PART I

Preliminaries

CHAPTER 1

Introduction

1.1 WHAT ARE CLINICAL TRIALS?

Clinical trials are clinical investigations. They have evolved with different meanings by different individuals and organizations at different times. For example, Meinert (1986) indicates that a clinical trial is a research activity that involves administration of a test *treatment* to some *experimental unit* in order to *evaluate* the treatment. Meinert (1986) also defines a clinical trial as a planned experiment designed to assess the efficacy of a treatment in humans by comparing the outcomes in a group of patients treated with the test treatment with those observed in a comparable group of patients receiving a control treatment, where patients in both groups are enrolled, treated, and followed over the same time period. This definition indicates that a clinical trial is used to evaluate the effectiveness of a treatment. Piantadosi (1997) simply defined a clinical trial as an experimental testing of medical treatment on human subjects. On the other hand, Spilker (1991) considers clinical trials as a subset of clinical studies that evaluate investigational medicines in phases I, II, and III clinical studies which are the class of all scientific approaches to evaluate medical disease prevention, diagnostic techniques, and treatments. This definition is somewhat narrow in the sense that it restricts the clinical investigation to be conducted by pharmaceutical companies during various stages of clinical development of pharmaceutical entities which are intended for marketing approval. The Code of Federal Regulations (CFR) defines a clinical trial as the clinical investigation of a drug that is administered or dispensed to or used involving one or more human subjects (21 CFR 312.3). Three important key words in these definitions of clinical trials are *experimental unit*, *treatment*, and *evaluation* of the treatment.

1. *Experimental Unit.* An *experimental unit* is usually referred to as a subject from a targeted population under study. Therefore, the experimental unit is usually used to specify the intended study population to which the results of the study are inferenced. For example, the intended population could be patients with certain diseases at certain stages or healthy human subjects. In practice, although a majority of clinical trials are usually conducted in patients to evaluate certain test treatments, it is not uncommon that some clinical trials may involve healthy human subjects. For example, at very early phase trials of clinical

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development, initial investigation of a new pharmaceutical entity may involve only a small number of healthy subjects, say, fewer than 30. Large primary prevention trials are often conducted with healthy human subjects with a size of tens of thousands of subjects. See, for example, *Physician's Health Study* (PHSRG, 1989), *Helsinki Health Study* (Frick et al., 1987), *Women's Health Trial* (Self et al., 1988), and *Women Health Initiative Study* (Women Health Initiative Study Group, 1998).

2. *Treatment.* In clinical trials a *treatment* can be a placebo or any combination of a new pharmaceutical identity (e.g., a compound or drug), a new diet, a surgical procedure, a diagnostic test, a medial device, a health education program, or no treatment. For example, in the *Physician's Health Study*, one treatment arm is a combination of low-dose aspirin and beta carotene. Other examples include lumpectomy, radiotherapy, and chemotherapy as a combination of surgical procedure and drug therapy for breast cancer; magnetic resonance imaging (MRI) with a contrast imaging agent as a combination of diagnostic test and a drug for enhancement of diagnostic enhancement; or a class III antiarrhythmic agent and an implanted cardioverter defibrillator as a combination of a drug and a medical device for treatment of patients with ventricular arrhythmia. As a result, a *treatment* is any intervention to be evaluated in human subjects regardless of whether it is a new intervention to be tested or serves as a referenced control group for comparison.

3. *Evaluation.* In his definition of clinical trials, Meinert (1986) emphasizes the *evaluation* of efficacy of a test treatment. However, it should be noted that the assessment of safety of an intervention such as adverse experiences, elevation of certain laboratory parameters, or change in findings of physical examination after administration of the treatment is at least as important as that of efficacy. Recently, in addition to the traditional evaluation of effectiveness and safety of a test treatment, clinical trials are also designed to assess quality of life, pharmacogenomics, and pharmacoeconomics such as cost-minimization, cost–effectiveness, and cost–benefit analyses to human subjects associated with the treatment under study. It is therefore recommended that clinical trials should not only evaluate the effectiveness and safety of the treatment but also assess quality of life, utility of biomarkers, pharmacoeconomics, and outcomes research associated with the treatment.

Throughout this book we define a clinical trial as a clinical investigation in which treatments are administered, dispensed, or used involving one or more human subjects for evaluation of the treatment. By this definition, the experimental units are human subjects either with a preexisting disease under study or healthy. Unless otherwise specified, clinical trials in this book are referred to as all clinical investigations in human subjects that may be conducted by pharmaceutical companies, clinical research organizations such as the U.S. National Institutes of Health (NIH), university hospitals, or any other medical research centers.

1.2 HISTORY OF CLINICAL TRIALS

We humans since our early days on earth have been seeking or trying to identify some interventions, whether they be a procedure or a drug, to remedy ailments that afflict ourselves and our loved ones. In this century the explosion of modern and advanced science and technology has led to many successful discoveries of promising treatments such as new medicines. Over the years there has been a tremendous need for clinical investigations

of these newly discovered and promising medicines. In parallel, different laws have been enacted and regulations imposed at different times to ensure that the discovered treatments are effective and safe. The purpose of imposing regulations on the evaluation and approval of treatments is to minimize potential risks that they may have for human subjects, especially for those treatments whose efficacy and safety are unknown or are still under investigation.

In 1906, the United States Congress passed the *Pure Food and Drug Act*. The purpose of this act is to prevent misbranding and adulteration of food and drugs. However, the scope of this act is rather limited. No preclearance of drugs is required. Moreover, the act does not give the government any authority to inspect food and drugs. Since the act does not regulate the claims made for a product, the Sherley Amendment to the act was passed in 1912 to prohibit labeling medicines with false and fraudulent claims. In 1931, the U.S. Food and Drug Administration (FDA) was formed. The provisions of the FDA are intended to ensure that (1) food is safe and wholesome, (2) drugs, biological products, and medical devices are safe and effective, (3) cosmetics are unadulterated, (4) the use of radiological products does not result in unnecessary exposure to radiation, and (5) all of these products are honestly and informatively labeled (Fairweather, 1994).

The concept of testing marketed drugs in human subjects did not become a public issue until the Elixir Sulfanilamide disaster occurred in the late 1930s. The disaster was a safety concern of a liquid formulation of a sulfa drug that caused more than 100 deaths. This drug had never been tested in humans before its marketing. This safety concern led to the passage of the *Federal Food, Drug and Cosmetic Act* (FD&C Act) in 1938. The FD&C Act extended its coverage to cosmetics and therapeutic devices. More important, the FD&C Act requires the pharmaceutical companies to submit full reports of investigations regarding the safety of new drugs. In 1962, a significant Kefauver–Harris Drug Amendment to the FD&C Act was passed. The Kefauver–Harris Amendment not only strengthened the safety requirements for new drugs but also established an efficacy requirement for new drugs for the first time. In 1984, the Congress passed the *Price Competition and Patent Term Restoration Act* to provide for increased patent protection to compensate for patent life lost during the approval process. Based on this act, the FDA was also authorized to approve generic drugs only based on bioavailability and bioequivalence trials on healthy male subjects. It should be noted that the FDA also has the authority for designation of prescription drugs or over-the-counter drugs. In the United States, on average, it will take a pharmaceutical company about 10 to 12 years for development of a promising pharmaceutical entity with an average cost between $800 million and $1 billion U.S. dollars. Drug development is a lengthy and costly process. This lengthy process is necessary to ensure the safety and efficacy of the drug product under investigation. On average, it may take more than 2 years for regulatory authorities such as the FDA to complete the review of the new drug applications submitted by the sponsors. This lengthy review process might be due to limited resources available at the regulatory agency. As indicated by the U.S. FDA, they will be able to improve the review process of new drug applications if additional resources are available. As a result, in 1992, the U.S. Congress passed the *Prescription Drug User Fee Act* (PDUFA), which authorizes the FDA to utilize the *user fee* financed by the pharmaceutical industry to provide additional resources for the FDA's programs for development of drug and biologic products. However, the PDUFA must be reauthorized by the U.S. Congress every 5 years. Since its enactment in 1992, this program has enabled the FDA to reduce the average time required for review of a new drug application from 2 years to 1.1 years in 2011. In 1997, the U.S. Congress also passed the *Food and Drug Administration Modernization Act* (FDAMA) to enhance the FDA's missions and its operations for the increasing technological, trade,

and public health complexities in the 21st century by reforming the regulation of food, drugs, devices, biologic products, and cosmetics. On the other hand, the Biologic Price Competition and Innovation (BPCI) Act passed in 2009 provides an abbreviated approval pathway for biological products shown to be biosimilar to, or interchangeable with, an FDA-licensed reference biological product.

The concept of randomization in clinical trials was not adapted until the early 1920s (Fisher and Mackenzie, 1923). Amberson et al. (1931) first considered randomization of patients to treatments in clinical trials to reduce potential bias and consequently to increase statistical power for detection of a clinically important difference. At the same time, a Committee on Clinical Trials was formed by the Medical Research Council of Great Britain (Medical Research Council, 1931) to promulgate good clinical practice by developing guidelines governing the conduct of clinical studies from which data will be used to support application for marketing approval. In 1937, the NIH awarded its first research grant in a clinical trial. At the same time, the U.S. National Cancer Institute (NCI) was also formed to enhance clinical research in the area of cancer. In 1944, the first publication of results from a multicenter trial appeared in *Lancet* (Patulin Clinical Trials Committee, 1944). Table 1.2.1 provides a chronological account of historical events for both clinical trials and the associated regulations for treatments intended for marketing approval. Table 1.2.1 reveals that the advance of clinical trials goes hand in hand with the development of regulations.

Olkin (1995) indicated that there are at least 8000 randomized controlled clinical trials conducted each year, whose size can include as many as 100,000 subjects. As more clinical trials are conducted worldwide each year, new service organizations and/or companies have emerged to provide information and resources for the conduct of clinical trials. Table 1.2.2 provides a summary of resources available for clinical trials from a web-based clinical trial listing service called CenterWatch.® These trials are usually sponsored by the pharmaceutical industry, government agencies, clinical research institutions, or, more recently, a third party such as health maintenance organizations (HMOs) or insurance companies. In recent years, clinical trials conducted by the pharmaceutical industry for marketing approval have become more extensive. However, the sizes of clinical trials funded by other organizations are even larger. The trials conducted by the pharmaceutical industry are mainly for the purpose of registration for marketing approval. Therefore, they follow a rigorously clinical development plan, which is usually carried out in phases (e.g., phases I, II, and III trials, which will be discussed later in this chapter) that progress from very tightly controlled dosing of a small number of normal subjects to less tightly controlled studies involving large numbers of patients.

To eliminate many instances of unethical clinical research, falsification and fabrication of clinical data, and unreported or unknown clinical research in the past, the National Library of Medicine (NLM) of the National Institutes of Health (NIH) in collaboration with the FDA developed a website for registration of clinical trials (`http://www.ClinicalTrials.gov`) after the passage of the PDUFA in 1997. Around 110,000 trials sponsored by the NIH, other federal agencies, and private industry currently have registered in the ClinicalTrials.gov. Trials listed in the database are conducted in all 50 states of the United States and in 174 other countries. In addition, under the U.S. Public Law 110-85 (Food and Drug Administration Amendments Act of 2007), the `ClinicalTrials.gov` Results Database allows data providers to report summary results of registered clinical trials. On the other hand, the World Health Organization (WHO) also established the International Clinical Trial Registry Platform (ICTRP) to facilitate registration of the WHO Registration Data Set on all clinical

Table 1.2.1 Significant Historical Events in Clinical Trials and Regulations

Year	Clinical Trials	Regulations
1906		Pure Food and Drug Act (Dr. Harvey Wiley)
1912		Sherley Amendment
1923	First randomization to experiments (Fisher and Mackenzie, 1923)	
1931	First randomization of patients to treatments in clinical trials (Amberson et al., 1931) Committee on clinical trials by the Medical Research Council of Great Britain (Medical Research Council, 1931)	Formation of U.S. Food and Drug Administration
1937	Formation of National Cancer Institute and First Research Grant by National Institutes of Health (National Institutes of Health, 1981)	
1938		U.S. Federal Food, Drug and Cosmetic Act (Dr. R. Tugwell)
1944	First publication of results from a multicenter trial (Patulin Clinical Trial Committee, 1944)	
1952	Publication of *Elementary Medical Statistics* (Mainland, 1952)	FDA makes designation of Prescription Drug or OTC
1962	Publication of *Statistical Methods in Clinical and Preventive Medicine* (Hill, 1962)	Amendment to the U.S. Food, Drug, and Cosmetic Act
1966		Mandated creation of the local boards (IRB) for funding by U.S. Public Health Service
1976		Medical Device Amendment to the U.S. Food, Drug, and Cosmetic Act (1976)
1977		Publication of *General Considerations for Clinical Evaluation of Drugs* (HEW (FDA), 1977)
1984		Drug Price Competition and Patent Term Restoration Act (Waxman and Hatch, 1984)
1985		NDA rewrite
1988		Publication of *Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Applications* (FDA, 1988)
1990		Publication of *Good Clinical Practice for Trials on Medicinal Products in the European Community* (EC Commission, 1990)
1987		Treatment IND (FDA, 1987)
1992		Parallel track and accelerated approval (FDA, 1992) Prescription Drug User Fee Act
1997		Publication of *Good Clinical Practice: Consolidated Guidelines* (ICH, 1996b) U.S. FDA Modernization Act
2009		Biologic Price Competition and Innovation (BPCI) Act

Table 1.2.2 Summary of Resources for Clinical Trials

Description	Resources
Number of clinical trials	41,000
Clinical investigators	25,000
Academic clinical research center	600
Pharmaceutical, biotechnology, and medical device companies	275
Contract research organizations (CROs)	250
Companies providing services to clinical trials	130
Financial and investment professionals for clinical trials	100

Source: CenterWatch® Clinical Trials Listing Service (`http://www.centerwatch.com`).

trials, and public accessibility of that information (`http://www.who.int.ictrp`). In 2004, the International Committee of Medical Journal Editors (ICMJE) published its statement of the requirement of clinical trial registration as a precondition of publication (De Angelis et al., 2004).

