Chapter 2
The Regulatory Environment

The relevance and importance of the regulatory environment cannot be overemphasized.

2.1 Introduction

This chapter introduces the regulatory environment in which new drug development is conducted. This is largely a result of the work of the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use. The ICH is an amalgamation of expertise from various agencies and organizations across the world.

The ICH arose since the regulations for submitting documentation requesting marketing approval of a drug were historically quite different between countries. Data requirements around the world were dissimilar, meaning that studies often had to be repeated to satisfy national regulatory requirements if marketing permission was desired in multiple countries. This lack of uniformity meant that nonhuman animal (nonclinical) and human (clinical) studies had to be repeated, resulting in additional and unnecessary use of animal, human, and material resources. It also meant that bringing a drug to market in various countries took longer than necessary, delaying its availability to patients.

Harmonisation of regulatory requirements was pioneered by the European Community (now the European Union) in the 1980s, as it moved toward the development of a single market for pharmaceuticals. The success achieved in Europe demonstrated that harmonisation was feasible. The harmonisation process was then extended to include Japan and the United States. The ICH was formed from a government body and an industry association from each of these regions. These bodies and associations as listed by Molzon (2006) are

- The European Commission and the European Federation of Pharmaceutical Industries and Associations (The European Medicines Agency is also a party to the ICH).
• The United States Food and Drug Administration (specifically, the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research), and the Pharmaceutical Research and Manufacturers of America.

2.1.1 Goals of the ICH

The ICH has several goals, including

• Maintaining a forum for a constructive dialog between regulatory authorities and the pharmaceutical industry on differences in technical requirements for marketing approval in the European Union, the United States, and Japan in order to ensure a more timely introduction of new drugs and hence their availability to patients.
• Facilitating the adoption of new or improved technical research and development approaches that update or replace current practices. These new or improved practices should permit a more economical use of animal, human, and material resources without compromising safety.
• Monitoring and updating harmonized technical requirements leading to a greater mutual acceptance of research and development data.
• Contributing to the protection of public health from an international perspective.
• Encouraging the implementation and integration of common standards of documentation and submission of regulatory applications by disseminating harmonized guidelines.

To facilitate the last goal, the ICH has produced many guidance documents for sponsors to use in various aspects of drug development research and documentation, including drug safety, efficacy, and quality. Readers are referred to the ICH web site for more detailed information (http://www.ich.org).

2.2 The Food and Drug Administration

Since there are many regulatory agencies throughout the world, I have used the general phrase regulatory agency wherever possible in this book rather than singling out a particular one. However, since I live and work in the United States, specific reference to its regulatory agency does occur.

The United States government has three branches (executive, legislative, and judicial), and several agencies are part of the executive branch, which is charged with carrying out the statutory laws created by the legislative branch. Agencies therefore create regulations or administrative law. The regulatory agency responsible for the governance of new drug development in the United States is the Food and Drug Administration (FDA).
The FDA is housed within the Public Health Service, part of the Department of Health and Human Services. Redefined in the FDA Modernization Act of 1997, the FDA’s relatively broad mission includes providing reasonable assurances that foods and cosmetics (both of which are regulated products) are safe and that drugs and devices (also regulated products) are safe and effective. Several program centers facilitate the FDA’s operations, including

- The Center for Drug Evaluation and Research (CDER).
- The Center for Biologics Evaluation and Research (CBER).
- The Center for Veterinary Medicine (CVM).
- The Center for Devices and Radiological Health (CDRH).
- The Center for Food Safety and Applied Nutrition (CFSAN).

To accomplish its mission, the FDA’s internal structure includes the Office of Regulatory Affairs, which is responsible for ensuring that regulated products comply with public health laws and regulations. Within this office are the Office of Enforcement and the Office of Criminal Investigations. The FDA is therefore a law enforcement agency. To carry out such enforcement it has both administrative and judicial means at its disposal. It typically attempts to achieve compliance with its statutes using administrative means, such as inspections of products and manufacturing facilities, notices of violation of regulations, recalls (voluntary and mandatory) of regulated products from the marketplace, and (adverse) publicity. Should these administrative means fail to achieve compliance, however, the FDA can utilize the US court system and the Department of Justice’s assistance to invoke its judicial tools, which include seizure, injunction, and prosecution.

The FDA becomes involved in new drug development when nonclinical research conducted by a sponsor starts to indicate that the investigative drug has potential benefits in humans. Regulatory oversight does not apply to drug discovery and design, or to some of the earlier aspects of nonclinical development. However, many later aspects of nonclinical development and all aspects of clinical development are conducted under regulatory governance. This governance also includes manufacturing processes.

