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Statistics and the Drug Development Process

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1.1 Introduction

This introductory chapter begins with a brief history of the drug development process and the evolution of statistics and statisticians in that process. This is followed by a more detailed summary of the various elements that comprise the discovery, development, approval, and manufacture of new therapeutic entities.

1.2 History

The evolution of the statistics and information management professions in the pharmaceutical industry has had two primary drivers. The first was the change from an industry that was fragmented and focused on the manufacture of nostrums and cure-alls compared with the cutting edge, highly scientific, research-oriented industry that exists today. The second was the growth of governmental control over the pharmaceutical industry in the latter half of the twentieth century. Figure 1.1 depicts significant drug regulatory milestones in the United States.

Prior to the twentieth century, there was little control over the content and claim structure of medicinal products. To address this issue, the U.S. Congress passed the Pure Food and Drug Act in 1906. This legislation was designed to protect the population against unscrupulous individuals and companies who would intentionally misbrand or adulterate the therapies of that time. Although well intended, neither this legislation, nor subsequent legislation during the ensuing 25 years had any clearly positive effect on improving the quality, safety, or effectiveness of medicinal products available to the population.

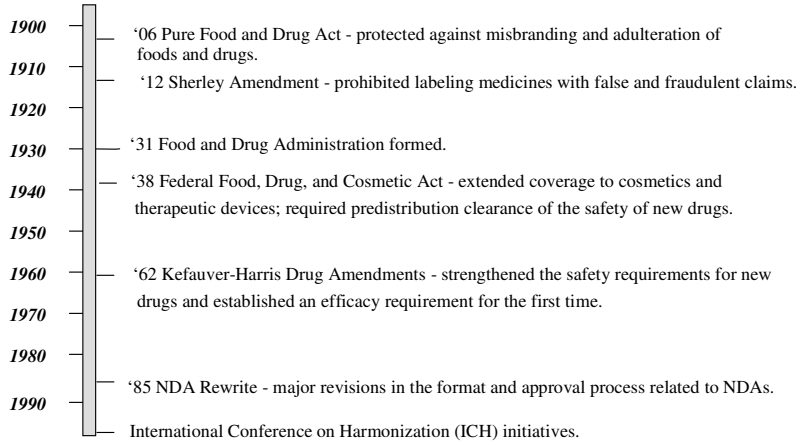

Figure 1.1. Significant drug regulatory milestones in the United States. Modified from Johnson (1987, p. 8), by courtesy of Marcel Dekker, Inc.

The year 1931 marked the creation of the Food and Drug Administration (FDA) in the United States and concentrated the responsibility and authority for regulation of pharmaceuticals into a specific federal agency. However, the most important drug legislation of this period was to come 7 years later, in 1938. In this year, Congress passed the Food, Drug, and Cosmetic Act which, for the first time, required premarketing approval of the *safety* of new drugs. This was the first legislation that provided the FDA with the authority to prohibit the marketing of new medicinal products (including devices and cosmetics), unless the manufacturer demonstrated that the product had an acceptable safety profile for its intended use. Prior to this legislation, a manufacturer could sell its products without performing any studies on health effects, and detection of any safety problems was only possible after they had manifested themselves in the patient population.

It was also about this time that the first statisticians were employed in the pharmaceutical industry. During the ensuing quarter of a century, the number of statisticians and their influence grew slowly. Initially, statisticians had little authority and were primarily employed as analysts in nonclinical research and manufacturing settings.

In the 1950s a substance called thalidomide was developed in Germany and promoted as a sleeping medication and a treatment for morning sickness in pregnant women. Clinical testing of the drug began in Western Europe in 1955, and later in the United States. The drug was marketed under various names in

different countries, including Contergan (Germany), Distavan (England), and Kevadon (Canada). In the early 1960s it became apparent that thalidomide was teratogenic and linked to thousands of birth defects in Western Europe. The FDA denied approval of the drug, and public interest in drug regulation was aroused. In response, in October of 1962, the United States Congress passed the Kefauver–Harris Drug Amendments, which strengthened drug safety requirements by requiring extensive animal pharmacological and toxicological testing before a drug could be tested in humans (see Drews, 1999, pp. 142–145, and www.fda.gov/fdac/special/newdrug/benlaw.html).