According to the report on new drug development by the U.S. Government Accounting Office (GAO) in November 2006, the average time that a pharmaceutical company spends getting a drug to market is 15 years. Of this figure, 6.5 years are spent in drug discovery and preclinical studies and another 7 years in clinical trials to obtain the required information for market registration. Although as a result of PDUFA, the review time at the U.S. FDA has been reduced to 1.5 years, the total length of drug research, development, and review time for a successful drug is 15 years. However, on average, only 1 of 10,000 compounds will be found safe and effective and be approved by the FDA. Table 1.2.3 provides a summary of median review time at the Center for Drug Review and Research (CDER) at the U.S. FDA in 2006 (Galson, 2008).

For example, for the drugs receiving priority status, the median review time is only 6 months. The median review time for the standard New Drug Applications (NDAs) and Biologic License Applications (BLAs) is 12 months. However, it is not surprising that new molecular entities require more than 6 months to review. This lengthy clinical development process is necessary to assure the efficacy and safety of the drug product. As a result, this lengthy development period sometimes does not allow access to promising drugs or therapies by subjects with serious or life-threatening illnesses. Kessler and Feiden (1995) point out that the FDA may permit promising drugs or therapies currently under investigation to be available to patients with serious or life-threatening diseases under the *treatment IND* in 1987. The *Parallel Track Regulations* in 1992 allow promising therapies for serious or life-threatening diseases to become available with considerably fewer data

Table 1.2.3 Summary of Median Review Time at CDER of the U.S. FDA in 2006

Number of Approved Drugs	Median Review Time in Months
Priority NDAs and BLAs (21)	6
Priority NMEs and New BLAs (10)	6
Standard NDAs and BLAs (80)	12
Standard NMEs and New BLAs (12)	12.5

NMEs = new molecular entities; NDAs = new drug applications; BLAs = biologic license applications.
Source: FDA talk paper on August 8, 2007 at `www.fda.gov`.

than required for approval. In the same year, the FDA published the regulations for the *Accelerated Approval* based only on surrogate endpoints to accelerate the approval process for promising drugs or therapies indicated for life-threatening diseases.

The size of trials conducted by the pharmaceutical industry can be as small as a dozen subjects for the phase I trial in humans, or it can be as large as a few thousand for support of approval of ticlopidine for stroke prevention (Temple, 1993). The design of the trial can be very simple as the single-arm trial with no control group, or it can be very complicated as a 12-group factorial design for the evaluation of the dose responses of combination drugs. Temple (1993) points out that information accumulated from previous experience in the database of preapproval New Drug Applications (NDAs) or Biologic License Applications (BLAs) can range from a few hundred subjects (e.g., contrast imaging agents) to 4000 or 5000 subjects (antidepressants or antihypertensives, antibiotics, etc.). Recently, due to the small effect size of vaccines for primary prevention, the number of subjects in a new drug application can reach ten thousand. For example, the four placebo-controlled, double-blind, randomized phase II and two phase III trials for establishing the efficacy of the HPV vaccine Gardasil include 20,541 women 16 to 26 years of age at enrollment.

When the safety profile and mechanism of action for the efficacy of a new drug or therapy are well established, probably after its approval, a simple but large confirmatory trial is usually conducted to validate the safety and effectiveness of the new drug or therapy. This kind of trial is large in the sense that there are relaxed entrance criteria to enroll a large number of subjects (e.g., tens of thousands) with various characteristics and care settings. The purpose of this kind of trial is to increase the exposure of a new drug or therapy to more subjects with the indicated diseases. For example, the first *Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries Trial* (GUSTO I, 1993) enrolled over 41,000 subjects in 1081 hospitals from 15 countries, while in the *Physician's Health Study* funded by the NIH over 22,000 physicians were randomized to one of four arms in the trial. In addition, these trials usually follow subjects for a much longer period of time than most trials for marketing approval. For example, the *Helsinki Heart Study* followed a cohort of over 4000 middle-aged men with dyslipidemia for five years (Frick et al., 1987). The recent *Prostate Cancer Prevention Trial* (PCPT) plans to follow 18,000 healthy men over age 55 for seven years (Feigl et al., 1995). Such trials are simple in the sense that only a few important data are collected from each subject. Because the sizes of these trials are considerably larger, they can detect relatively small yet important and valuable treatment effects that previous smaller studies failed to detect. Sometimes, public funded clinical trials can also be used as a basis for approval of certain indications. An example is the combined therapy of leuprolide with flutamide for patients with disseminated, previously untreated D_2 stage prostate cancer. Approval of flutamide was based on a study funded by the NCI.

On the other hand, health care providers such as HMOs or insurance companies will be more interested in providing funding for rigorous clinical trials to evaluate not only efficacy and safety of therapies but also quality of life, pharmacoeconomics, and outcomes. The purpose of this kind of clinical trial is to study the cost associated with the health care provided. The concept is to minimize the cost with the optimal therapeutic effect under the same quality of health care. Temple (1993) points out that from the results of the study of *Systolic Hypertension in the Elderly* (SHEP), a potential savings of $6 billion per year can be provided by the treatment regimen of chlorthalidone with a beta blocker backup such a atenolol as compared to the combined treatment of an angiotensin converting enzyme (ACE) inhibitor with a calcium channel blocker backup.

1.3 REGULATORY PROCESS AND REQUIREMENTS

Chow and Liu (1995b) indicated that the development of a pharmaceutical entity is a lengthy process involving drug discovery, laboratory development, animal studies, clinical trials, and regulatory registration. The drug development can be classified into nonclinical, preclinical, and clinical development phases. As indicated by *USA Today* (February 3, 1993), approximately 75% of drug development is devoted to clinical development and regulatory registration. In this section, we focus on the regulatory process and requirements for clinical development of a pharmaceutical entity.

For marketing approval of pharmaceutical entities, the regulatory process and requirements may vary from country (or region) to country (or region). For example, the European Community (EC), Japan, and the United States have similar but different requirements as to the conduct of clinical trials and the submission, review, and approval of clinical results for pharmaceutical entities. In this section, for simplicity, we focus on the regulatory process and requirements for the conduct, submission, review, and approval of clinical trials currently adopted in the United States. As indicated earlier, the FDA was formed in 1931 to enforce the FD&C Act for marketing approval of drugs, biological products, and medical devices. With very few exceptions, since the enactment of the FD&C Act, treatment interventions such as drugs, biological products, and medical devices either currently on the market or still under investigation are the results of a joint effort between the pharmaceutical industry and the FDA. To introduce the regulatory process and requirements for marketing approval of drugs, biological products, and medical devices, it is helpful to be familiar with the functional structure of the FDA.

1.3.1 The Food and Drug Administration

The FDA is a subcabinet organization within the Department of Health and Human Services (HHS), which is one of the major cabinets in the U.S. government. The FDA is headed by a commissioner with several deputy or associate commissioners to assist him/her in various issues such as regulatory affairs, management and operations, health affairs, science, legislative affairs, public affairs, planning and evaluation, and consumer affairs. Under the office of the commissioner, there are currently six different centers of various functions for evaluation of food, drugs, and cosmetics. They are the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), the Center for Devices and Radiological Health (CDRH), the National Center for Toxicological Research (NCTR), the Center for Veterinary Medicine (CVM), and Center for Food Safety and Applied Nutrition (CFSAN).

Recently, in the interest of shortening the review process, the sponsors are required to provide a user's fee for review of submission of applications to the FDA. In October 1995, the CDER was reorganized to reflect the challenge of improving efficiency and shortening the review and approval process as demanded by the U.S. Congress and the pharmaceutical industry. Figure 1.3.1 provides the current structure of the CDER at the FDA, which is composed of 12 major *offices*. These offices include Office of Management, Office of Communications, Office of Compliance, Office of Planning and Informatics, Office of Regulatory Policy, Office of Executive Programs, Office of Medical Policy, Office of New Drugs, Office of Pharmaceutical Science, Office of Surveillance and Epidemiology, Office of Counter-Terrorism and Emergency Coordination, and Office of Translational Sciences. The Office of New Drugs is responsible for drug evaluation, which consists of six offices,

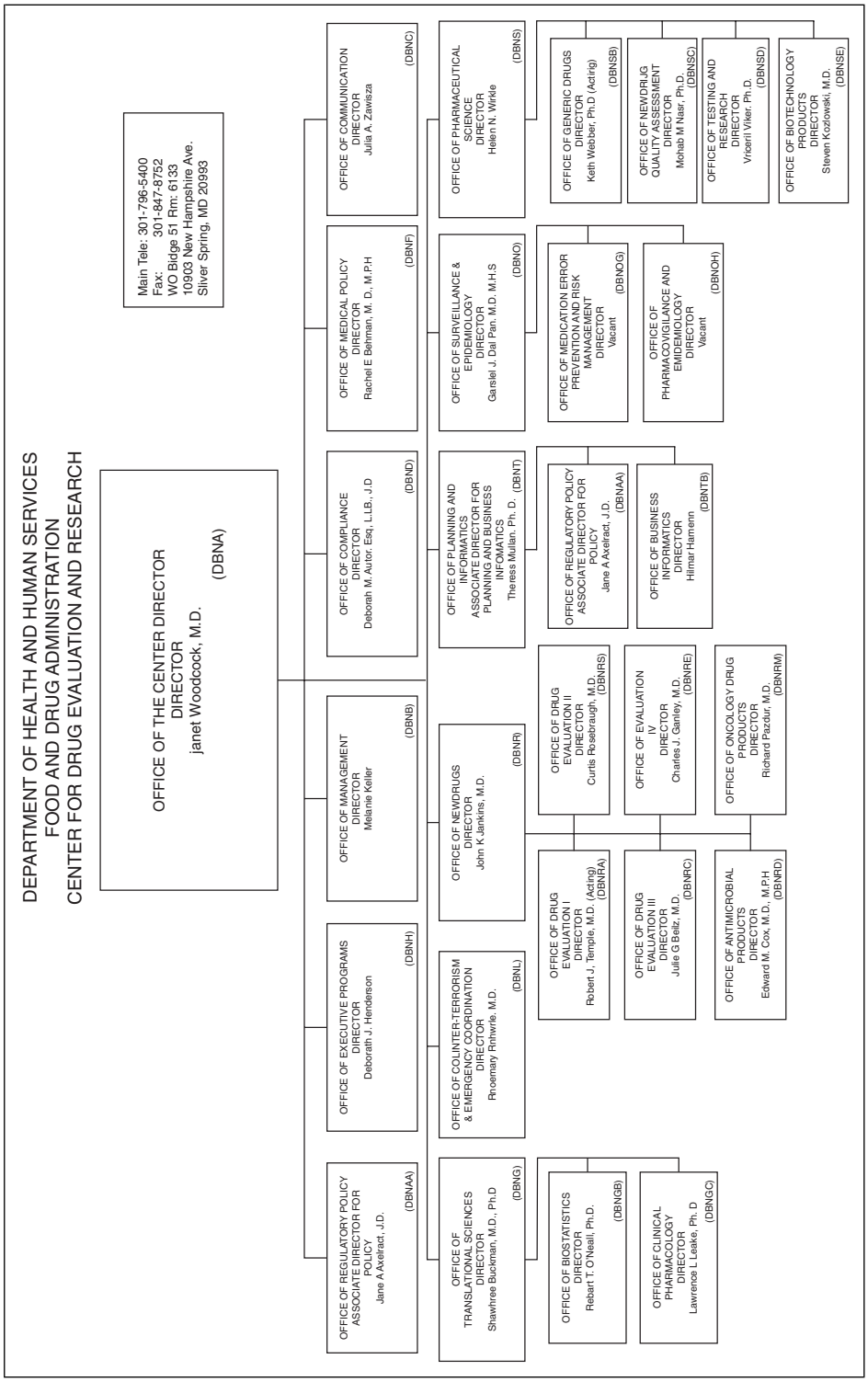

Figure 1.3.1 Center for Drug Evaluation and Research.

including Offices of Drug Evaluation I–IV, Office of Antimicrobial Products, and Office of Oncology Drug Products. On the other hand, the Office of Pharmaceutical Science consists of four offices, including Office of New Drug Quality Assessment, Office of Generic Drugs, Office of Testing and Research, and Office of Biotechnology Products. Furthermore, the CDER recently established the Office of Translational Sciences in recognition of the importance of translational sciences in drug evaluation. The Office of Translational Sciences includes the Office of Clinical Pharmacology and the Office of Biostatistics. In addition, to overcome the recent emerging safety crises by some diabetic drug products and the drug products of the class of Cox-2 inhibitors, the FDA established the Office of Surveillance and Epidemiology, which consists of the Office of Medication Error Prevention and Risk Management and the Office of Pharmacovigilance and Epidemiology. Note that each of these offices consists of several divisions. Figures 1.3.2, 1.3.3, and 1.3.4 provide the respective organizations of the Offices of New Drugs, Pharmaceutical Science, and Translation Sciences. Note that the CBER has a similar functional structure though it has fewer offices than the CDER.

