
  - Measurements may be made:
    - At-line, in close proximity to the process stream.
    - Online, where sample is diverted (and may be returned).
    - Inline, where sample is not removed from process stream.
  - Much more rapid results vs. sample removal to a laboratory for analysis and, indeed, much more data, the volume of which would be controlled by computer-based knowledge systems.
  - Proper design of process equipment and placement of analyzer is critical to ensure that the data collected is relevant.
- Process Control Tools
  - Once the critical attributes have been determined and process analyzers are properly in place and detecting critical parameters, process controls must be designed that will in real time provide adjustments to the operation(s) controlling all of the critical parameters.
  - Use the cumulative data to construct algorithms that enable the process controllers to adjust operations to achieve an endpoint of product quality attribute(s) rather than an endpoint based on time.
  - Implementation across the manufacturing platform would yield vast quantities of real-time data that could be used to fine-tune and optimize the final drug product attributes.
- Continuous Improvement and Knowledge Management Tools
  - In short, knowledge is power.
    - The more relevant data collected, the better quality final drug product.
    - Collection of data over the lifecycle of the product, in addition to improving quality, would facilitate regulatory evaluation of postapproval changes.

Risk-Based Approach

Given an inverse relationship between the level of process understanding and the risk of producing a poor product for a defined system, it should be possible to develop less stringent regulatory approaches to manage change requests. Risk-based analysis and management may form a separate system.

Integrated Systems Approach

Advances in information gathering and dissemination drive a push for an integrated approach to drug product development, as opposed to a handoff from one department to another. Development, manufacturing, quality assurance, and information management should work together as a team in as early a stage as possible. Toward that end, the FDA has developed a new regulatory strategy that includes a PAT team approach to joint training, certification, CMC review, and cGMP inspections.

Real-Time Release

The FDA has indicated that it is willing to validate real-time release based on a combination of in-process controls and assessed material attributes. In real-time release, material attributes as well as process parameters are measured and controlled.

### 1.13.3 Strategy for Implementation

The FDA believes that current regulations are broad enough t allow implementation of PAT, but understands that flexibility, coordination, and communication is critical.

The FDA strategy includes:

- A PAT team approach for CMC review and cGMP inspections.
- Joint training and certification of PAT review, inspection, and compliance staff.
- Scientific and technical support for the PAT review, inspection, and compliance staff.
- The recommendations provided in their guidance.

#### 1.13.3.1 PAT Regulatory Approach

One goal of the guidance is to tailor the FDA's usual regulatory scrutiny to meet the needs of PAT-based innovations that:

- Improve the scientific basis for establishing regulatory specifications.
- Promote continuous improvement.
- Improve manufacturing while maintaining or improving quality.

## 1.14 Conclusion

This chapter is intended to be a broad overview of the regulatory aspects of pharmaceutical manufacturing. As such, I have focused on the regulatory agencies of the United States, embodied in the CFR.

There are independent organizations that contribute to, and in fact are indispensable to, the regulatory environment. Listed below are a few broken into rough categories though they often overlap with other designations.

## References

1 United States Pharmacopeia (USP) – annual compendium of drug information. www.usp.org (accessed 12 December 2017).
2 AOAC International – publishes Official Methods of Analysis of the AOAC. www.aoac.org (accessed 12 December 2017).

3 International Conference on Harmonization (ICH). www.ich.org (accessed 12 December 2017).
4 International Organization for Standardization (ISO) – also harmonization. https://www.iso.org/home.html (accessed 12 December 2017).

## Further Reading

American Society for Quality (ASQ). https://asq.org.in/ (accessed 12 December 2017).
ASTM International – wide ranging international standards organization. www.astm.org (accessed 12 December 2017).
International Society for Pharmaceutical Engineering (ISPE) – Guides. www.ispe.org (accessed 12 December 2017).
National Formulary (NF) – publishes in conjunction as the USP-NF. This pharmacopeia has a role in U.S. Law for drugs that do not conform to USP-NF standards. www.uspnf.com (accessed 12 December 2017).