2.2.1 The Code of Federal Regulations

The *Federal Register* is a collection of substantive regulations that is published by the government every weekday with the exception of federal holidays. The *Code of Federal Regulations* (CFR), which is revised annually, is a codification of the general and permanent rules published in the *Federal Register*. It is divided into 50 titles, each of which is further divided into subchapters, parts, subparts, and sections. The FDA regulations are in Title 21 of the CFR, commonly referred to as 21 CFR. Individual regulations have more detailed identifiers; 21 CFR 310.3, for example, provides the code’s definition of a new drug.
2.3 cGMP, cGLP, and cGCP

These three acronyms are common in literature pertaining to new drug development. They refer to good manufacturing practice (GMP), good laboratory practice (GLP), and good clinical practice (GCP). The various stages of new drug development should be conducted according to the appropriate regulations and guidances. The initial letter c in each case stands for current. Sometimes you may see the abbreviation cGxP used to refer to all three of these practices. The implication here is that, in the years between rewrites of regulations and guidances, certain modifications in the generally accepted best way of performing a certain activity (best practices) may occur. Therefore, while the guidance as written in the most recent version reflects the official stance, it is considered wise to conform to the modified ideology as appropriate.

2.4 Regulatory Aspects of New Drug Development

There are many regulatory requirements for new drug development and approval. Before a sponsor submits a request for a drug to be registered for human use, a tremendous amount of highly specified laboratory testing, nonclinical work, and clinical trials need to be performed. In all cases, the procedures and results must be documented appropriately. From a regulatory perspective, if the research is not documented, for all intents and purposes it has not been done.

This applies to nonclinical development as well as clinical development. Nonclinical work is reported to the FDA in an Investigational New Drug Application (IND). This document is reviewed to see if clinical work should be allowed to start. Once the clinical development program is completed, all of the developmental work will be reported to the FDA in a New Drug Application (NDA) or a Biologicals License Application (BLA). If the review of these documents goes well, the drug will be approved for marketing.

The new drug development and approval process includes several principal steps:

- Nonclinical testing.
- Submission of an IND.
- FDA review of the IND.
- Preparation and submission of an NDA or a BLA following clinical research.
- FDA review and approval of the NDA or BLA. Following an initial review, the agency may ask for more documentation before granting marketing approval.

The highly abbreviated descriptions in the following sections are intended to serve as an introduction to, and an indicator of the importance of, the regulatory environment.
2.5 Sponsor and Regulatory Agency Responsibilities

Sponsors and regulatory agencies each have roles and responsibilities for drug products. Marketing approval of a drug is a contract between the sponsor and the regulatory agency, and the conditions of the approval are spelled out in detail and also condensed in the prescribing information. Any planned changes on the part of the sponsor need to be presented to the agency, and new approval is necessary in many cases. The regulatory agency’s roles and responsibilities include

- Approving the clinical trial application.
- Approving drugs that have been scientifically evaluated to provide evidence of a satisfactory benefit–risk ratio (the balance between the therapeutic advantages of receiving the drug and possible risks).
- Monitoring the safety of the marketed drug.
- In serious cases, withdrawing the license for marketing. This can occur for various reasons, including failure of adequate additional information being included in the prescribing information after adverse reactions are reported and failure to be compliant with regulations concerning drug manufacture.

The sponsor’s roles and responsibilities include

- Keeping all pertinent documentation related to the drug up to date and ensuring it complies with standards set by the current state of scientific knowledge and the regulatory agency.
- Collecting, compiling, and evaluating safety data and submitting regular reports to the regulatory agency.
- Taking rapid action where necessary. This includes withdrawal of a particular batch of the drug or withdrawal of the entire product if warranted.

The relevance and importance of the regulatory environment cannot be overemphasized. This overview of the roles and responsibilities of both the sponsor and the regulatory agency serves to illustrate the interaction between the two, both before and after a drug is approved for marketing. Regulatory affairs professionals keep in constant dialog with regulatory agencies throughout the drug development process.

2.6 The Investigational New Drug Application

If all has gone well in a nonclinical development program, a sponsor submits an IND (the acronym for Investigational New Drug Application does not include an “A”). The term investigational new drug, or just investigational drug, describes an
unapproved drug that is to be evaluated in clinical trials. The IND is the vehicle via which a sponsor advances to its clinical development program.

An IND is actually a request for an exemption from a particular federal statute. Current federal law requires that a drug has been approved for marketing before it can be transported or distributed across state lines. Therefore, officially, an investigational new drug cannot be shipped across state lines in interstate commerce because, by definition, it has not been approved for marketing. Given the predominance of multicenter clinical trials in drug development (particularly in the later-stage clinical trials), a sponsor will very likely want to ship the investigational new drug to clinical investigators in many states. The sponsor therefore has to request an exemption from the statute prohibiting this. The IND is the vehicle via which the sponsor technically obtains this exemption from the FDA.