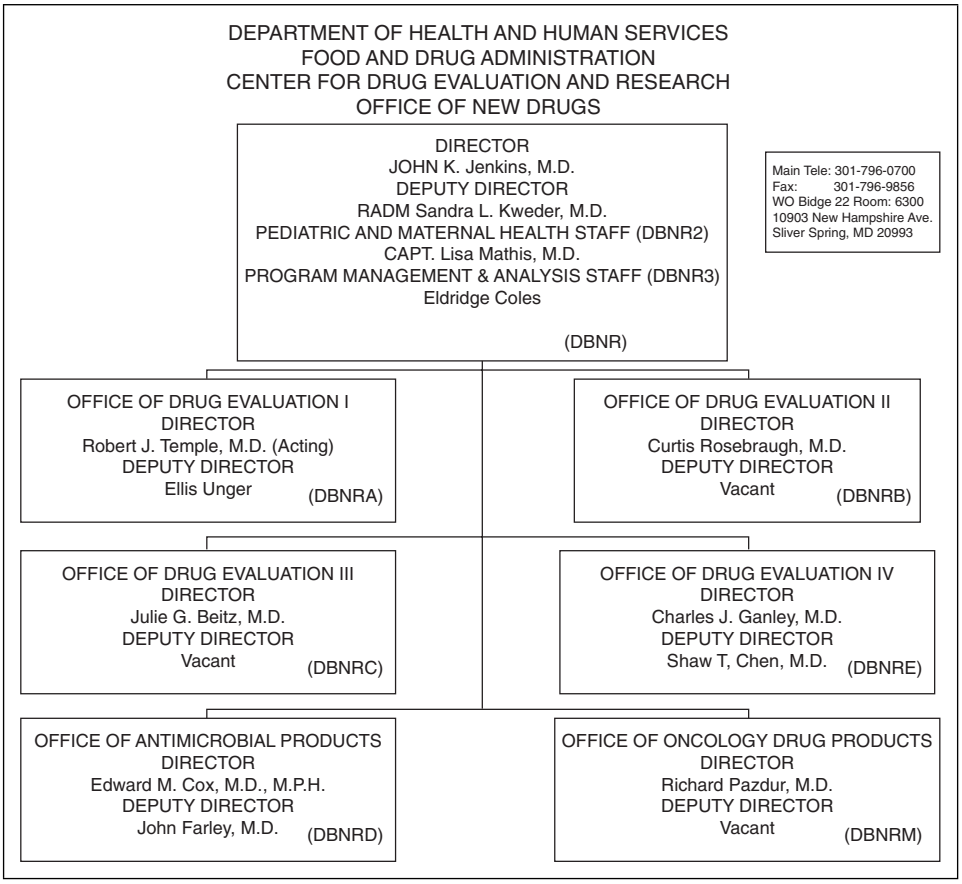

Figure 1.3.2 Office of New Drugs.

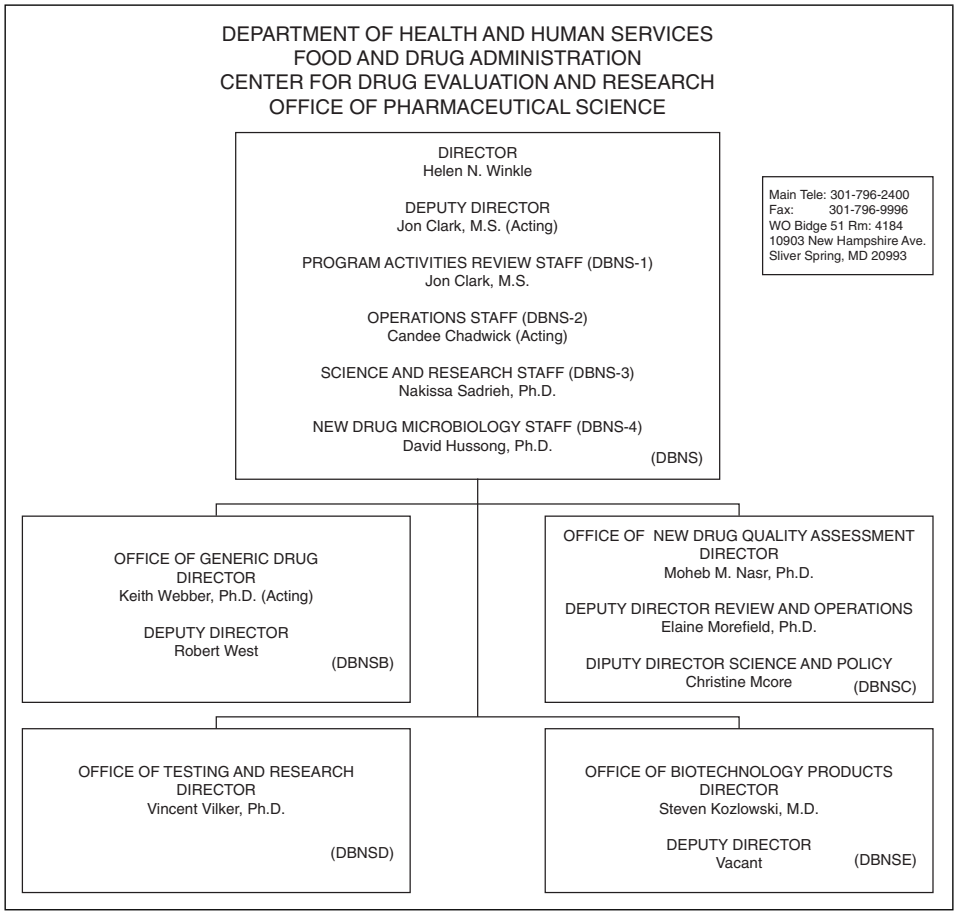

Figure 1.3.3 Office of Pharmaceutical Science.

1.3.2 FDA Regulations for Clinical Trials

For evaluation and marketing approval of drugs, biological products, and medical devices, the sponsors are required to submit substantial evidence of effectiveness and safety accumulated from adequate and well-controlled clinical trials to the CDER, CBER, or CDRH of the FDA, respectively. The current regulations for conducting clinical trials and the submission, review, and approval of clinical results for pharmaceutical entities in the United States can be found in the CFR (e.g., see 21 CFR Parts 50, 56, 312, and 314). These regulations are developed based on the FD&C Act passed in 1938. Table 1.3.1 summarizes the most relevant regulations with respect to clinical trials. These regulations cover not only pharmaceutical entities such as drugs, biological products, and medical devices under investigation but also the welfare of participating subjects and the labeling and advertising of pharmaceutical products. It can be seen from Table 1.3.1 that pharmaceutical entities can roughly be divided into three categories based on the FD&C Act and hence the CFR. These categories include drug products, biological products, and medical devices. For the first category, a drug is as defined in the FD&C Act (21 U.S.C. 321) as an article that is

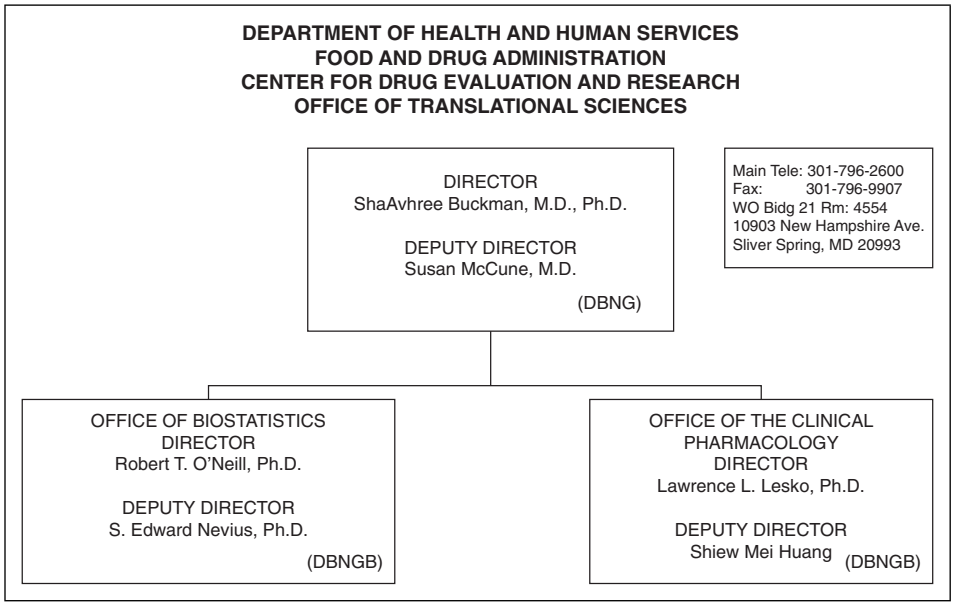

Figure 1.3.4 Office of Translational Sciences.

Table 1.3.1 U.S. Codes of Federal Regulation (CFR) for Clinical Trials Used to Approve Pharmaceutical Entities

CFR Number	Regulations
21 CFR 50	Protection of human subjects
21 CFR 54	Financial disclosure by clinical investigators
21 CFR 56	Institutional review boards (IRBs)
21 CFR 312	Investigational new drug (IND) application
Subpart E	Treatment IND
21 CFR 314	Applications for FDA approval to market a new drug
Subpart C	Abbreviated applications
Subpart H	Accelerated approval
21 CFR 601	Establishment license and product license applications (ELAs and PLAs)
Subpart E	Accelerated approval
21 CFR 316	Orphan drugs
21 CFR 320	Bioavailability and bioequivalence requirements
21 CFR 330	Over-the-counter (OTC) human drugs
21 CFR 812	Investigational device exemptions (IDEs)
21 CFR 814	Premarket approval (PMA) of medical devices
21 CFR 60	Patent term restoration
21 CFR 201	Labeling
21 CFR 202	Prescription drug advertising
21 CFR 203	Prescription drug marketing

(1) recognized in the U.S. Pharmacopeia, official Homeopathic Pharmacopeia of the United States, or official National Formulary, or a supplement to any of them; (2) intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in humans or other animals, or (3) intended to affect the structure or function of the body of humans or other animals. For the second category, a biological product is defined in the 1944 *Biologics Act* (46 U.S.C. 262) as a virus, therapeutic serum, toxin, antitoxin, bacterial or viral vaccine, blood, blood component or derivative, allergenic product, or analogous product, applicable to the prevention, treatment, or cure of disease or injuries in humans. Finally, a medical device is defined as an instrument, apparatus, implement, machine contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory that—similar to a drug—is (1) recognized in the official National Formulary or the U.S. Pharmacopeia or any supplement in them; (2) intended for use in the diagnosis of disease in humans or other animals; or (3) intended to affect the structure or function of the body of humans or other animals.

The CDER of the FDA has jurisdiction over administration of regulation and approval of pharmaceutical products classified as a *drug*. These regulations include Investigational New Drug (IND) Application and New Drug Application (NDA) for new drugs, orphan drugs, and over-the-counter (OTC) human drugs and Abbreviated New Drug Application (ANDA) for generic drugs. On the other hand, the CBER is responsible for enforcing the regulations of biological products through processes such as an Establishment License Application (ELA) or Product License Application (PLA). Administration of the regulations for medical devices belongs to the jurisdiction of the CDRH through Investigational Device Exemptions (IDEs) and Premarket Approval (PMA) of Medical Devices and other means.

A treatment for a single illness might consist of a combination of drugs, biological products, and/or medical devices. If a treatment consists of a number of drugs, then it is called a combined therapy. For example, leuprolide and flutamide are used for the treatment of disseminated, previously untreated D_2 stage prostate cancer. However, if a treatment consists of a combination of drugs, biologics, and/or devices such as a drug with a device, a biologic with a device, a drug with a biologic, or a drug with a biologic in conjunction with a device, then it is defined as a combined product. For a combined product consisting of different pharmaceutical entities, the FDA requires that each entity should be reviewed separately by appropriate centers at the FDA. In order to avoid confusion of jurisdiction over a combination product and to improve efficiency of the approval process, the principle of primary mode of action of a combination product was established in the *Safe Medical Devices Act* (SMDA) in 1990 (21 U.S.C. 353). In 1992, based on this principle, three intercenter agreements were signed between the CDER and CBER, between the CDER and CDRH, and between the CBER and CDRH to establish the ground rules for assignment of a combined product and intercenter consultation (Margolies, 1994).

1.3.3 Phases of Clinical Development

In a set of new regulations promulgated in 1987 and known as the *IND Rewrite*, the phases of clinical investigation adopted by the FDA since the late 1970s is generally divided into three phases (21 CFR 312.21). These phases of clinical investigation are usually conducted sequentially but may overlap.

