Clinical Drug Trials and Tribulations

Second Edition, Revised and Expanded

edited by

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Clinical Drug Trials and Tribulations

DRUGS AND THE PHARMACEUTICAL SCIENCES

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To my wife, Adrian; my three sons, Allen III, Mike, and Dan; and my eight grandchildren. Thank you for your love, support, and understanding of my many absences from our family life while out in the fascinating pursuit of clinical drug development. This book is also dedicated to all patients—past, present, and future—who volunteer to participate in clinical drug trials. Without them, no drug could ever be shown to be safe or efficacious. These individuals are the silent heroes behind every advancement in drug therapy.

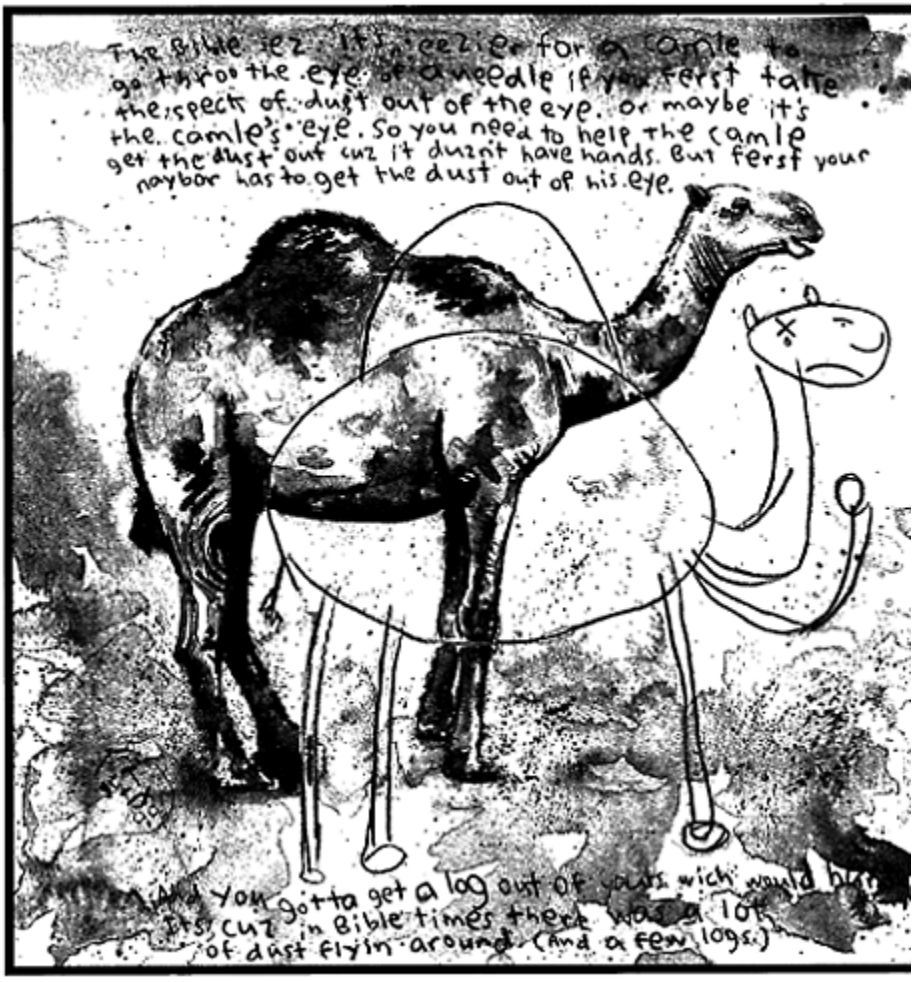
Allen Cato

To my mentor, best friend, partner, and co-founder of Cato Research, Allen, who has taught me to think rationally about drug development rather than check boxes; to Dr. Joy Cavagnaro, who has taught me how to think “backwards” relative to planning drug development programs; to my mother, who, as an accomplished writer, instilled in me at an early age the need to rewrite every paragraph at least five times; and to my father, whose constant support and encouragement allowed me to attempt and achieve tasks that others said were impossible.

Lynda Sutton

To my family, friends, colleagues, and all whose lives may be improved by the development of new therapies. Thanks also to my mentors at the University of North Carolina and in the pharmaceutical industry from whom I learned the science of pharmacokinetics and how to apply these diverse principles to drug development. In particular, I thank my father for emphasizing to me that, in addition to all the scientific disciplines involved, common sense and creativity are also necessary components of proficient drug development.

Allen Cato III



And again I say unto you, It is easier for a camel to go through the eye of a needle, than for a rich man to enter into the kingdom of God.

Matthew 19:24

Preface

The drug development industry continues to be a highly charged, fascinating, and ever-evolving field. The industry has changed significantly in the 14 years since the first edition of Clinical Drug Trials and Tribulations was published, and this second edition of this book addresses those changes and continues to explore the problems and challenges that individuals in this industry experience daily.