The Kefauver–Harris Drug Amendments clearly established the future of statisticians and statistics in the pharmaceutical industry. Although preapproval documentation of safety had already been required for approval of new therapies, there were no requirements that new drugs needed to be efficacious. This legislation not only strengthened drug safety requirements, but also, for the first time, required premarketing approval of the *efficacy* of new medicines. The consequence of this requirement was the creation of large organizations within the pharmaceutical industry (and in the FDA) that were dedicated to the design, implementation, and evaluation of clinical trials. Since these trials were now required for the approval of new drugs, the number of statisticians needed to participate in this responsibility grew at an extraordinary pace. In 1962, the pharmaceutical industry employed less than 100 statisticians; by the year 2000, this figure had increased to more than 3000. For this reason, the Kefauver–Harris legislation has been affectionately called "The Statisticians' Full Employment Act" by pharmaceutical statisticians.

This new opportunity for statisticians completely changed the nature of their roles and responsibilities. Where their roles had previously been in nonclinical environments, clinical statisticians became increasingly more common. Today, approximately 90% of all statisticians in the pharmaceutical industry are involved in clinical trials.

During the succeeding 20 years after the passage of the Kefauver–Harris Drug Amendments, both the industry and the FDA suffered inefficiencies due to a need for structure and guidance with respect to the submission and approval process for new drugs. This was addressed in the mid-1980s by a document referred to as the "FDA Rewrite." This manuscript clarified the format and content of submissions in support of new drugs. Approximately two-thirds of this document discusses issues of importance to statisticians.

About this time, the need for some codification of "Good Clinical Practices" (GCP) became apparent. Although the U.S. regulations defined basic scientific requirements for acceptable evidence in support of new drugs, many countries relied on testimonials from respected physicians as critical elements of their review. These inconsistencies were addressed during the 1990s by an organized cooperation among regulatory, industrial, and academic representatives from the European Union, Japan, and the United States. The initiatives developed by the International Conference on Harmonization (ICH) address many critical areas and have benefited greatly from substantial expert statistical input. In fact, one

complete guidance (*E-9, Statistical Principles for Clinical Trials*) provides an excellent treatise on this topic.

The past 40 years have seen an enormous change in the roles, responsibilities, and authority of statisticians in the pharmaceutical industry. The profession has evolved from a small group of analysts to a fraternity of several thousand scientists involved in all aspects of discovery, development, manufacturing, and education.

1.3 The Drug Development Process

The discovery and development of new therapeutic entities is a highly technical, multidisciplinary process that presents a plethora of challenges that demand solutions from many scientific and technical disciplines. Although each of several specialties plays a critical role at any specific stage, statistics and information management are essential throughout the process.

The evolution of a new drug from concept to patient consists of both sequential and parallel processes (Figure 1.2). The process begins with efforts to discover a new therapeutic molecule. Although the ultimate target is man, the potential agent must be tested in selected animal models to determine whether it may have potential therapeutic activity. If the results of this screening process are positive, the compound is then subjected to a variety of safety evaluations in various animal species to determine whether its projected safety profile is consistent with the risks of administering it to humans.

The clinical component of the research process is further refined by three relatively well-defined phases (Phases I, II, and III) that characterize the stage of the product in its clinical development prior to registration. These first three phases and Phase IV (conducted after approval of the product) are more or less sequential, providing an opportunity to evaluate the current information before proceeding to the next phase of research. Since the statistician is usually more familiar with the data, its analysis, and its interpretation than any other individual on the project team, his or her contributions to each phase of these processes are critical.

Concurrent with the clinical development stage of the process are those components associated with the expected manufacture of the product after approval by regulatory agencies. The basic active ingredient is never given to patients alone. The active moiety must be formulated with other chemicals and compounds to optimize its ability to reach its therapeutic destination. Thus development of the final formulation is a critical step. This must be done as early in the process as possible, since the majority of Phase II and III studies must be done with the final formulation to obviate the need for additional studies and extending the development timeline.

Once the final formulation is defined and characterized, processes for the economical and efficient manufacturing of the product must be developed. Concurrent with this activity, various stability studies must be conducted to determine how long a product will retain its therapeutic potency after manufacture.