Phase I clinical investigation provides an initial introduction of an investigational new drug to humans. The primary objectives of phase I clinical investigation are twofold. First,

it is to determine the metabolism and pharmacologic activities of the drug in humans, the side effects associated with increasing doses, and early evidence on effectiveness. Second, it is to obtain sufficient information about the drug's pharmacokinetics and pharmacological effects to permit the design of well-controlled and scientifically valid phase II clinical studies. Thus, phase I clinical investigation includes studies of drug metabolism, bioavailability, dose ranging, and multiple doses. Phase I clinical investigation usually involves 20 to 100 normal volunteer subjects or patients. In general, protocols for phase I studies are less detailed and more flexible than for subsequent phases, but they must provide an outline of the investigation and also specify in detail those elements that are critical to safety. For phase I investigation, the FDA's review focuses on the assessment of safety. Therefore, extensive safety information such as detailed laboratory evaluations are usually collected at very intensive schedules.

Phase II studies are the first controlled clinical studies of the drug, and they involve no more than several hundred patients. The primary objectives of phase II studies are not only to initially evaluate the effectiveness of a drug based on clinical endpoints for a particular indication or indications in patients with the disease or condition under study but also to determine the dosing ranges and doses for phase III studies and the common short-term side effects and risks associated with the drug. Although the clinical investigation usually involves no more than several hundred patients, expanded phase II clinical studies may involve up to several thousand patients. Note that some pharmaceutical companies further differentiate this phase into phases IIA and IIB. Clinical studies designed to evaluate dosing are referred to as phase IIA studies, and studies designed to determine the effectiveness of the drug are called phase IIB.

Phase III studies are expanded controlled and uncontrolled trials. The primary objectives of phase III studies are not only to gather the additional information about effectiveness and safety needed to evaluate the overall benefit–risk relationship of the drug but also to provide an adequate basis for physician labeling. Phase III studies, which can involve from several hundred to several thousand patients, are performed after preliminary evidence regarding the effectiveness of the drug has been demonstrated. Note that studies performed after submission before approval are generally referred to as phase IIIB studies.

In drug development, phase I studies refer to an early stage of clinical pharmacology, and phase II and III studies correspond to a later stage of clinical development. For different phases of clinical studies, the investigational processes are regulated differently: for example, the FDA review of submissions in phase I ensures that subjects are not exposed to unreasonable risks, while the review of submissions in phases II and III also ensures that the scientific design of the study is likely to produce data capable of meeting statutory standards for marketing approval.

Phase IV trials generally refer to studies performed after a drug is approved for marketing. The purpose for conducting phase IV studies is to elucidate further the incidence of adverse reactions and determine the effect of a drug on morbidity of mortality. In addition, a phase IV trial is also conducted to study a patient population not previously studied, such as children. In practice, phase IV studies are usually considered useful market-oriented comparison studies against competitor products.

Note that there is considerable variation within the pharmaceutical industry in categorizing clinical studies into phases. For example, in addition to phases I through IV trials described above, some pharmaceutical companies consider clinical studies conducted for new indications and/or new formulations (or dosage forms) as phase V studies.

1.4 INVESTIGATIONAL NEW DRUG APPLICATION

As indicated in the previous section, different regulations exist for different products, such as IND and NDA for drug products, ELA and PLA for biological products, and IDE and PMA for medical devices. However, the spirit and principles for the conduct, submission, review, and approval of clinical trials are the same. Therefore, for the purpose of illustration, we only give a detailed discussion on INDs and NDAs for drug products.

Before a drug can be studied in humans, its sponsor must submit an IND to the FDA. Unless notified otherwise, the sponsor may begin to investigate the drug 30 days after the FDA has received the application. The IND requirements extend throughout the period during which a drug is under study. As mentioned in Sections 312.1 and 312.3 of 21 CFR, an IND is synonymous with *Notice of Claimed Investigational Exemption for a New Drug*. Therefore, an IND is, legally speaking, an exemption to the law that prevents the shipment of a new drug for interstate commerce. Consequently, the drug companies that file an IND have flexibility of conducting clinical investigations of products across the United States. However, it should be noted that different states might have different laws that may require the sponsors to file separate IND applications to the state governments. As indicated by Kessler (1989), there are two types of INDs—commercial and noncommercial. A commercial IND permits the sponsor to gather the data on the clinical safety and effectiveness needed for an NDA. If the drug is approved by the FDA, the sponsor is allowed to market the drug for specific uses. A noncommercial IND allows the sponsor to use the drug in research or early clinical investigation to obtain advanced scientific knowledge of the drug. Note that the FDA itself does not investigate new drugs or conduct clinical trials. Pharmaceutical manufacturers, physicians, and other research organizations such as the NIH may sponsor INDs. If a commercial IND proves successful, the sponsor ordinarily submits an NDA. During this period the sponsor and the FDA usually negotiate over the adequacy of the clinical data and the wording proposed for the label accompanying the drug, which sets out description, clinical pharmacology, indications and usage, contraindications, warnings, precautions, adverse reactions, and dosage and administration.

By the time an IND application is filed, the sponsor should have enough information about the chemistry, manufacturing, and controls of the drug substance and drug product to ensure the identity, strength, quality, and purity of the investigational drug covered by the IND application. In addition, the sponsor should provide adequate information about pharmacological studies for absorption, distribution, metabolism, and excretion (ADME) and acute, subacute, and chronic toxicological studies and reproductive tests in various animal species to support that the investigational drug is reasonably safe to be evaluated in clinical trials of various durations in humans.

A very important component of an IND application is the general investigational plan, which is in fact an abbreviated version of the clinical development plan for the particular pharmaceutical entity covered by the IND. However, the investigational plan should identify the phases of clinical investigation to be conducted that depend on the previous human experience with the investigational drug. Usually if a new investigational drug is developed in the United States, it is very likely that at the time of filing the IND application, no clinical trial on humans has ever been conducted. Consequently, the investigational plan might consist of all clinical trials planned for each stage of phases I, II, and III during the entire development period. On the other hand, some investigational pharmaceutical entities may be developed outside the United States. In this case, sufficient human experiences may have already been accumulated. For example, for an investigational drug, suppose that

the clinical development plan outside the United States has already completed the phase II stage. Then the initial safety and pharmacological ADME information can be obtained from phase I clinical trials. In addition, phase II dose–response (ranging) studies may provide adequate dose information for the doses to be employed in the planned phase III studies. Consequently, the investigational plan may only include the plan for phase III trials and some trials for a specific subject population such as renal or hepatic impaired subjects. However, all information and results from phases I and II studies should adequately be documented in the section of previous human experience with the investigational drug in the IND application. A general investigational plan may consist of more than one protocol depending on the stage of the clinical investigational plan to be conducted.

An IND application plays an important role in the clinical development of a pharmaceutical entity. An IND application should include all information about the drug product available to the company up to the time point of filing. Table 1.4.1 lists the contents of an IND submission provided in Section 312.23 (a) (6) of 21 CFR that a sponsor must follow and submit. A cover sheet usually refers to the form of FDA1571. The form reinforces the sponsor's commitment to conduct the investigation in accordance with applicable regulatory requirements. A table of contents should also be included to indicate the information attached in the IND submission. The general investigational plan should clearly state the rationale for the study of the drug, the indication(s) to be studied, the approach for the evaluation of the drug, the kinds of clinical trials to be conducted, the estimated number of patients, and any risks of particular severity or seriousness anticipated. For completeness, an investigator's brochure should also be provided. As mentioned earlier, the central focus of the initial IND submission should be on the general investigational plan and protocols for specific human studies. Therefore, a copy of protocol(s), which includes study objectives, investigators, criteria for inclusion and exclusion, study design, dosing schedule, endpoint measurements, and clinical procedure, should be submitted along with the investigational plan and other information such as chemistry, manufacturing, and controls, pharmacology and toxicology, previous human experiences with the investigational drug, and any additional information relevant to the investigational drug. Note that the FDA requires that all sponsors should submit an original and two copies of all submissions to the IND file, including the original submission and all amendments and reports.

Table 1.4.1 Documents to Accompany an IND Submission

Form FDA 1571 (a cover sheet)
Table of contents
Introductory statement
General investigational plan
Investigator's brochure
Protocol(s)
Study protocols
Investigator data
Facilities data
Institutional Review Board data
Chemistry, manufacturing, and controls data
Pharmacology and toxicology data
Previous human experiences
Additional information

1.4.1 Clinical Trial Protocol

To ensure the success of an IND, a well-designed protocol is essential when conducting a clinical trial. A protocol is a plan that details how a clinical trial is to be carried out and how the data are to be collected and analyzed. It is an extremely critical and important document, since it ensures the quality and integrity of the clinical investigation in terms of its planning, execution, and conduct of the trial as well as the analysis of the data. Section 312.23 of 21 CFR provides minimum requirements for the protocol of a clinical trial. In addition, the *Guideline for the Format and Content of the Clinical and Statistical Sections of an Application* was issued by the CDER of the FDA in October 1988. Appendix C of this guideline describes key elements for a well-designed protocol. All of these requirements and elements are centered around experimental units, treatments, and evaluations of the treatments as discussed previously in Section 1.1.

Table 1.4.2 gives an example for format and contents of a well-controlled protocol for a majority of clinical trials. A well-designed protocol should always have a protocol cover sheet to provide a synopsis of the protocol. A proposed protocol cover sheet can be found in Appendix C of the 1998 FDA guideline. The objective of the study should clearly be stated at the beginning of any protocols. The study objectives are concise and precise statements of prespecified hypotheses based on clinical responses for evaluation of the drug product under study. The objectives usually consist of the primary objective, secondary objectives, and sometimes the subgroup analyses. In addition, these objectives should be such that they can be translated into statistical hypotheses. The subject inclusion and exclusion criteria should also be stated unambiguously in the protocol to define the targeted population to which the study results are inferred. The experimental design then employed should be able to address the study objectives with certain statistical inference. A valid experimental design should include any initial baseline or run-in periods, the treatments to be compared, the study configuration such as parallel, crossover, or forced titration, and duration of the treatment. It is extremely important to provide a description of the control groups with the rationale as to why the particular control groups are chosen for comparison.

The methods of blinding used in the study to minimize any potential known biases should be described in detail in the protocol. Likewise, the protocol should provide the methods of assignment for subjects to the treatment groups. The methods of assignment are usually different randomization procedures to prevent any systematic selection bias and to ensure comparability of the treatment groups with respect to pertinent variables. Only randomization of subjects can provide the foundation of a valid statistical inference. A well-designed protocol should describe the efficacy and safety variables to be recorded, the time that they will be evaluated, and the methods to measure them. In addition, the methods for measuring the efficacy endpoints such as symptom scores for benign prostatic hyperplasia or some safety endpoints such as some important laboratory assay should be validated and results of validation need to be adequately documented in the protocol. The FDA guideline also calls for designation of primary efficacy endpoints. From the primary objective based on the primary efficacy endpoint, the statistical hypothesis for sample size determination can then be formulated and stated in the protocol. The treatment effects assumed in both null and alternative hypotheses with respect to the experimental design employed in the protocol and the variability assumed for sample size determination should be described in full detail in the protocol, as should the procedures for accurate, consistent, and reliable data. The statistical method section of any protocol should address general statistical issues often encountered in the study. These issues include randomization and blinding, handling

Table 1.4.2 Format and Contents of a Protocol

1. Protocol cover sheet
2. Background
3. Objectives
   - Primary
   - Secondary
4. Study plan
   - Study design
   - Subject inclusion criteria
   - Subject exclusion criteria
   - Treatment plan
5. Study drugs
   - Dose and route
   - Method of dispensing
   - Method and time of administration
   - Description of controls
   - Methods of randomization and blinding
   - Package and labeling
   - Duration of treatment
   - Concomitant medications
   - Concomitant procedures
6. Measurements and observations
   - Efficacy endpoints
   - Safety endpoints
   - Validity of measurements
   - Time and events schedules
   - Screening, baseline, treatment periods, and post-treatment follow-up
7. Statistical methods
   - Database management procedures
   - Methods to minimize bias
   - Sample size determination
   - Statistical general considerations
     - Randomization and blinding
     - Dropouts, premature termination, and missing data
     - Baseline, statistical parameters, and covariates
     - Multicenter studies
     - Multiple testing
     - Subgroup analysis
     - Interim analysis
   - Statistical analysis of demography and baseline characteristics
   - Statistical analysis of efficacy data
   - Statistical analysis of safety data

Table 1.4.2 (*Continued*)

8. Adverse events
   - Serious adverse events
   - Adverse events attributions
   - Adverse event intensity
   - Adverse event reporting
   - Laboratory test abnormalities
9. Warning and precautions
10. Subject withdrawal and discontinuation
   - Subject withdrawal
   - End of treatment
   - End of study
11. Protocol changes and protocol deviations
   - Protocol changes
   - Protocol deviation
   - Study termination
12. Institutional review and consent requirements
   - Institutional review board (IRB)
   - Informed consent
13. Obligations of investigators and Administrative aspects
   - Study drug accountability
   - Case report forms
   - Laboratory and other reports
   - Study monitoring
   - Study registry
   - Record retention
   - Form FDA 1572
   - Signatures of investigators
   - Confidentiality
   - Publication of results
14. Flow chart of studies activities
15. References
16. Appendixes

of dropouts, premature termination of subjects, and missing data, defining the baseline and calculation of statistical parameters such as percent change from baseline and use of covariates such as age or gender in the analysis, the issues of multicenter studies, and multiple comparisons and subgroup analysis.