The information presented is directed both at the fortunate individuals already involved in drug development and at those adventuresome sorts who are considering entering the field. We hope this book will provide readers with insights into this exciting arena and begin to explain the complicated process of developing a promising new drug.

Although this book has some elements of a "how-to" publication, it really is meant to address the "whys" of development, such as why certain decisions are made in the development of a new chemical entity and the consequences of those decisions. Certainly, the one rule of clinical drug development seems to be that things never turn out as designed or expected. The number of difficult decisions that must be made during the course of clinical drug development seems endless, as are the daily tribulations and challenges that have never before been encountered. We explore these issues by discussing topics such as international regulation and deregulation, venture capital investment, the Investigational New Drug application process, informed consent, and changes in manufacturing. These areas are affecting the way nonclinical and clinical studies are conducted today, and examining them brings to light many of the intriguing tribulations of clinical trials.

No book is ever written alone, and we are thankful to the many individuals involved in the production of this one. First, we want to thank all the chapter authors, who contributed their time, energy, and expertise to this effort despite busy work schedules. In addition, we acknowledge the efforts of the individuals who assisted with the issuance of the first edition, in particular Linda Cocchetto, Robert Sutton, and Paul Stang. We also thank Barbara Proujan, Tricia Eimers, and Paula Brown for their work on this project. And lastly, thanks to Trish Nolan. Without her perseverance, the second edition as presented now would not exist. Our everlasting gratitude goes to all of these dedicated, hard-working people. Although we're sure they could write about their own tribulations in producing this volume, together we have produced a book that will provide further insight into this challenging field.

Allen Cato
Lynda Sutton
Allen Cato III

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Clinical Drug Trials and Tribulations

1
Current Challenges and Future Directions of Drug Development

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It may be easier for a camel to pass through the eye of a needle than it is for a new chemical entity to reach the marketplace. Drug development is a long and costly process fraught with tribulation. The tortuous pathway traveled by a new drug from synthesis to sale requires the constant percolation of data through rigorous clinical and regulatory filters. This process is complex, and success cannot be guaranteed. The ability to always predict which drug will have all the qualities necessary to gain regulatory approval and to be marketed remains as elusive as a camel in a needle's eye.

New drugs do make it from discovery to the market, but only at the approximate rate of one in every 10,000 new molecules synthesized. It is a long, costly, and extremely risky process involving a steady progression through multiple stages, with treacherous decision points along the way. Most of all, it is a process involving the constant percolating of data through rigorous filters strewn with tribulations and complicated by the difficulty of making decisions that affect human health when all the facts are not known.

Despite the daunting challenge of bringing a new drug from discovery to market, new medicines continue to be developed that may have a significant effect on our health. You may wonder, "What has medicine done for mankind lately?" In the United States, the adult life expectancy increased by nearly 30 years over the last century, primarily because of the availability and management of vaccines and immunization schedules, antibiotics, and sanitation measures. As evidenced by the following statistics from the Centers for Disease Control (CDC) (1), the development of vaccines has had a major impact on our health:

> Smallpox killed an average of more than 1500 people per year between 1900 and 1904; it is now eradicated worldwide, and children are no longer vaccinated against the disease.
>
> Polio struck more than 16,000 people annually in the early 1950s; today, it has been eliminated from the Western Hemisphere.

During the past 50 years, vaccines also have been responsible for drastically reducing the

morbidity and mortality from measles, Haemophilus influenzae type b (Hib), diphtheria, pertussis, tetanus (DPT, typically administered together), hepatitis B, and chicken pox. In addition to improved health, substantial economic benefits have been realized. For example, the CDC estimates that the United States recoups its investment in the eradication of smallpox every 26 days. Despite the obvious advances of modern medicine, many patients still have infectious, chronic, or genetic diseases and will benefit from the research of today finding the effective treatments of tomorrow. Pharmaceutical research targeting the top 12 major medical needs exceeds $645 billion annually in direct medical expense and lost productivity. The diseases included in this figure are Alzheimer's disease, arthritis, asthma, cancer, congestive heart failure, coronary heart disease, depression, diabetes, hypertensive disease, osteoporosis, schizophrenia, and stroke (2). Just as it did 50 years ago, innovation continues today to bring us new knowledge through genetic research, molecular biology, and enhanced computer technology. This is the promising future of drug development.

However, developing the vaccines or any of the drugs potentially used to treat the indications listed above is a substantial undertaking. To comprehend clearly the magnitude of the drug-development process, it is useful to consider the many different areas involved. Figure 1 depicts some of the key disciplines contributing to the process. Information from each of these areas feeds into a common funnel with a filter, where multiple decisions must be made progressively regarding the compound's survival, or lack thereof.