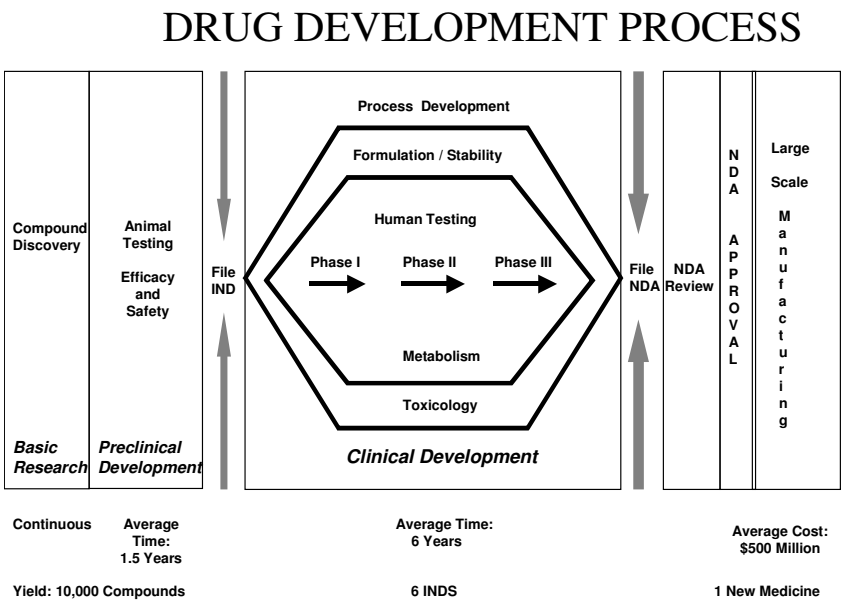

Figure 1.2. Schema for the drug development process.

1.3.1 Discovery

As recently as the 1970s, drug discovery was a very inefficient process. At that time, much of the new drug discovery process was based on experience. Molecule modification, rather than novel molecule discovery, was the rule. The consequence was that truly novel therapeutic entities were relatively uncommon.

Today, genomics, high throughput screening, informatics, robotics, and other highly technical advances are used by scientists to identify the tens of thousands of new molecules required to produce one new lead. However, the capability of identifying large numbers of potential new leads requires state-of-the-art screening procedures to identify the small number that will ultimately be used in clinical trials. In addition to effective selection procedures, sophisticated modeling processes, such as computer-assisted drug design, are used to modify the molecule to optimize its potential therapeutic benefit.

1.3.2 Preclinical Pharmacology

Introducing a new chemical into a human being carries a significant risk. If the potential agent does not demonstrate the expected benefit, no risk is acceptable. To determine whether the new drug should proceed to the next step in development, carefully designed studies, in well-defined animal models, are conducted.

These studies must be definitive regarding the therapeutic benefit expected in man, must yield a targeted initial range of doses for man, but must minimize the utilization of animals.

1.3.3 Preclinical Toxicology

Drug therapies must not only be effective; they must have a safety profile that is consistent with their benefit and their indication. For example, an ointment to treat a mild rash must be totally benign. However, many cancer therapies have been approved for use despite having poor safety profiles, because their potential benefit far outweighed their unpleasant side effects.

Safety assessment programs differ according to the nature of the therapy. Drugs designed to be administered acutely and infrequently will require a different battery of safety assessment than will a product designed for a patient to take for the rest of his or her life. The anticipated patient exposure, class of agent, age and gender of patient, etc., will determine the specific studies that will be required.

A portion of these evaluations will be conducted before the first introduction of the drug in man. As mentioned previously, the product must give evidence of efficacy and have acceptable safety to proceed. If the entire preclinical safety profile were required before human testing began, there could be an unacceptable delay in the development process and ultimate availability to the practicing physician. For this reason, safety assessment in animals continues throughout the clinical programs in humans.

1.3.4 Clinical Research

Clinical development of new therapeutic agents is traditionally partitioned into four sequential, but overlapping, phases. The clinical research portion of new drug development varies in duration with the nature of the disease being treated, the duration of any positive or negative effects of the drug, and the intended period of administration. In general, 2 years would be an absolute minimum for the clinical phase of a new agent, while products such as hormonal contraceptives would require a much longer period of clinical development.

Phase 1: Clinical Pharmacology

The initial introduction of a new agent into humans is a scientifically exciting period in its development. The goals of this stage of development include determining initial tolerability, developing a range of doses to pursue in patients, and characterizing the drug's pharmacokinetics. Phase I studies are commonly conducted in normal, male, volunteers who do not possess the disease that will be studied in later phases. The reason for using male normals at this stage is threefold. First, there is not enough evidence of therapeutic benefit to substitute the new agent for a patient's therapy. Second, normal subjects provide a more

homogeneous population, unaffected by concurrent therapies and diseases that might confound the interpretation of results in patients. Third, women of childbearing potential are generally excluded because any risk associated with a potential pregnancy is unacceptable at this stage of development.

To obtain initial safety and tolerance information, a group of subjects is given the lowest dose suggested for humans by the animal toxicology studies. If the tolerability is acceptable in these subjects, they (or a different group) are given a higher dose. The process continues until unacceptable toxicity is observed. For products in which the safety profile is expected to be poor (such as cytotoxic agents), these studies will be conducted in patients. When the studies in this phase have been completed, a range of doses will have been defined that possesses an acceptable safety profile to permit introduction to patients.