If interim analyses or administrative examinations are expected, the protocol needs to describe any planned interim analyses or administrative examinations of the data and the composition, function, and responsibilities of a possible outside data-monitoring committee. The description of interim analyses consists of monitoring procedures, the variables to be analyzed, the frequency of the interim analyses, adjustment of nominal level of significance,

and decision rules for termination of the study. In addition, the statistical methods for analyses of demography and baseline characteristics together with the various efficacy and safety endpoints should be described fully in the protocol. The protocol must define adverse events, serious adverse events, attributions, and intensity of adverse events and describe how the adverse events are reported. Other ethical and administration issues should also be addressed in the protocol. They are warnings and precautions, subject withdrawal and discontinuation, protocol changes and deviations, institutional review board and consent form, obligation of investigators, case report form, and others. Finally, the statement of investigator (Form FDA 1572) should also be included in the protocol.

It should be noted that once an IND submission is in effect, the sponsor is required to submit a protocol amendment if there are any changes in protocol that significantly affect the subjects' safety. Under 21 CFR 312.30(b) several examples of changes requiring an amendment are given. These examples include (1) any increase in drug dosage, duration, and number of subjects, (2) any significant change in the study design, and (3) the addition of a new test or procedure that is intended for monitoring side effects or an adverse event. In addition, the FDA also requires an amendment be submitted if the sponsor intends to conduct a study that is not covered by the protocol. As stated in 21 CFR 312.30(a) the sponsor may begin such study provided that a new protocol is submitted to the FDA for review and is approved by the institutional review board. Furthermore, when a new investigator is added to the study, the sponsor must submit a protocol amendment and notify the FDA of the new investigator within 30 days of the investigator being added. Note that modifications of the design for phase I studies that do not affect critical safety assessment are required to be reported to the FDA only in the annual report.

1.4.2 Institutional Review Board

Since 1971 the FDA has required that all proposed clinical studies be reviewed both by the FDA and an institutional review board (IRB). The responsibility of an IRB is not only to evaluate the ethical acceptability of the proposed clinical research but also to examine the scientific validity of the study to the extent needed to be confident that the study does not expose its subjects to unreasonable risk (Petricciani, 1981). An IRB is formally designated by a public or private institution in which research is conducted to review, approve, and monitor research involving human subjects. Each participating clinical investigator is required to submit all protocols to an IRB. An IRB must formally grant approval before an investigation may proceed, which is in contrast to the 30-day notification that the sponsors must give the FDA. To ensure that the investigators are included in the review process, the FDA requires that the clinical investigators communicate with the IRB. The IRB must monitor activities within its institutions.

The composition and function of an IRB are subject to FDA requirements. Section 56.107 in Part 56 of 21 CFR states that each IRB should have at least five members with varying backgrounds to promote a complete review of research activities commonly conducted by the institution. In order to avoid conflict of interest and to provide an unbiased and objective evaluation of scientific merits, ethical conduct of clinical trials, and protection of human subjects, the CFR enforces a very strict requirement for the composition of members of an IRB. The research institution should make every effort to ensure that no IRB is entirely composed of one gender. In addition, no IRB may consist entirely of members of one profession. In particular, each IRB should include at least one member whose primary concerns are in the scientific area and at least one member whose primary concerns are in nonscientific areas. On the other hand, each IRB should include at least one member

who is not affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution. Furthermore, no IRB should have a member participate in the IRB's initial or continuous review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

1.4.3 Safety Report

The sponsor of an IND is required to notify the FDA and all participating investigators in a written IND safety report of any adverse experience associated with use of the drug. Adverse experiences that need to be reported include serious and unexpected adverse experiences. A serious adverse experience is defined as any experience that is fatal, life-threatening, requiring inpatient hospitalization, prolongation of existing hospitalization, resulting in persistent or significant disability/incapacity, or congenital anomaly/birth defect. An unexpected adverse experience is referred to as any adverse experience that is not identified in nature, severity, or frequency in the current investigator brochure or the general investigational plan or elsewhere in the current application, as amended.

The FDA requires that any serious and unexpected adverse experience associated with use of the drug in the clinical studies conducted under the IND be reported in writing to the agency and all participating investigators within 10 working days. The sponsor is required to fill out the FDA–1639 form to report an adverse experience. Fatal or immediately life-threatening experiences require a telephone report to the agency within three working days after receipt of the information. A follow-up of the investigation of all safety information is also expected.

1.4.4 Treatment IND

During the clinical investigation of the drug under an IND submission, it may be necessary and ethical to make the drug available to those patients who are not in the clinical trials. Since 1987 the FDA permits an investigational drug to be used under a treatment protocol or treatment IND if the drug is intended to treat a serious or immediately life-threatening disease, especially when there is no comparable or satisfactory alternative drug or other therapy available to treat that stage of the disease in the intended patient population. The FDA, however, may deny a request for treatment use of an investigational drug under a treatment protocol or treatment IND if the sponsor fails to show that the drug may be effective for its intended use in its intended patient population or that the drug may expose the patients to an unreasonable and significant additional risk of illness or injury.

1.4.5 Withdrawal and Termination of an IND

At any time a sponsor may withdraw an effective IND without prejudice. However, if an IND is withdrawn, the FDA must be notified and all clinical investigations conducted under the IND submission shall be ended. If an IND is withdrawn because of a safety reason, the sponsor has to promptly inform the FDA, all investigators, and all IRBs with the reasons for such withdrawal.

If there are any deficiencies in the IND or in the conduct of an investigation under an IND submission, the FDA may terminate an IND. If an IND is terminated, the sponsor must end all clinical investigations conducted under the IND submission and recall or dispose of all unused supplies of the drug. Some examples of deficiencies in an IND are discussed under 21 CFR 312.44. For example, the FDA may propose to terminate an IND if it finds

that human subjects would be exposed to an unreasonable and significant risk of illness or injury. In such a case, the FDA will notify the sponsor in writing and invite correction or explanation within a period of 30 days. A terminated IND is subject to reinstatement based on additional submissions that eliminate such risk. In this case, a regulatory hearing on the question of whether the IND should be reinstated will be held.

1.4.6 Communication with the FDA

The FDA encourages open communication regarding any scientific or medical question that may be raised during the clinical investigation. Basically, it is suggested that such communication be arranged at the end of the phase II study and prior to a marketing application. The purpose of an end-of-phase II meeting is to review the safety of the drug proceeding to phase III. This meeting is helpful not only in that it evaluates the phase III plan and protocols but also in that it identifies any additional information necessary to support a marketing application for the uses under investigation. Note that a similar meeting may be held at the end of phase I in order to review results of tolerance/safety studies and the adequacy of the remaining development program. At the end of phase I, a meeting would be requested by a sponsor when the drug or biologic product is being developed for a life-threatening disease and the sponsor wishes to file under the expedited registration regulations. The purpose of pre-NDA meetings is not only to uncover any major unresolved problems but also to identify those studies that are needed for establishment of drug effectiveness. In addition, the communication enables the sponsor to acquaint FDA reviewers with the general information to be submitted in the marketing application. More importantly, the communication provides the opportunity to discuss (1) appropriate methods for statistical analysis of the data and (2) the best approach to the presentation and formatting of the data.

1.5 NEW DRUG APPLICATION

For approval of a new drug, the FDA requires at least two adequate well-controlled clinical studies be conducted in humans to demonstrate substantial evidence of the effectiveness and safety of the drug. The *substantial evidence* as required in the Kefaurer–Harris amendments to the FD&C Act in 1962 is defined as the evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports to have as represented under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof. Based on this amendment, the FDA requests that reports of adequate and well-controlled investigations provide the primary basis for determining whether there is *substantial evidence* to support the claims of new drugs and antibiotics. Section 314.126 of 21 CFR provides the definition of an adequate and well-controlled study, which is summarized in Table 1.5.1. It can be seen from Table 1.5.1 that an adequate and well-controlled study is judged by eight criteria specified in the CFR. These criteria are objectives, method of analysis, design of studies, selection of subjects, assignment of subjects, participants of studies, assessment of responses, and assessment of the effect.

Each study should have a very clear statement of objectives for clinical investigation such that they can be reformulated into statistical hypotheses and estimation procedures. In addition proposed methods of analyses should be described in the protocol and actual

Table 1.5.1 Characteristics of an Adequate and Well-Controlled Study

Criteria	Characteristics
Objectives	Clear statement of investigation's purpose
Methods of analysis	Summary of proposed or actual methods of analysis
Design	Valid comparison with a control to provide a quantitative assessment of drug effect
Selection of subjects	Adequate assurance of the disease or conditions under study
Assignment of subjects	Minimization of bias and assurance of comparability of groups
Participants of studies	Minimization of bias on the part of subjects, observers, and analysts
Assessment of responses	Well-defined and reliable
Assessment of the effect	Requirements of appropriate statistical methods

statistical methods used for analyses of data should be described in detail in the report. Each clinical study should employ a design that allows a valid comparison with a control for an unbiased assessment of drug effect. Therefore, selection of a suitable control is one key to integrity and quality of an adequate and well-controlled study. The CFR recognizes the following controls: placebo concurrent control, dose-comparison concurrent control, no treatment control, active concurrent control, and historical control. Next, the subjects in the study should have the disease or condition under study. Furthermore, subjects should be randomly assigned to different groups in the study to minimize potential bias and ensure comparability of the groups with respect to pertinent variables such as age, gender, race, and other important prognostic factors. All statistical inferences are based on such randomization and possibly stratification to achieve these goals. However, bias will still occur if no adequate measures are taken on the part of subjects, investigator, and analysts of the study. Therefore, blinding is extremely crucial to eliminate the potential bias from this source. Usually an adequate and well-controlled study is at least double blinded, whereby investigators and subjects are blinded to the treatments during the study. However, currently a triple-blind study in which the sponsor (i.e., clinical monitor) of the study is also blinded to the treatment is not uncommon. Another critical criterion is the validity and reliability of assessment of responses. For example, the methods for measurement of responses such as symptom scores for benign prostate hyperplasia should be validated before their usage in the study (Barry et al., 1992). Finally, appropriate statistical methods should be used for assessment of comparability among treatment groups with respect to pertinent variables mentioned above and for unbiased evaluation of drug effects.

Section 314.50 of 21 CFR specifies the format and content of an NDA, which is summarized in Table 1.5.2. The FDA requests that the applicant should submit a complete archival copy of the new drug application form with a cover letter. In addition, the sponsor needs to submit a review copy for each of the six technical sections with the cover letter, application form (356H) of (a), index of (b), and summary of (c) as given in Table 1.5.2 to each of six reviewing disciplines. The reviewing disciplines include chemistry reviewers for chemistry, manufacturing, and controls; pharmacology reviewers for nonclinical pharmacology and toxicology; medical reviewers for the clinical data section; and statisticians for the statistical technical section. The outline of review copies for clinical reviewing divisions include (1) cover letter, (2) application form (356H), (3) index, (4) summary, and (5) clinical section. The outline of review copies for the statistical reviewing division consists of (1) cover letter, (2) application form (356H), (3) index, (4) summary, and (5) statistical section.

Table 1.5.2 A Summary of Contents and Format of a New Drug Application (NDA)

Cover letter
(a) Application form (365H)
(b) Index
(c) Summary
(d) Technical sections
  (1) Chemistry, manufacturing, and controls section
  (2) Nonclinical pharmacology and toxicology section
  (3) Human pharmacology and bioavailability section
  (4) Microbiology (for anti-infective drugs) section
  (5) Clinical data section
  (6) Statistical section
  (7) Pediatric use section
(e) Samples and labeling
(f) Case report forms and tabulations
  (1) Case report tabulations
  (2) Case report forms
  (3) Additional data
(g) Other

Note: Based on Section 314.50 of Part 21 of Codes of Federal Regulation (4-1-2010 edition).

Table 1.5.3 provides a summary of the format and content of a registration dossier for the European Medicines Agency (EMEA), which is based on the Organization of Common Technical Document (CTD) issued as topic M4 by the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use in 2004. A comparison of Table 1.5.2 and Table 1.5.3 reveals that the information required by the FDA and ECC for marketing approval of a drug is similar although in different formats. However, no statistical technical section is required in the ECC registration. In October 1988, to assist an applicant in presenting the clinical and statistical data required as part of an NDA submission, the CDER of the FDA issued the *Guideline for the Format and Content of the Clinical and Statistical Sections of an Application* under 21 CFR 314.50, which is summarized in Table 1.5.4. The guideline indicates the preference of having one integrated clinical and statistical report rather than two separate reports. A complete submission should include clinical section [21 CFR 314.50(d)(5)], statistical section [21 CFR 314.50(d)(6)], and case report forms and tabulations [21 CFR 314.50(f)]. The same guideline also provides the content and format of the fully integrated clinical and statistical report of a controlled clinical study in an NDA. A summary of it is given in Table 1.5.5.