Figures 2 and 3 illustrate the process broken down into preclinical and clinical segments. Keep in mind, however, that the process is a dynamic one. The various disciplines listed are constantly interacting, and the entire flow of data requires constant feedback and fine tuning. For example, a compound's toxicity, however slight, may be considered to outweigh its pharmacological effect. This information would be given by the toxicologist to the chemist, who would make other compounds with slight modifications, attempting to retain the pharmacological effect while decreasing or eliminating the toxic effect.

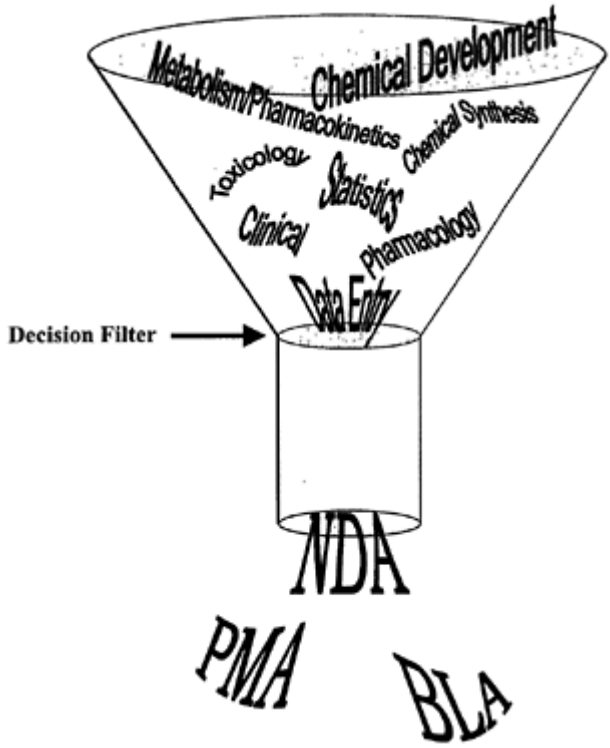

Figure 1 Overall drug development.

Once a compound has been synthesized in the lab and tested in animals, an Investigational New Drug (IND) application is submitted to the U.S. Food and Drug Administration (FDA), requesting permission to initiate clinical studies of the drug in humans. The IND summarizes the preclinical work and includes the first clinical protocol. It is not until the drug has been experimentally tested in humans under controlled conditions (after Phase III) that the company may file an application to market the drug (a New Drug Application [NDA] if filed with the FDA, or a Marketing Authorization Application [MAA] if filed in Europe). The application summarizes all preclinical (safety and efficacy in animals), clinical (safety and efficacy in humans), and manufacturing data known about the drug, and requests permission to market this new drug.

Figure 4 illustrates the attrition ratio of a new chemical entity as it works its way from synthesis through preclinical development to IND, and subsequently through clinical development to NDA. An attrition ratio of 10,000:1 (not considered good betting odds by most people) is the bad news. The good news is that 95% of all drugs for which an NDA is submitted are ultimately approved for marketing.

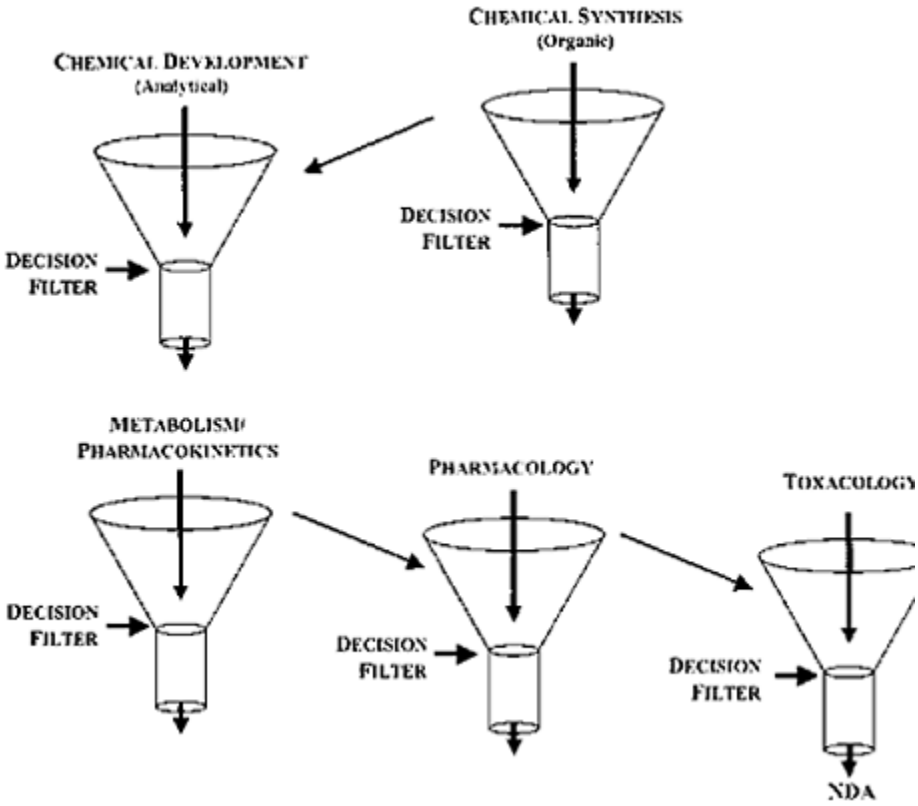

Figure 2 Preclinical drug development.