Although one generally thinks about the way a drug treats the patient, pharmacokinetics characterizes the manner in which the patient treats the drug. The broad components of pharmacokinetics include absorption, distribution, metabolism, and excretion (ADME) of the product and its metabolites. These processes are determined by sophisticated mathematical modeling and complex computer programs.

Studies to garner this information are usually designed to administer the drug to 10–20 subjects and collect blood and urine samples at selected time points over several hours. The resultant profile is then carefully modeled to estimate its component parameters. These kinds of results are essential for determining dosing regimens and characterizing how different populations may vary with respect to their ultimate therapeutic response.

A variation of this type of study, the bioavailability or bioequivalence study, is conducted in various forms throughout the development process to determine whether changes in the formulation, dosage form, manufacturing process, etc., will affect the way the body handles the drug. These types of studies are also sensitive for determining the potential effects of food, concomitant therapies, and concurrent illnesses, such as compromised liver function.

Phase II: Early Studies in Patients

When a tolerable dose range has been identified and the pharmacokinetics have been determined, there is sufficient evidence to proceed to patients. These early studies in patients are usually decisive regarding whether the product will continue to the large scale, expensive, studies of Phase III.

These initial studies in patients with the disease of interest have three related objectives. Similar to the Phase I tolerance studies in normal volunteers, the lowest dose which provides clinical benefit must be determined. This is determined in a manner similar to the tolerance studies of Phase I, but doses are increased until a therapeutic effect is observed, rather than toxicity.

Once the bottom of the dose–response curve is estimated, studies are designed to determine the effect of administering higher doses. Different studies address two similar, but different, questions. First, are higher doses more effective, per se, i.e., if a higher does is given, does it evoke a better effect? Second, for patients in whom a specific dose fails, will increasing the dose provide bene-

fit? The designs of these studies are different, and in general, a study designed to answer one of the questions will not answer the other.

At this stage in the development process, pharmacokinetic studies will be conducted in the target patient population to identify any differences in pharmacokinetics that may attend the disease, or its common concomitant medications, or whether there are changes in functional physiology that may be associated with the condition.

Phase III: Confirmation Studies

Although a substantial amount of time, effort, patient exposure, and resources have been expended in the development process to this point, Phase III and the attendant process elements from this point forward will dwarf what has occurred previously. All available information regarding efficacy, safety, pharmacokinetics, animal toxicology, etc., will be intellectually integrated to determine whether proceeding to the implementation of Phase III is warranted.

Phases I and II research is designed to provide a basis upon which to determine whether to proceed to Phase III. For this reason, early phase research is highly focused and exposes a minimal number of subjects and patients to the experimental therapy. Phases I and II could total as few as 100 subjects/patients; each followed for a short period. This consequently limits the number of patients who have access to the drug, the variety of populations that have received it, the duration of exposure, and long-term observation for continuing efficacy or tachyphylaxis. In addition, little information is available regarding adverse experiences and the long-term safety of the drug.

Phase III is typically comprised of a set of several studies. Since Phase III will provide the primary clinical basis upon which regulatory agencies will make a decision to approve or reject the compound, the goals of these studies are to provide conclusive evidence of efficacy, to fully characterize the adverse experience profile, to gain experience in a truly clinical environment with many of its uncontrolled elements, and to obtain safety and efficacy information in special groups or patients. These large, and (often) long, studies regularly compare the new agent against the current standard of care, are usually multicenter, often multinational, and routinely enroll hundreds of patients per study. The entire registration dossier often comprises information from well over 1000 patients.

At the conclusion of the Phase III studies, the information from them and all other sources is compiled into a dossier for submission to regulatory agencies. This will be described in more detail in Section 1.4.

Phase IV: Post-Approval Studies

The clinical research process does not end with the submission and approval of the New Drug Application (NDA) or dossier. Research continues for three very important reasons. First, despite the enormous quantity of information that is submitted in support of registration, patient exposure is tiny compared to the product's ultimate utilization. It is for this reason that pharmaceutical compa-

nies conduct additional studies in thousands of patients in an effort to learn as much as possible about the adverse experiences of their drug and to make this information available to the medical community. These studies are usually epidemiological in nature and often continue for several years after the product is first introduced.