1.5.1 Expanded Access

A standard clinical development program of phases I, II, and III clinical trials and traditional approval of a new pharmaceutical entity through the IND and NDA processes by the FDA will generally take between 8 and 12 years with an average cost around US$1 billion. Kessler and Feiden (1995) indicated that, on average, the FDA receives around 100 original

Table 1.5.3 Organization of Common Technical Document by EMEA

Module 1:	Administrative Information and Prescribing Information
	1.1 Table of Contents of the Submission Including Module 1
	1.2 Documents Specific to Each Region (e.g., application forms, prescribing information)
Module 2:	Common Technical Document Summaries
	2.1 Common Technical Document Table of Contents (Modules 2–5)
	2.2 CTD Introduction
	2.3 Quality Overall Summary
	2.4 Nonclinical Overview
	2.5 Clinical Overview
	2.6 Nonclinical Written and Tabulated Summaries
	Pharmacology
	Pharmacokinetics
	Toxicology
	2.7 Clinical Summary
	Biopharmaceutic Studies and Associated Analytical Methods
	Clinical Pharmacology Studies
	Clinical Efficacy
	Clinical Safety
	Literature References
	Synopses of Individual Studies
Module 3:	Quality
	3.1 Table of Contents of Module 3
	3.2 Body of Data
	3.3 Literature References
Module 4:	Nonclinical Study Reports
	4.1 Table of Contents of Module 4
	4.2 Study Reports
	4.3 Literature References
Module 5:	Clinical Study Reports
	5.1 Table of Contents of Module 5
	5.2 Tabular Listing of All Clinical Studies
	5.3 Clinical Study Reports
	5.4 Literature References

NDAs each year. For each NDA submission, the FDA requires substantial evidence of efficacy and safety be provided with fully matured and complete data generated from at least two adequate and well-controlled studies before it can be considered for approval. This requirement is necessary for drugs with marginal clinical advantages and for treatment of conditions or diseases that are not life-threatening. However, if the diseases are life-threatening or severely debilitating, then the traditional clinical development and approval process might not be soon enough for the subjects whose life may be saved by the promising drugs. According to Section 312.81 in 21 CFR, life-threatening diseases are defined as (1)

Table 1.5.4 Summary of the Clinical and Statistical Section of an NDA

A. List of investigators; list of INDs and NDAs
B. Background/overview of clinical investigations
C. Clinical pharmacology
D. Control clinical studies
E. Uncontrolled clinical studies
F. Other studies and information
G. Integrated summary of effectiveness data
H. Integrated summary of safety data
I. Drug abuse and overdosage
J. Integrated summary of benefits and risks of the drug

Source: Based on *Guideline for the Format and Content of the Clinical and Statistical Sections of an Application* (July 1988, Center for Drug Evaluation and Research, FDA).

the diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted and (2) diseases or conditions with potentially fatal outcomes, where the endpoint of clinical trial analysis is survival. On the other hand, severely debilitating diseases are those that cause major irreversible morbidity. Since 1987 regulations have been established for early access to promising experimental drugs and for accelerated approval of drugs for treatment of life-threatening or severely debilitating diseases.

Expanded access is devised through treatment IND (Section 312.34 of 21 CFR) and parallel track regulations. For a serious or immediately life-threatening disease with no satisfactory therapy available, as mentioned before, a treatment IND allows promising new drugs to be widely distributed even when data and experience are not sufficient enough for a full marketing approval. On the other hand, for example, for patients infected with human

Table 1.5.5 Summary of Format and Contents of a Fully Integrated Clinical and Statistical Report for a Controlled Study in an NDA

A. Introduction
B. Fully integrated clinical and statistical report of a controlled clinical study
    1. Title page
    2. Table of contents for the study
    3. Identity of the test materials, lot numbers, etc.
    4. Introduction
    5. Study objectives
    6. Investigational plan
    7. Statistical methods planned in the protocol
    8. Disposition of patients entered
    9. Effectiveness results
    10. Safety results
    11. Summary and conclusion
    12. References
    13. Appendices

Source: Based on *Guideline for the Format and Content of the Clinical and Statistical Sections of an Application* (July 1988, Center for Drug Evaluation and Research, FDA).

immunodeficiency virus (HIV) who are not qualified for clinical trials and have no other alternative treatment, parallel track regulations issued in 1992 provide a means for these patients to obtain experimental therapy very early in the development stage through their private physicians. In 1992 the FDA also established regulations for accelerated approval of the drug for serious or life-threatening diseases based on a surrogate clinical endpoint other than survival or irreversible morbidity (Subpart H of Section 314 in 21 CFR). A concept for approval called *Telescoping Trials* has also emerged (Kessler and Feiden, 1995). Under this concept, phase III clinical trials might be totally eliminated. For example, the FDA might consider approval of a drug for a serious disease which, during phase II clinical trials, demonstrates a positive impact on survival or irreversible morbidity. A successful example of expanded access and accelerated approval provided by these regulations is the review and approval of dideoxyinosine (ddI) of Bristol-Myers Squibb Company for patients with HIV. An expanded access to ddI was initiated in September 1989. The new drug application based on the data of phase I clinical trials with no control group was filed in April 1991. The FDA granted conditional approval of the drug in October 1991 based on a clinical surrogate endpoint called a CD4+ lymphocyte count. With the data from phases II and III clinical trials submitted in April 1992, the approval of ddI was broadened in September 1992. Another example for fast-track development and accelerated approval is the case of fludarabine phosphate (fludara) for treatment of refractory chronic lymphocytic leukemia (CLL) (Tessman, Gipson, and Levins, 1994). Fludara is the first new drug approved for this common form of adult leukemia in the United States over 50 years. The NDA, filed in November 1989 and approved in April 1991, was in fact based on retrospective analyses of phase II clinical trials conducted by the NCI through cooperative groups including Southwest Oncology Group (SWOG) and M. D. Anderson Cancer Center in Houston, Texas. In addition, an early access to the drug was provided in 1989 through NCI's Group C protocol, which is equivalent to NCI's version of treatment IND. The last example is the approval of Gleevec (omatinib mesylate) oral treatment for patients with chronic myeloid leukemia (CML) by the U.S. FDA in 2001. Gleevec is a specific inhibitor of tyrosine kinase enzymes that plays an important role in CML. Under accelerated approval regulation and orphan drug status, the U.S. FDA reviewed and approved the marketing application in less than 3 months. This approval for three phases of CML was based on separate single-arm studies using surrogate endpoints such as major cytogenetic response. One of these studies was recently published (Kantarjian et al., 2002). However, the then U.S. FDA acting commissioner, B. A. Schwetz, D.V.M., Ph.D., indicated that further studies are needed to evaluate whether Gleevec provides an actual clinical benefit, such as improved survival.

1.5.2 Abbreviated New Drug Application

An abbreviated NDA (ANDA) is usually reserved for drug products (e.g., generics) that duplicate products previously approved under a full NDA. For an ANDA, reports of nonclinical laboratory studies and clinical investigations except for those pertaining to in vivo bioavailability of the drug product are not required. The information may be omitted when the FDA has determined that the information already available to it is adequate to establish that a particular dosage form of a drug meets the statutory standards for safety and effectiveness. The duplicate products are usually referred to as products with the same active ingredient(s), route of administration, dosage form, strength, or condition of use that may be made by different manufacturers.

As mentioned earlier, under the *Drug Price Competition and Patient Term Restoration Act* passed in 1984, the FDA may approve generic drug products if the generic drug companies can provide evidence that the rates and extents of absorption of their drug products do not show a significant difference from those of the innovator drug products when administered at the same molar dose of the therapeutic moiety under similar experimental conditions (21 CFR 320). The *Drug Price Competition and Patent Term Restoration Act* states the FDA's authority for all generic drug approvals through an ANDA submission for bioequivalence review. An ANDA submission should include product information, pharmacokinetic data and analysis, statistical analysis, analytical methodology and validation, and clinical data. In the ANDA submission the FDA requires the sponsor to provide necessary information regarding the drug product such as formulation, potency, expiration dating period (or shelf life), and dissolution data. For example, the dissolution profile of the generic drug product should be comparable to that of the innovator drug product for drug release. Before the conduct of a bioavailability and bioequivalence study, the FDA also requires the sponsor to provide validation data for the analytical method used in the study. The analytic method should be validated according to standards specified in the U.S. Pharmacopeia and National Formulary (USP/NF, 2002). For example, the analytical method needs to be validated in terms of its accuracy, precision, selectivity, limit of detection, limit of quantitation, range, linearity, and ruggedness (Chow and Liu, 1995b). For pharmacokinetic data, descriptive statistics should be given by the sampling time point and for each pharmacokinetic response. To ensure the validity of bioequivalence assessment, the Division of Bioequivalence, Office of Generic Drugs of the CDER at the FDA issued *Guidances on Bioavailability and Bioequivalence Studies for Orally Administrated Drug Products—General Consideration* in March 2003 and *Statistical Approaches to Establishing Bioequivalence* in January 2001, respectively. The guidance sets forth regulations for valid statistical analysis for bioequivalence assessment. Note that detailed information regarding statistical design and analysis of bioavailability and bioequivalence studies can be found in Chow and Liu (2008). In addition, any relevant clinical findings, adverse reactions, and deviation from the protocol need to be included in the ANDA submission.

1.5.3 Supplemental New Drug Application

A supplemental NDA (SNDA) is referred to as documentation submitted to the FDA on a drug substance or product that is already the subject of an approved NDA. Supplements may be submitted for a variety of reasons such as labeling changes, a new or expanded clinical indication, or a new dosage form. For example, for labeling changes, the sponsor may want to add a new specification or test method or changes in the methods, facility, or controls to provide increased assurance that the drug will have the characteristics of identity, strength, quality, and purity that it purports to possess. For drug substance and/or drug product, the sponsor may want to relax the limits for a specification, establish a new regulatory analytical method, or delete a specification or regulatory analytical method. In addition, the sponsor may want to extend the expiration date of the drug product based on data obtained under a new or revised stability testing protocol that has not been approved in the application or to establish a new procedure for reprocessing a batch of the drug product that fails to meet specification. However, it should be noted that in an SNDA, the sponsor is required to fully describe the change in each condition established in an approved application beyond the variation already provided for in the application.

1.5.4 Advisory Committee

The FDA has established advisory committees, each consisting of clinical, pharmacological, and statistical experts and one consumer advocate (not employed by the FDA) in designated drug classes and subspecialties. The responsibilities of the committees are to review data presented in NDAs and to advise the FDA as to whether there exists substantial evidence of safety and effectiveness based on adequate and well-controlled clinical studies. In addition, the committee may also be asked at times to review certain INDs, protocols, or important issues relating to marketed drugs and biologics. The advisory committees not only supplement the FDA's expertise but also allow an independent peer review during the regulatory process. Note that the FDA usually prepares a set of questions for the advisory committee to address at the meeting. The following is a list of some typical questions:

1. Are there two or more adequate and well-controlled trials?
2. Have the patient populations been characterized well enough?
3. Has the dose–response relationship been characterized sufficiently?
4. Do you recommend the use of the drug for the indication sought by the sponsor for the intended patient population?

The FDA usually will follow the recommendations made by the Advisory Committee for marketing approval, though they do not have to do so legally.

1.6 CLINICAL DEVELOPMENT AND PRACTICE

Clinical research and development in the pharmaceutical environment is to scientifically evaluate the benefits and risks of promising pharmaceutical entities at a minimal cost and within a very short time frame. To ensure the success of the development of the pharmaceutical entity, a clinical development plan is necessary.

1.6.1 Clinical Development Plan

A clinical development plan (CDP) is a description of clinical studies that will be carried out in order to assess the safety and effectiveness of the drug. A clinical development plan typically includes a development rationale, listing of trial characteristics, timeline, cost, and resource requirements. A good and flexible clinical development plan is extremely crucial and important to the success and unbiased assessment of a potential pharmaceutical entity. Although a typical CDP is based primarily on the validity of medical and scientific considerations, other factors that involve issues such as biostatistics, regulations, marketing, and management are equally important. For a successful CDP, we first need to define a product profile for the promising pharmaceutical entity before any clinical development. Table 1.6.1 lists essential components of a product profile. These components set the goals and objectives for the clinical development program of a pharmaceutical entity. A clinical development program is referred to as the set of different clinical trial plans at different stages with milestones for assessment and decision making to evaluate the goals and objectives stated in the product profile. For example, if the drug product under development is for an indication intended for a particular population, the relative merits and disadvantages of the product as compared to other products either on the market or still under development should objectively be assessed. In order to evaluate the relative

Table 1.6.1 Components of a Pharmaceutical Product Profile

Target population
Innovation potentials
Therapeutic concepts
Innovative elements
Technological advances
Patent status
Route of administrations
Doses
Formulations
Regimens
Duration of dosing
Status of market
Current competitors
On market
Under development
Advantages
Disadvantages
Minimum requirements
Efficacy
Safety
Termination criteria
Efficacy
Safety
Time frames
Milestones

merits, minimum requirements and termination criteria on the effectiveness and safety of the product are usually set. These requirements and criteria are evaluated through statistical analysis of data collected from a series of clinical trials. The deadlines for milestones and decision making should also be scheduled in the CDP according to the time when certain clinical trials to evaluate the requirements and criteria are completed and the data are adequately analyzed. Since a huge investment is usually necessarily committed to develop a new pharmaceutical entity, information based on efficacy and safety alone may not be enough to evaluate a potential product. It is therefore recommended that cost-effectiveness and quality of life be evaluated, especially for the me-too products in a saturated market. In this case, requirements and criteria for cost-effectiveness and quality of life need to be included at milestones and/or decision-making points. As indicated earlier, although many factors such as statistics, marketing, regulations, and management need to be considered in a CDP, the scientific validity of clinical investigations is the key to the success of a clinical development program.