The tribulations involved in getting a compound through all the decision funnels is a costly process, as seen in Fig. 5. The cost per new drug approved is growing steadily every year. On average, the cost in 1987 was $231 million per approved drug, but by 1998 that figure had increased to $500 to $600 million or more (3). As figures demonstrate, the costs are approximately split between preclinical and clinical development. This average cost represents the expenses in maintaining a full preclinical and clinical research unit for each new drug approved. It perhaps makes it easier to understand why large pharmaceutical companies are sometimes reluctant to pursue development of new drugs likely to have a sales potential of less than several hundred million dollars per year (see Chapter 13 on orphan drugs for a more thorough discussion). This reluctance on the part of large companies leaves opportunities for smaller companies to develop new drugs with smaller potential earnings. If successful, these smaller companies may then grow into large pharmaceutical companies and provide additional treatments that otherwise might have never been made available to patients in need.

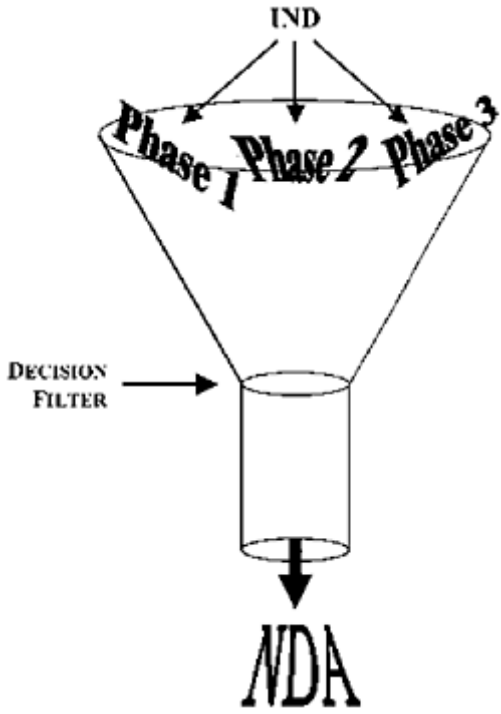

Figure 3 Clinical drug development.

Drug development is not only a costly process, it is time-consuming as well (Fig. 6). Although all pharmaceutical companies and many doctors and patients would like to see the FDA approval times reduced, it is obvious that if approval times were substantially reduced, it would still require many years for the development of a new chemical entity. In fact, the average time of review by the FDA has decreased over the past few years, but the actual time to market has remained about the same because the clinical development time has increased (3, 4).

The lengthy time required for drug development markedly reduces the patent life remaining after drug approval for marketing (Table 1). The shrinking patent protection afforded newly marketed drugs is one reason patent applications are usually not filed with the first synthesis of a new compound. Pharmacological and toxicological testing is usually performed before a patent is filed; it usually takes a year or two before the patent is accepted and officially issued. Therefore, the remaining patent life is still slightly greater than the original patent life minus the total developmental time (Fig. 6). The delay in patent filing helps explain why pharmaceutical companies are somewhat secretive about their preclinical research process. The danger in delaying filing for a patent is the risk that another