The regulations pertaining to INDs are located in 21 CFR 312 and provide detailed guidance for both content and format. Interestingly, a sponsor does not hear from the FDA if the FDA’s review is positive. The FDA reviewers have 30 days to respond to the sponsor following submission of the IND. If the sponsor has not been contacted in that window, they have implied permission to commence the clinical development program described in the IND.

In scientific terms, the purpose of an IND is to provide detailed documentation that will allow the FDA to conclude that it is reasonable for the sponsor to proceed to clinical trials. Generally, this includes data and information in four broad areas:

- **Animal pharmacology and toxicology studies.** These nonclinical data permit an assessment of whether the product is considered to be reasonably safe for initial testing in humans. The phrase “considered to be reasonably safe” may sound somewhat less than definitive or reassuring, but it is simply the case that no amount of nonclinical testing can guarantee that a drug will be absolutely safe when administered to humans. As in many instances in the new drug development process, an informed judgment has to be made, on this occasion by the regulatory agency.

- **Manufacturing information.** These data address the composition, manufacture, stability, and controls used for manufacturing the drug. This information is provided to document the sponsor’s ability to produce and supply consistent batches of high-quality drug.

- **Clinical study protocols.** Protocols include precise accounts of the design, methodology, and analysis considerations necessary to conduct the proposed studies and analyze their results. Therefore, design, methodology, and analysis information must be submitted in study protocol format before administering the investigational drug to the first human subject. These detailed protocols for the proposed initial-phase clinical studies are provided to allow the FDA to assess whether the trials will expose subjects to unnecessary risks.

- **Investigator information.** Information on the qualifications of clinical investigators is provided to allow assessment of whether they are qualified to fulfill their duties at the investigational sites used during the clinical trials.
2.6.1 Review of the Investigational New Drug Application

When submitting an IND, a sponsor should state the goals that make up the overall clinical development program. When originally submitted, the general investigational plan should outline the overall plan, but it only need articulate the studies to be conducted during the first year of clinical development. Subsequent IND updates provide additional details. The FDA’s overall review process consists of several reviews, including medical/clinical, chemistry, pharmacology/toxicology, and statistical.

2.6.1.1 The Medical/Clinical Review

This review is conducted by medical officers who are almost always physicians. Medical reviewers are responsible for evaluating the safety of the clinical protocols in an IND. Typically, a company will open an IND with a single study and then add new study protocols over time. Protocols are reviewed to determine if the subjects will be protected from unnecessary risks and if the respective study designs will provide data relevant to evaluating the safety and efficacy of the drug. Under federal regulations, proposed Phase I trials are evaluated almost exclusively for safety considerations. The initial IND is amended and updated over time to add new study protocols, submit reports of completed studies, and keep the FDA informed of all the data that the company is gathering on the investigational drug. When evaluating study protocols for Phase II and Phase III trials, the reviewers must also ensure that these studies are of sufficient scientific quality to be capable of providing data that can support marketing approval.

2.6.1.2 The Chemistry Review

Chemists are responsible for reviewing the chemistry and manufacturing control (CMC) sections of the IND. These sections address issues related to drug identity, manufacturing control, and analysis. Drug manufacturing and processing procedures need to ensure that the compound is stable and can be consistently made to high standards. The IND should describe any chemistry and manufacturing differences between the nature of the investigational drug proposed for clinical use and the drug product that was used in the animal toxicology trials that formed the basis for the sponsor’s conclusion that it was safe to proceed to clinical studies. If there are any such differences, the sponsor should discuss if and how these differences might affect the safety profile of the clinical drug product.

2.6.1.3 The Pharmacology/Toxicology Review

This review is conducted by pharmacologists and toxicologists who evaluate the results of animal testing and attempt to relate animal drug effects to potential drug effects in humans. The IND should provide a description of the pharmacological effects and the mechanism(s) of action of the drug in animals (if known).
and information on the pharmacokinetics (absorption, distribution, metabolism, and excretion) of the drug. An integrated summary of the toxicological effects of the drug in vitro and in animals is also required. (In cases where species specificity or other considerations make many or all animal toxicological models irrelevant, the sponsor is encouraged to contact the agency to discuss toxicological testing.)

2.6.1.4 The Statistical Review

The CDER has several offices, including the Office of Pharmacoepidemiology and Statistical Science. This office contains the Office of Biostatistics. One of the Office of Biostatistics’ responsibilities is to develop statistical and mathematical methods to enhance the drug review process in various areas, including

- Pharmacokinetics and pharmacodynamics.
- Bioavailability and bioequivalence.
- Drug safety monitoring.
- Demonstration of efficacy.
- Chemical testing and product quality assessment and control.