In the pharmaceutical industry, clinical development of a pharmaceutical entity starts with seeking alternatives or new drug therapies for an existing health problem or a newly identified health problem. The health problem of interest may be related to virus-induced diseases, cardiovascular disease, cancer, or other diseases. Once the health problem is selected or identified, whether it is worth developing an alternative or a new pharmaceutical entity for this particular disease is a critical development decision point. A clear decision point can increase the success of the project and consequently reduce the risk and cost. Suppose that it is decided to proceed with the development of a pharmaceutical entity

(e.g., enzymes or receptors). A number of chemical modifications and ADME tests in animals may be necessary before it can be tested on humans. ADME studies are used to determine how a drug is taken up by the body, where it goes in the body, the chemical changes it undergoes in the body, and how it is eliminated from the body. ADME studies describe the pharmacokinetics and bioavailability of a drug. If the drug shows promising effectiveness and safety in animals, the sponsor normally will make a decision to go for an IND submission. As indicated in Section 1.4, an IND submission is a synthesis process that includes formulation, analytical method development and validation, stability, animal toxicity, pharmacokinetic/ pharmacology, previous human experience, and clinical development. The sponsor will then prepare a registration document that combines all the relevant data to allow the FDA to review and decide whether to approve marketing of the new drug. As discussed in Section 1.5, an NDA submission should include chemistry, pharmacology, toxicology, metabolism, manufacturing, quality controls, and clinical data along with the proposed labeling.

1.6.2 Good Clinical Practice

Good clinical practice (GCP) is usually referred to as a set of standards for clinical studies to achieve and maintain high-quality clinical research in a sensible and responsible manner. The FDA, the Committee for Medicinal Products for Human Use (CHMP) for the EMEA, the Ministry of Health, Labour & Welfare (MHLW) of Japan, and other countries worldwide have each issued guidelines on good clinical practices. For example, the FDA promulgated a number of regulations and guidelines governing the conduct of clinical studies from which data will be used to support applications for marketing approval of drug products. The FDA regulations refer to those regulations specified in 21 CFR Parts 50, 56, 312, and 314, while the FDA guidelines are guidelines issued for different drug products such as *Guidelines for the Clinical Evaluation of Anti-Anginal Drugs* and *Guidelines for the Clinical Evaluation of Bronchodilator Drugs*. On the other hand, the European Community established the principles for their own GCP standard in all four phases of clinical investigation of medicinal products in July 1990. Basically, these guidelines define the responsibilities of sponsors, monitors, and investigators in the initiation, conduct, documentation, and verification of clinical studies to establish the credibility of data and to protect the rights and integrity of study participants.

In essence, GCP concerns patient protection and the quality of data used to prove the efficacy and safety of a drug product. GCP ensures that all data, information, and documents relating to a clinical study can be confirmed as being properly generated, recorded, and reported through the institution by independent audits. Therefore, the basic GCP concerns are not only the protection of study subjects through informed consent and consultation by ethics committees such as an IRB but also the responsibilities of the sponsors and monitors to establish written procedures for study monitoring and conduct and to ensure that such procedures are followed. In addition, GCP emphasizes the responsibilities of the investigator to conduct the study according to the protocol and joint responsibilities for data reporting, recording, analysis, and archiving as well as prompt reporting of serious adverse events. Moreover, GCP calls for the most appropriate design for a valid statistical evaluation of the hypotheses of the clinical trials. The chosen design must suit the purpose with the best possible fit. Incorporating the concerns of GCP in the protocol will ensure a protocol of high standard, which in turn will help generate high-quality data.

Study conduct according to GCP standards requires regular visits to study centers to monitor trial progress. The activities of the sponsor's monitors that will affect the

investigator and support staff should be stated in the protocol. Not only is this courteous, but it prevents misunderstanding, facilitates cooperation, and aids the speedy acquisition of a completed case report form. The activities include frequency of monitoring visits, activities while on site (e.g., auditing CRFs), and departments to be visited (e.g., pharmacy). The practical effects of adopting GCP are that the investigator is audited by the sponsor's monitors (to confirm data on CRFs are a true transcript of original records), by a sponsor administratively separate from the clinical function, and, in some countries, by the national regulatory agency. The sponsor's monitors are audited by a compliance staff and by national regulatory agencies to confirm the accuracy of data recorded and the implementation of all written procedures such as standard operating procedure (SOP) and protocol.

Most of pharmaceutical companies and research institutions have a protocol review committee (PRC) to evaluate the quality and integrity of the protocol and hence to approve or disapprove the protocol. Some companies also ask the principal study medical monitor and statistician to submit a case report form (CRF) and a statistical analysis plan with mock tables and listing for presentation of the results to a PRC at the same time when the protocol is submitted for review.

Lisook (1990) has assembled a GCP packet to assist the sponsors in the planning, execution, data analysis, and submission of results to the FDA. A summary of this GCP packet is given in Table 1.6.2. Most of these regulations have been discussed in the previous sections of this chapter. To improve the conduct and oversight of clinical research and to

Table 1.6.2 References to Keep at Hand for Good Clinical Practice

1. Information on FDA regulations
2. Center for Drug Evaluation and Research publications
3. Clinical Investigations (excerpt from the *Federal Register*, September 27, 1977)
4. Protection of Human Subjects, Informed Consent Forms
5. New Drug, Antibiotic, and Biologic Drug Product Regulations; Final Rule (excerpt from the *Federal Register*, March 19, 1987)
6. Investigational New Drug, Antibiotic, and Biologic Drug Product Regulations; Treatment Use and Sale; Final Rule (excerpt from the *Federal Register*, May 22, 1987)
7. *Guideline for the Monitoring of Clinical Investigations*
8. Investigational New Drug, Antibiotic, and Biologic Drug Product Regulations; Procedure Intended to Treat Life-Threatening and Severely Debilitating Illness; Interim Rule (excerpt from the *Federal Register*, October 22, 1988)
9. FDA IRB (Institutional Review Board) Information Sheets
10. FDA Clinical Investigator Sheet
11. Reprint of Alan B. Lisook, M.D. FDA audits of clinical studies: policy and procedure, *Journal of Clinical Pharmacology*, 30 (April 1990), 296–302.
12. Federal Policy for the Protection of Human Subjects; Notices and Rules (excerpt from the *Federal Register*, June 18, 1991)
13. *FDA Compliance Program Guidance Manual—Clinical Investigators* (December 8, 2008)
14. *FDA Compliance Program Guidance Manual—Sponsors, Contract Research Organization and Monitors* (March 11, 2011)
15. *FDA Compliance Program Guidance Manual—Institutional Review Board* (September 30, 1997)
16. FDA *Compliance Program Guidance Manual—In Vivo Bioequivalence* (October 1, 1999)

Table 1.6.3 Review Steps for the ICH Guidelines

Step 1: Consensus Building

1. Harmonized topic identified
2. Expert working group (EWG) formed
3. Each party has a topic leader and a deputy
4. Rapporteur for EWR selected
5. Other parties represented on EWG as appropriate
6. Produce a guideline, policy statement, and "points to consider"
7. Agreement on scientific issues
8. Sign-off and submit to the ICH steering committee

Step 2: Confirmation of Six-Party Consensus

1. Review of ICH document by steering committee
2. Sign-off by all six parties
3. Formal consultation in accord with regional requirements

Step 3: Regulatory Consultation and Discussion

1. Regulatory rapporteur appointed
2. Collection and review of comments across all three regions
3. Step 2 draft revised
4. Sign-off by EWR regulatory members

Step 4: Adoption of an ICH Harmonized Tripartite Guideline

1. Forward to steering committee
2. Review and sign-off by three regulatory members of ICH
3. Recommend for adoption to regulatory bodies

Step 5: Implementation

1. Recommendations are adopted by regulatory agencies
2. Incorporation into domestic regulations and guidelines

ensure the protection of subjects participating in the FDA-regulated clinical research, the U.S. FDA established the Office of Good Clinical Practice (OGCP) within the Office of the Commissioner and its Office of Special Medical Programs. This new office has distinct roles from the Office of Human Research Protections (OHRP) of the Department of Health and Human Services (DHHS). These distinct roles include (1) coordination of the FDA's policies, (2) provision of leadership and direction through the administration of the FDA's Human Subject Protection/Good Clinical Practice Steering Committee, (3) coordination of the FDA's Bioresearch Monitoring Program, (4) contribution to the international GCP harmonization activities, (5) planning and conducting training and outreach programs, and

Table 1.6.4 Summary of the Number of ICH Guidelines or Draft Guidelines

	Step 1	Step 2	Step 3	Step 4	Step 5
Efficacy	0	0	0	0	22
Safety	0	1	0	0	14
Quality	0	4	0	0	36
Multidiscipline	0	0	0	0	6

Table 1.6.5 The ICH Clinical Guidelines or Draft Guidelines

1. ElA: The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions
2. E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting
3. E2B: Data Elements for Transmission of Individual Case Safety Reports
4. E2B(M): Data Elements for Transmission of Individual Case Safety Reports – Questions and Answers
5. E2B(R): Electronic Transmission of Individual Case Safety Reports Message Specification
6. E2C: Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs
7. E2D: Postapproval Safety Data Management: Definitions and Standards for Expedited Reporting
8. E2E: Pharmacovigilance Planning
9. E2F: Development Safety Update Report
10. E3: Structure and Content of Clinical Studies
11. E4: Dose–Response Information to Support Drug Registration
12. E5: Ethnic Factors in the Acceptability of Foreign Clinical Data
13. E6: Good Clinical Practice: Consolidated Guideline
14. E7: Studies in Support of Special Populations: Geriatrics
15. E8: General Considerations for Clinical Trials
16. E9: Statistical Principles for Clinical Trials
17. E10: Choice of Control Group in Clinical Trials
18. E11: Clinical Investigation of Medicinal Products in the Pediatric Population
19. E12A: Principles for Clinical Evaluation of New Antihypertensive Drugs
20. E14: Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-antiarrhythmic Drugs
21. E15: Pharmacogenomics Definitions and Sampling Coding
22. E16: Genomic Biomarkers Related to Drug Response: Context, Structure, and Format of Qualification Submission
23. M2: eCTD: Electronic Common Technical Document Specification
24. M3(R2): Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals
25. M4: Common Technical Document for the Registration of Pharmaceuticals for Human Use—Main Document

    Organization

    Granularity Annex

    Efficacy

    Safety

    Safety Appendices

    Quality

(6) serving as a liaison with OHRP and other federal agencies and other stakeholders committed to the protection of human research participants.

In the past, as demonstrated in Tables 1.5.2, 1.5.3, and 1.5.5, health regulatory authorities in different countries have different requirements for approval of commercial use of drug products. As a result, considerable resources had been spent by the pharmaceutical industry

Table 1.6.6 Table of Contents for the Guideline on General Considerations for Clinical Trials

in the preparation of different documents for applications of the same pharmaceutical product to meet different regulatory requirements requested by different countries or regions. However, because of globalization of the pharmaceutical industry, arbitrary differences in regulations, increase of health care costs, need for reduction of time for patients to access new drugs and reduction of experimental use of humans and animals without compromising safety, the necessity to standardize these similar yet different regulatory requirements has been recognized by both regulatory authorities and the pharmaceutical industry. Hence, the International Conference on Harmonisation (ICH) of Technical Requirements for the Registration of Pharmaceuticals for Human Use was organized in 1990 to provide an opportunity for important initiatives to be developed by regulatory authorities as well as industry association for the promotion of international harmonization of regulatory requirements.