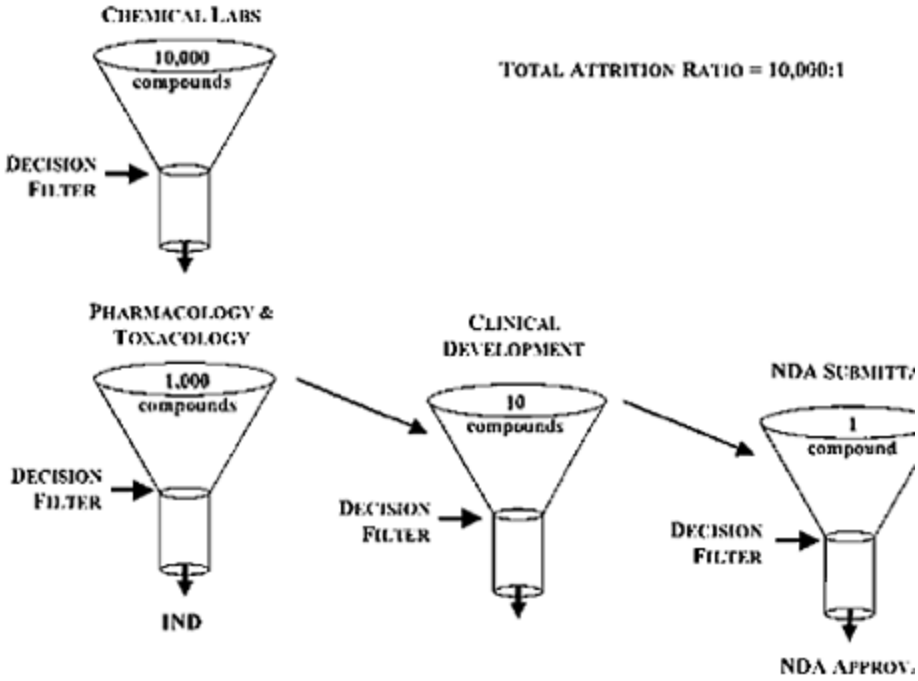

Figure 4 Attrition rate for overall drug development (average).

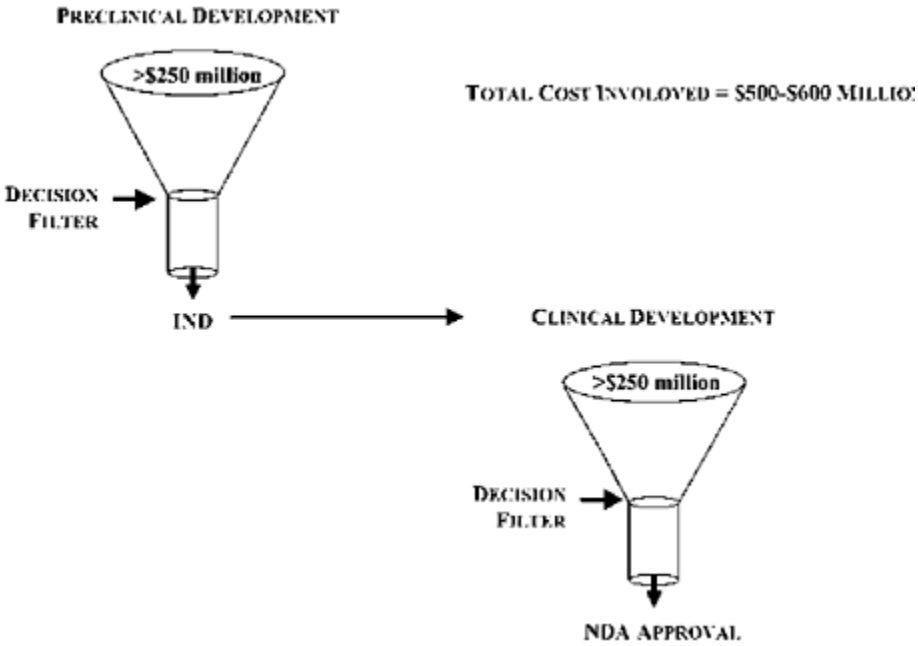

Figure 5 Average cost of overall drug development.

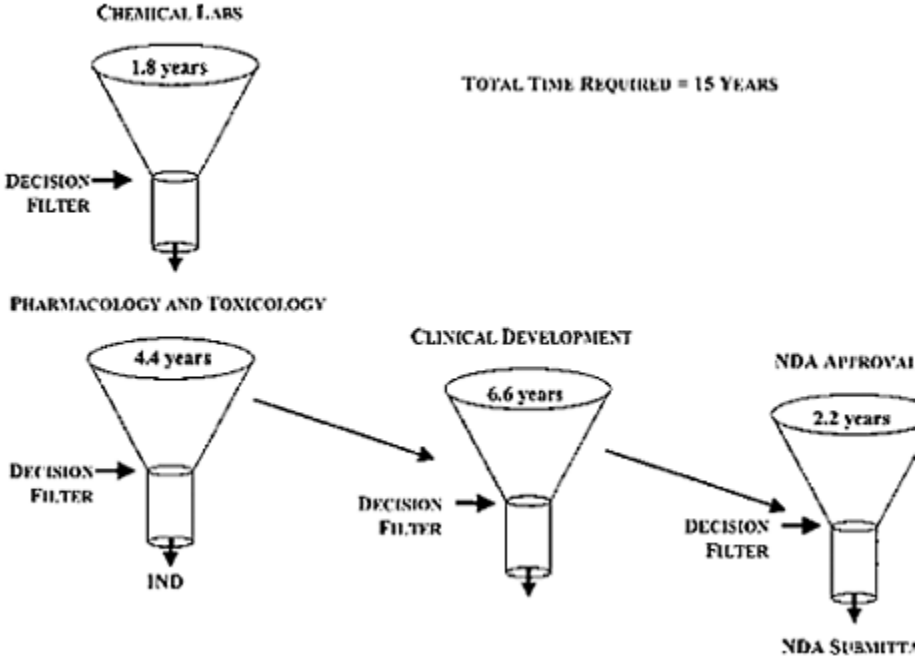

Figure 6 Average time required for overall drug development.