The Office of Biostatistics has taken the lead in the development of several guidance documents on specific topics, including ICH E9, Statistical Principles in Clinical Trials, and ICH E10, Choice of Control Groups in Clinical Trials. It is advisable for sponsors to follow these guidances.

In the IND statistical review, study protocols are reviewed somewhat differently according to the phase of the proposed study. Phase I study protocols, which are evaluated for safety, may not receive a statistical review. Study protocols for studies in which efficacy is evaluated and the results of which are intended to be used as supportive evidence of efficacy will likely receive a statistical review. This may be particularly likely if the study includes a large sample size. Most Phase III trials receive a statistical review. Since Phase III trials are undertaken to provide compelling evidence of both safety and efficacy, all of the design, methodology, and analysis considerations need to be addressed satisfactorily, making many aspects of the protocol of interest to the statistical reviewers. Questions of interest to the statisticians include

- Does the design facilitate collection of data that are appropriate for addressing the study objectives and reduce the potential for bias?
- Are the primary endpoints relevant?
- Have the criteria that will be used to determine efficacy been precisely specified?
- Have the randomization schedule and all aspects of methodology (operational and measurement) been detailed adequately?
- Have sample size estimates been conducted appropriately and is the study powered as needed?
• Has adequate statistical care been taken in analytical strategies dealing with repeated measurements and with missing data?
• Are the planned analytical strategies appropriate for the design and capable of providing answers?

The statistical review may also take a more global view and, in addition to evaluating the aspects of each protocol in a stand-alone fashion, evaluate how it fits in with and adds to the overall drug development program.

Following initial clearance of an IND (INDs are never formally “approved”) and throughout the time that the studies included in it are being conducted, the IND application must be updated continuously. In addition to annual reports, protocol amendments must be submitted any time that a protocol is changed or if the sponsor wishes to use a new study protocol. Study reports of completed trials are also submitted so that documentation is submitted as it becomes available. This “build as you go” concept is central to the IND philosophy, and a company should not withhold information about an investigational product from the FDA.

2.7 The New Drug Application

At the completion of the clinical trials conducted using an investigational drug, and the completion of all nonclinical studies being conducted contemporaneously, a New Drug Application (NDA: this time the acronym does include an “A”) is filed. The regulations pertaining to NDAs are located in 21 CFR 314 and, as for INDs, provide detailed guidance for both content and format.

Typically, sponsors meet with the FDA to discuss the content and format of an NDA prior to its preparation. Pre-NDA meetings can be crucial for the sponsor to understand the content and format that will best facilitate the review process for a given submission.

Historically, NDAs, like other regulatory documents, were submitted on paper, and the total amount of paperwork was considerable. A typical paper NDA submission might constitute 400 volumes, each 400 pages long. The process has been moving toward electronic submission for some time, which has many advantages, including the fact that hyperlinks can be incorporated that allow a reviewer to navigate directly from one part of the submission to another. This is particularly valuable for statistical reviewers who may wish to navigate from the Methods section of a clinical study report to tabulated data presented in the Results section and then to the supporting raw data sets.

2.7.1 Statistical Review of the New Drug Application

The comments here focus on the statistical review of the NDA. The major difference between an IND and an NDA submission is that, when the NDA is submitted, the
studies proposed in the IND have been conducted, and analysis and interpretation of the data collected are included. The FDA’s review of the NDA focuses on determining if it finds the evidence concerning safety, efficacy, and manufacturing ability to be compelling and if it is therefore prepared to approve the drug for marketing. The FDA’s statistical reviewers play a major role in making this determination. Statistical reviewers typically review both the Statistics and Clinical Data sections, and they are also available to review other sections.

Statisticians conducting the review of an NDA evaluate the statistical relevance of the data presented so that they can provide the medical officers with information concerning how well the findings are likely to generalize to the larger patient population in the country. They evaluate the extent of any deviations from the protocols submitted in the IND in the conduct of the study as well as the overall quality of the data collected. All clinical study protocol amendments are reviewed to see what deviations from the original study design have occurred and how these (and deviations that were not detailed in protocol amendments) may have influenced the data.

Having access to all study data in electronic form allows the FDA’s statisticians to replicate all analyses that are reported, and, importantly, to conduct any alternative and additional analyses they feel are warranted and which may help them to reach an informed decision concerning approval of the drug for marketing.

Additional insights into the Office of Biostatistics’ most up-to-date thinking can be found in the statistical reviews and evaluations written by their statisticians during the review of NDAs. Once drugs are approved, these reports become public domain documents, allowing a window into the FDA statisticians’ thinking.

**Further Readings**


New Drug Development
An Introduction to Clinical Trials: Second Edition
Turner, J.R.
2010, XXV, 256 p., Hardcover