The ICH was originally concerned with tripartite harmonization of technical requirements for the registration of pharmaceutical products among three regions: the European Union, Japan, and the United States. Basically, the ICH Steering Committee (SC) is the governing body consisting of six cosponsors: European Commission of the European Union, the European Federation of Pharmaceutical Industries' Associations (EFPIA), the Japanese Ministry of Health, Labor and Welfare (MHLW), the Japanese Pharmaceutical Manufacturers Association (JPMA), the Centers for Drug Evaluation and Research and Biologics Evaluation and Research of the U.S. FDA, and the Pharmaceutical Research and Manufacturers of America (PhRMA). Each of its six cosponsors has two seats on the SC: one from a regulatory authority and one from the pharmaceutical industry, from each of the three regions. The functions of the ICH steering committee include (1) determining policies and procedures, (2) selecting topics, (3) monitoring progress, and (4) overseeing preparation of biannual conferences. The ICH Steering Committee also includes observers from the World Health Organization, Health Canada, and the European Free Trade Area (EFTA). In addition, two seats of the ICH Steering Committee are given to the International

Table 1.6.7 Table of Contents for the ICH Guideline on Good Clinical Practice: Consolidated Guideline

Introduction

1. Glossary
2. The Principles of ICH GCP
3. The Institutional Review Board/Independent Ethics Committee (IRB/IEC)
   - 3.1 Responsibilities
   - 3.2 Composition, functions, and operations
   - 3.3 Procedures
   - 3.4 Records
4. Investigators
   - 4.1 Investigators' qualifications and agreements
   - 4.2 Adequate resources
   - 4.3 Medical care of trial subjects
   - 4.4 Communication with IRB/IEC
   - 4.5 Compliance with protocol
   - 4.6 Investigational products
   - 4.7 Randomization procedures and unblinding
   - 4.8 Informed consent of trial subjects
   - 4.9 Records and reports
   - 4.10 Progress reports
   - 4.11 Safety reporting
   - 4.12 Premature termination or suspension of a trial
   - 4.13 Final report(s) by investigator/institution
5. Sponsor
   - 5.1 Quality assurance and quality control
   - 5.2 Contract research organization
   - 5.3 Medical expertise
   - 5.4 Trial design
   - 5.5 Trial management, data handling, recordkeeping, and independent data monitoring committee
   - 5.6 Investigator selection
   - 5.7 Allocation of duties and functions
   - 5.8 Compensation to subjects and investigators
   - 5.9 Financing
   - 5.10 Notification/submission to regulatory authority(ies)
   - 5.11 Confirmation of review of IRE/IEC
   - 5.12 Information on investigational product(s)
   - 5.13 Manufacturing, packaging, labeling, coding investigational product(s)
   - 5.14 Supplying and handling investigational product(s)
   - 5.15 Record access
   - 5.16 Safety information
   - 5.17 Adverse drug reaction reporting
   - 5.18 Monitoring

Table 1.6.7 (*Continued*)

- 5.19 Audit
- 5.20 Noncompliance
- 5.21 Premature termination or suspension of a trial
- 5.22 Clinical trial/study reports
- 5.23 Multicenter trials

6. Clinical Trial Protocol and Protocol Amendment(s)
   - 6.1 General information
   - 6.2 Background information
   - 6.3 Trial objectives and purpose
   - 6.4 Trial design
   - 6.5 Selection and withdrawal of subjects
   - 6.6 Treatment of subjects
   - 6.7 Assessment of efficacy
   - 6.8 Assessment of safety
   - 6.9 Statistics
   - 6.10 Direct access to source data/documents
   - 6.11 Quality control and quality assurance
   - 6.12 Ethics
   - 6.13 Data handling and recordkeeping
   - 6.14 Financing and insurance
   - 6.15 Publication
   - 6.16 Supplements
7. Investigator's Brochure
   - 7.1 Introduction
   - 7.2 General considerations
   - 7.3 Contents of the investigator's brochure
   - 7.4 Appendix 1
   - 7.5 Appendix 2
8. Essential Documents for the Conduct of a Clinical Trial
   - 8.1 Introduction
   - 8.2 Before the clinical phase of the trial commences
   - 8.3 During the clinical conduct of the trial
   - 8.4 After completion or termination of the trial

Federation of Pharmaceutical Manufacturers Association (IFPMA) which hosts the ICH Secretariat at Geneva, Switzerland, and participates as a nonvoting member of the SC, which coordinates the preparation of documentation. The Global Cooperation Group (GCG) was formed as a subcommittee of the ICH Steering Committee in 1999 in response to interest in the non-ICH regions. Currently, the GCG includes the following organizations and countries: Asia-Pacific Economic Cooperation (APEC), Association of Southeast Asian Nations (ASEAN), Pan American Network for Drug Regulatory Harmonization (PANDRH), Southern African Development Community (SADC), Australia, Brazil, China, Chinese Taipei, India, South Korea, Russia, and Singapore.

Table 1.6.8 Table of Contents for the ICH Guideline on Structure and Contents of Clinical Study Reports

Introduction to the guideline

1. Title page
2. Synopsis
3. Table of contents for the individual clinical study report
4. List of abbreviations and definition of terms
5. Ethics
6. Investigators and study administrative structure
7. Introduction
8. Study objectives
9. Investigational plan
10. Study patients
11. Efficacy evaluation
12. Safety evaluation
13. Discussion and overall conclusions
14. Tables, figures, graphs referred to but not included in the text
15. Reference list
16. Appendices

In order to harmonize technical procedures, the ICH has issued a number of guidelines and draft guidelines. After the ICH Steering Committee selected the topics, the ICH guidelines were initiated by a concept paper and went through a five-step review process shown in Table 1.6.3. The number of ICH guidelines and draft guidelines at various stages of the review process is given in Table 1.6.4. Table 1.6.5 provides a partial list of ICH guidelines pertaining to clinical trials. A complete updated list of the ICH guidelines or draft guidelines can be found at its website (`http://www.ich.org`). Table 1.6.6 gives the table of contents for the ICH guideline on general considerations for clinical trials. In addition, the table of contents of the ICH guidelines for good clinical practices—consolidated guidelines, for structure and content of clinical study reports, and for statistical principles for clinical trials—are given, respectively in Tables 1.6.7, 1.6.8, and 1.6.9. From these tables, it can be seen that these guidelines are not only for harmonization of design, conduct, analysis, and report for a single clinical trial but also for consensus in protecting and maintaining the scientific integrity of the entire clinical development plan of a pharmaceutical entity. Along this line, Chow (1997, 2003) introduced the concept of *good statistics practice* (GSP) in the drug development and regulatory approval process as the foundation of the ICH GCP. The concepts and principles stated in the ICH clinical guidelines will be introduced, addressed, and discussed in subsequent chapters of this book.

Although the primary goal of the ICH is to harmonize the technical procedures and documents for regulatory submissions, some regulatory agencies still request the unique documentation specific to region. For example, the integrated summary of effectiveness (ISE) and integrated summary of safety (ISS) in the Summary of the Clinical and Statistical Section of an NDA in Table 1.5.5 are unique to the U.S. FDA. In addition, the U.S. FDA points out that Section 2.7.3 Summary of Clinical Efficacy and Section 2.7.4 Summary of Clinical Safety in Module 2 of ICH M4—Efficacy do not describe the needed level of detail

Table 1.6.9 Table of Contents for the ICH Guideline on Statistical Principles for Clinical Trials

for an ISE and ISS. In addition, these clinical summary sections of M2 are limited only to 400 pages, whereas a typical ISS alone can often be substantially larger (FDA, 2009). On the other hand, Module 5 is designed to contain more in-depth analysis and has no space limitation. As a result, the U.S. FDA proposes that Section 5.3.5.3, Reports of Analysis of Data from More than One Study in Module 5, is the appropriate location of the ISE and ISS. In addition, the U.S. FDA issued a guidance on electronic format using eCTD specifications (FDA, 2008).

1.7 AIMS AND STRUCTURE OF THE BOOK

As indicated earlier, clinical trials are scientific investigations that examine and evaluate drug therapies in human subjects. Biostatistics has been recognized and extensively employed as an indispensable tool for the planning, conduct, and interpretation of clinical trials. In clinical research and development, the biostatistician plays an important role that contributes to the success of clinical trials. Well-prepared and open communication among clinicians, biostatisticians, and other related clinical research scientists will result in a successful clinical trial. Communication, however, is a two-way street: Not only (1) must the biostatistician effectively deliver statistical concepts and methodologies to his/her clinical colleagues but also (2) the clinicians must communicate thoroughly the clinical and scientific principles embedded in the clinical research to the biostatisticians. The biostatisticians can then formulate these clinical and scientific principles into valid statistical hypotheses under an appropriate statistical model. Overall, the integrity, quality, and success of a clinical trial depends on the interaction, mutual respect, and understanding between the clinicians and the biostatisticians.

The aim of this book is not only to fill the gap between clinical and statistical disciplines but also to provide a comprehensive and unified presentation of clinical and scientific issues, statistical concepts, and methodology. Moreover, this book focuses on the interactions between clinicians and biostatisticians that often occur during various phases of clinical research and development. This book also gives a well-balanced summarization of current and emerging clinical issues and recently developed corresponding statistical methodologies. Although this book is written from the viewpoint of pharmaceutical research and development, the principles and concepts presented in this book can also be applied to a nonbiopharmaceutical setting.

It is our goal to provide a comprehensive reference book for physicians, clinical researchers, pharmaceutical scientists, clinical or medical research associates, clinical programmers or data coordinators, and biostatisticians or statisticians in the areas of clinical research and development, regulatory agencies, and academia.

The scope of this book covers clinical issues, which may occur during various phases of clinical trials in pharmaceutical research and development, their corresponding statistical interpretations, concepts, designs, and analyses, which are adopted to address these important clinical issues. Basically, this book is devoted to the concepts and methodologies of design and analysis of clinical trials. As a result, this book can be divided into six parts: Preliminaries, Designs and Their Classifications, Analysis of Clinical Data, Issues in Evaluations, Recent Development, and Conduct of Clinical Trials. Each part consists of several chapters with different topics. Each part and each chapter are self-contained and can be read alone. But, at the same time, parts and chapters are arranged in a sensible manner such that there is a smooth transition between parts and from chapter to chapter within each part.

Part I covers Chapters 1 to 4. Chapter 1 provides an overview of clinical development for pharmaceutical entities, the drug research and development process in the pharmaceutical industry, regulatory review, and approval processes and requirements. Also included in this chapter are the aim and structure of the book. Chapter 2 introduces basic statistical concepts such as uncertainty, bias, variability, confounding, interaction, clinical significance and equivalence, and reproducibility and generalizability. Chapter 3 provides some fundamental considerations for choosing a valid and suitable design for achieving study objectives of clinical trials under various circumstances. Chapter 4 illustrates the concepts and different methods of randomization and blinding, which are critically indispensable for the success and integrity of clinical trials. Part II covers Chapters 5 to 7. Chapter 5 introduces different types of statistical designs for clinical trials. These study designs include parallel group, crossover, titration, enrichment, clustered, group-sequential, placebo-challenging, and blinder-reader designs. Also included in this chapter is the discussion of the relative merits and disadvantages of these study designs. Specific designs for cancer clinical trials are introduced in Chapter 6. These designs include standard escalation, accelerated titration, and the continual reassessment method (CRM) in determination of maximum tolerable dose (MTD) for phase I cancer trials. In addition, Simon's optimal two-stage design and randomized phase II designs are also discussed. Various types of clinical trials, including multicenter, superiority, dose–response, active control, equivalence and noninferiority, drug-to-drug interaction, combination, and bridging trials, are discussed in Chapter 7.

Chapters 8 through 11 in Part III cover methodologies and various issues that are commonly encountered in the analysis of clinical data. As clinical endpoints can generally be classified into three types—continuous, categorical, and censored data—different statistical methods for analysis of these three types of clinical data are necessary. Chapters 8, 9, and 10 discuss the advantages and limitations of statistical methods for analysis of continuous, categorical, and censored data, respectively. In addition, group-sequential procedures for interim analysis are also given in Chapter 10. Chapter 11 provides different procedures for sample size calculation for various types of data under different study designs. Part IV includes Chapters 12 and 13. Chapter 12 discusses statistical issues in analyzing efficacy data. These issues include baseline comparison, intention-to-treat analysis versus evaluable or per-protocol analysis, adjustment of covariates, multiplicity, the use of genomic information for assessment of efficacy, and data monitoring. Chapter 13 focuses on the issues for analysis of safety data, which include the extent of exposure, coding and analysis of adverse events, the analysis of laboratory data, and the use of genomic information for evaluation of drug safety.

Part V consists of five completely new chapters for this third edition. Chapter 14 provides recent development in biomarker development and design and analysis of targeted clinical trials. Chapter 15 concentrates on the trials for evaluation of diagnostic devices, which include study design, measures for diagnostic accuracy, results reporting, and sample size determination. Chapter 16 reviews the recent development for statistical methods for translational medicine. Chapter 17 provides a complete coverage of adaptive designs and a comprehensive review of the FDA guidance on adaptive designs. Finally, Chapter 18 gives an overview of the design and analysis of traditional Chinese medicine and alternative or complementary medicine. Issues of study protocols and clinical data management are provided in the final part. Chapter 19 focuses on the development of a clinical protocol. This chapter discusses the structure and components of an adequate and well-controlled clinical trial protocol, issues that are commonly encountered in protocol development, commonly seen deviations in the conduct of a clinical trial, clinical monitoring, regulatory audit and

inspection, and assessment of the quality and integrity of clinical trials. Chapter 20 summarizes basic standard operating procedures for good clinical data management practice. These standard operating procedures cover the development of case report forms (CRFs), database development and validation, data entry, validation and correction, database finalization and lock, CRF flow and tracking, and the assessment of clinical data quality.

For each chapter, whenever possible, real examples from clinical trials are included to demonstrate the clinical and statistical concepts, interpretations, and their relationships and interactions. Comparisons regarding the relative merits and disadvantages of the statistical methodology for addressing different clinical issues in various therapeutic areas are discussed wherever deemed appropriate. In addition, if applicable, topics for future research development are provided.