Table 1 Average Effective Patent Life (from NDA approval date)

Year	Patent life without extension	Patent life with Waxman-Hatch extension
1966	13.6 years	NA
1979	9.5 years	NA
1984	9.2 years	11.1 years
1987	10.4 years	12.2 years
1995	7.8 years	11.1 years

NA=not applicable—before Waxman-Hatch enacted.

Total patent life (from patent approval date)	20 years
Before June 8, 1995	17 years
After June 8, 1995	20 years

company or individual may discover the same treatment modality and be the first to file

the patent.

Having looked at an overview of the drug development process, it is appropriate to explain how the decision filter works. In preclinical testing of a drug, a toxicological screen is performed with the intent of demonstrating not only a safe dose, but also the toxic effects. In general, doses of drug that will induce significant toxicity are administered to animals. Some types of toxicity are more acceptable than others; for example, if animals were to die unexpectedly and sporadically throughout several dose ranges without less severe, prodromal preceding toxicities, administration to humans would be prohibitive. There would be no way to assure that the same phenomenon (e.g., unexpected death) would not occur in humans.

How, then, are such judgments made regarding "acceptable" potential toxicities? As an example, a great need exists for new antipsychotic compounds. One such compound was shown to induce lipidosis in the rat after 3 months' exposure, though no such effects were seen in the dog (Table 2). Lipidosis is the deposition of fat in cells, and if carried to an extreme, can kill the cell. In particular, lipidosis-induced vacuoles in the rat were noted in the spleen, liver, and lymphocytes. Because the anticipated dose in humans was 5–10 mg/kg per day, this finding in rats at 12–100 mg/kg per day was a cause of concern. The compound looked promising if the lipidosis problem could be solved. To help with the decision, a review of the literature was performed. As shown in Table 3, only one marketed compound known to have caused lipidosis in rats also had a similar effect in humans. Thioridazine (Mellaril), a widely used compound in humans, was used as a positive control (Table 2). In addition, many other compounds have been shown to induce lipidosis in rats but not in humans (5). These agents, like our compound, are mostly for central nervous system diseases. A decision had to be made to proceed to humans or to stop developing the compound. What would you do?

The actual decision made in this case was to proceed to clinical trials. The reasoning was as follows:

Table 2 Preclinical Toxicology (Anticipated dose in humans: 5–10 mg/kg/day)

Species	Drug	Dose (mg/kg/day)	Time (months)	Effect
Rat	Inv. drug	12–100	3	Lipidosis
Rat	Mellaril	24	3	Lipidosis
Dog	Inv. drug	20	3	No effect
Dog	Inv. drug	40	3	Increased liver weight

Table 3 Drugs Known to Induce Lipidosis

Drug	Therapeutic action
In animals	

Imipramine (Troframil)	Antidepressant
Fenfluramine (Pondimin)	Anorectic
Thioridazine (Mellaril)	Antipsychotic
Chlorcyclizine (Fedrazil)	Antihistamine
Zimelidine	Antidepressant
In humans and animals	
Chloroquine (Plaquenil)	Antimalarial

1. Other marketed compounds are known to induce lipidosis and lymphocyte vacuolization in laboratory animals, but not in humans.
2. A peripheral marker is available. Although the drug may induce fatty vacuolization in the liver, a liver biopsy is not needed to detect it because the process, should it occur, would likely be detected in the lymphocytes.
3. The cytoplasmic vacuolization observed in animals was found to be reversible when the drug was discontinued. Should lipidosis occur during clinical trials, subjects or patients should undergo a full recovery when the drug is discontinued.

The drug was subsequently tested in humans at dosages as high as 500 mg/day for up to 6 weeks. Blood was routinely drawn for careful examination of the lymphocytes and liver chemistries; no toxic effects were discerned. The compound ultimately failed the decision filter, however, because of its lack of efficacy.

I. PHASES OF CLINICAL DRUG DEVELOPMENT

The case described represents just one of many decisions that must be made before beginning clinical trials. Clinical drug trials are described as Phases I–V. The first trials in humans that test the drug for safety are considered Phase I. These studies usually employ normal volunteers, and may expose about 50 individuals to the drug. For known toxic compounds such as anticancer agents, only patients with the targeted illness would be used.