Critical diseases often demand taking more risk by using aggressive therapeutic approaches. This concept demands that regulatory agencies provide conditional approval for new drugs for cancer, AIDS, and other life-threatening illnesses in a shorter period of time and without the more complete knowledge of a product's safety and efficacy than would be required routinely. In these circumstances, approval may be granted conditional upon the sponsor's agreement to conduct additional studies after approval to completely characterize the product's safety and efficacy.

The third objective for conducting post-approval studies is to provide a sound foundation for marketing the new product. These studies are often very large or very small. The former are designed to provide large numbers of potential prescribers with the new drug; the latter are specific studies to characterize the new product in special populations or in unique clinical situations. In addition, these studies are often conducted in individual countries to focus on certain country-specific issues, such as competing products, different medical practices, pricing, and insurance related issues.

1.3.5 Concurrent Processes

The process described to this point has ignored a critical point in new drug development, i.e., pharmaceutical products do not leap from the head of the bench chemist to immediate introduction into the clinical research process. The sample product submitted with a New Drug Application (NDA) required its own evolution and development. Some of this development was required before the first unit was administered to humans. The remainder included continuing developments to optimize the product in various ways, characterize its properties, and define its manufacture.

Chemicals are not given to patients. The active component must be administered with a variety of other agents which give it desirable properties. Some of these properties are associated with its therapeutic effects. For example, the formulation should optimize absorption. Certain excipients may improve absorption; some may have a negative effect. Other considerations include the manufacture of the dosage form. Tablets are uniquely challenging, because the powder that forms the basis of the tablet must flow freely in the equipment, yet have the proper compressibility to form a tablet without crumbling.

Stability is a critical issue for all products. The approved useful life of all drugs is indicated on the label. Obviously, long stability without unusual storage conditions is important, both for ease of storage and administration, and to minimize the rate at which material becomes obsolete and unusable.

A pharmaceutical dosage form is a complex mixture of a number of components, each of which serves a different purpose in the product. The goal is to op-

timize the proper amount of each element to produce the best (by some definition) product. This optimization evolution continues throughout the development process. The results of this process are as essential to the approval of a new product as the results of the clinical program.

1.4 Submission and Review

The submissions may be called NDAs (New Drug Applications), NDSs (New Drug Submissions), registration dossiers, PMAs (premarketing applications), or many other terms. The specifics of these submissions vary from country to country, but the general document is an integrated summary of all safety and efficacy information, accompanied by the actual data or database.

The New Drug Application or registration dossier must provide information that is sufficient for a regulatory agency to determine whether the new product will be safe and effective if used as indicated, whether the sponsor has provided labeling that is consistent with the recommended use, and whether the sponsor can manufacture the new agent according to Good Manufacturing Practice guidelines which ensure quality, purity, and composition.

These documents are extraordinarily large and can easily exceed 100,000 pages if case reports or their tabulations are included. For this reason, most submissions are now provided in an electronic version (as well as paper, in many cases). Compact disks and hyperlinked submissions have made reviewing these documents more efficient. Links among clinical summaries, databases, statistical analyses, and case report forms have provided reviewers the capability to browse for important associations more readily than in the past. This has reduced the review time from years to months and has been responsible for more complete and valuable reviews.

1.5 Manufacturing

Pharmaceuticals are products. They are highly pure, highly regulated, and exquisitely manufactured products. They have clearly specified expirations, have specific instructions regarding their safety, efficacy, and instructions for use. And, in the end, they are a product like no other—a product that demands the precise requirements under which it is manufactured, because the public health is its measure.

Although the safety and efficacy of pharmaceuticals is required, their price is an important consideration to their affordability, and to some people, their availability. For this reason, optimization is of the highest priority in the manufacture of pharmaceuticals. Pharmaceutical scientists work hand in hand with engineers and statisticians to develop manufacturing processes which not only bring important products to the health of mankind, but which continually improve these products to raise their value and reduce their cost.

1.6 Summary

The discovery, development, regulatory approval, manufacture, and distribution of pharmaceutical products is a complex, time-consuming, and scientifically rigorous process. Unfortunately, because of its essential contribution to the public health, it can also have political elements that detract from its success. Historically, the process was evolutionary and followed a well-defined, yet pedantic, track toward approval. In the past, clinical research was equated with the practice of medicine, and although medical practice will always be an important component of clinical research, today's research depends to an enormous degree on information capture, management, and interpretation. The paradigm has changed, and the future of drug development will be more revolutionary than evolutionary. The use of statistics, computers, software, the internet, and other information management tools and concepts will not just be supportive of the process, they will be the process.

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Evolution of U.S. drug law, including the Kefauver–Harris Amendments

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