The first studies to define efficacy are considered Phase II. These studies are typically conducted to determine the best dosage regimen for the Phase III efficacy studies. In general, 100–300 patients would be entered into various con-trolled clinical trials during this phase. Phase III, considered an extension of Phases I and II, exposes a larger number of patients (e.g., 1000–3000) to the test drug under controlled trials to further delineate the safety and efficacy profile of the drug. For example, special studies in the pediatric or elderly population may be performed during Phase III (although the studies themselves may be Phase I-type studies). After a successful Phase III program, an NDA may be filed with the appropriate regulatory agency.

Phase IV studies may be done for two different reasons. Marketing-oriented trials may extend the recommended duration of treatment, or they may be primarily instructive in

nature to help familiarize more practitioners with the drug's efficacy and side effects. Phase IV trials may be required by the FDA as a condition of approval to extend the knowledge of the pharmacological effects of a drug while allowing simultaneous availability to patients. Phase V studies may extend the indications of a drug to an entirely different disease state. For example, propranolol (Inderal) was first marketed for the management of angina pectoris caused by coronary atherosclerosis. Indications were later extended to management of hypertension, reduction of mortality after myocardial infarction, adjunctive therapy for pheochromocytoma, management of hypertrophic subaortic stenosis, and prophylaxis of migraine headaches.

II. COMPONENTS OF THE CLINICAL TRIAL

Before discussing some of the problems that can arise during clinical trials, a brief review of some of the basic components constituting a clinical trial is in order. Figure 7 illustrates the study periods providing the framework for any clinical trial.

Prestudy activities include design and setup of the study, and poststudy activities include data entry, analysis, and report generation. Inclusion and exclusion criteria are determined early in the clinical development process, during the screening period. Before entry into the study, baseline determinations are made to which all subsequent changes will be compared. The heart of a trial is the treatment phase, which consists of drug safety modules and auxiliary modules (Fig. 8), many of which will repeat measurements made at the time of the initial screening or baseline. For Phase II and Phase III trials, specific parameters of efficacy will be assessed. The posttreatment period is the stage at which final measurements are made for safety; it is also the time to assess the effect of withdrawal of drug relative to elimination of the disease state or a return toward the baseline state.

Complex problems reach the decision filter at every stage of drug development, even in the early clinical pharmacology phase (Fig. 9). To delineate the pharmacokinetics of the compound in humans, it is common during Phase I to

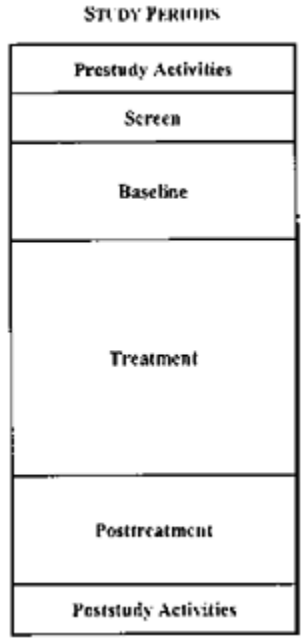

Figure 7 Primary clinical data modules in clinical trials.

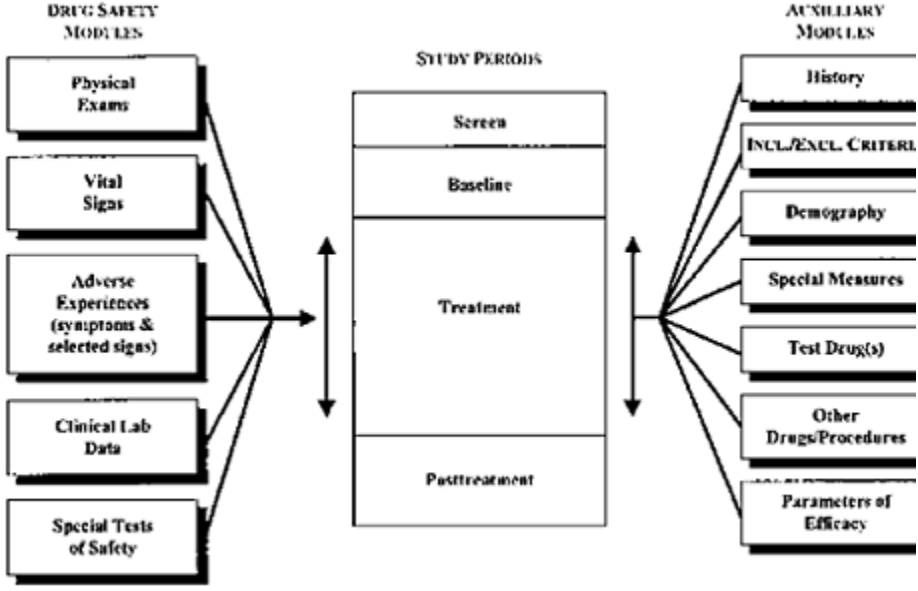

Figure 8 Primary clinical data modules in clinical trials.

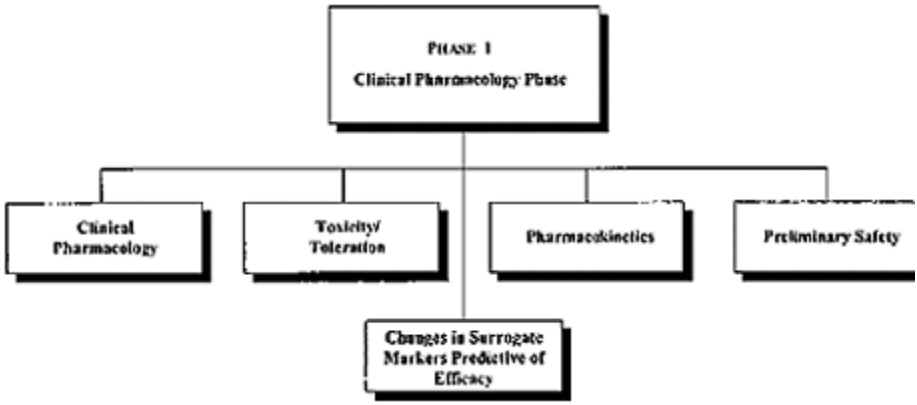

Figure 9 Investigational drug development.

measure blood concentrations of the test drug as dosage is increased. Sometimes the pharmacokinetic data of a study can illuminate problems inherent within the study. A case in point is the development of a drug in which three similar Phase III studies were conducted. In one of the studies, no patients in the active group had measurable concentrations. The placebo group's samples were then analyzed and it was discovered that the randomization scheme was reversed for this study. A second case in point is a Phase I bioequivalence study in which two patients with similar initials each had a single sample that drastically deviated from their expected profile. When the concentrations were transposed to each other's profile, they seemed to make sense, pharmacokinetically. Reanalysis confirmed the concentrations. The Phase I unit, which used bar-coded wristbands, emphatically denied that there could have been a mixup. A battery of tests was conducted on the remaining samples and proved that the samples had been switched. Several pages of the pharmacokinetic report discussed this issue, and, convincingly, the bioequivalence analysis was then conducted on the samples belonging to the appropriate subjects. The products were bioequivalent. Without moving the data to their appropriate places, the products were not bioequivalent.

A final case in point relates a problem that occurred during Phase I testing of an antidepressant compound. It illustrates that no matter how prepared you think you are, the unexpected or unanticipated can happen. The incident took place during a double-blind, placebo-controlled, dosage-titration trial in normal volunteers. Both plasma and urine samples were being collected for quantitative analysis of drug levels. Results demonstrated detectable levels of drug in all of the volunteers at the lowest dosage given. However, at the highest dosage administered, much to everyone's surprise, drug was not detected in some of the volunteers. Many possible explanations exist, including the following:

1. *The drug is inhibiting its own absorption at higher dosages.* Even if this phenomenon were true, detectable levels should exist in all volunteers.
2. *The assay was not working properly.* The appropriate amount of drug was recorded

from spiked samples randomly distributed throughout the test samples; this procedure made assay problems less likely.

3. *The drug is inducing its own metabolism.* Even so, although levels of drug at higher dosages might be lower, they should not be undetectable.
4. *Some volunteers failed to ingest drug.* The test site used elaborate procedures to ensure that volunteers ingested the test drug. This type of problem was endemic when prisoners were commonly used as volunteers. They would swallow the drug, then go to the bathroom and induce vomiting.
5. *Placebo and active drug are mixed.* Such a situation could arise either before dosing (packaging error), or after dosing (sampling or labeling error after blood and urine are collected). If blood and urine specimens were mislabeled, some instances might occur in which detectable drug existed in blood but not in urine, or vice versa. In no instance, however, did this situation occur. Because blood and urine samples were collected from the placebo volunteers to keep the study double-blind, those specimens were analyzed. In some cases, drug was detected, with both urine and blood samples correlating positively or negatively. Finally, drug was analyzed that had been packaged for backup volunteers in case of dropouts. An absence of drug was demonstrated in some of the "active" volunteers, and drug was detected in some of the "placebo" volunteers.

Because an elaborate system of checks and crosschecks was in place to guard against the possibility of drug mispackaging, it was impossible to think about such a wholesale mixup. After considerable inquiry, an almost impossible reason surfaced. A disgruntled employee had deliberately sabotaged the packaging by intentionally mixing drug and placebo.

A packaging error such as the one described is extremely costly. In this case, the study had to be repeated, with the following consequences:

1. Volunteers had to be reexposed to the test drug and associated procedures.
2. The cost of doing the Phase I trial doubled.
3. The development of the drug was delayed for 3 months.

A new drug can potentially reach sales of hundreds of millions of dollars in its first year. The ultimate dollar cost of a 3-months' delay is obvious, in addition to the fact that patients are denied the use of the drug for 3 months. The

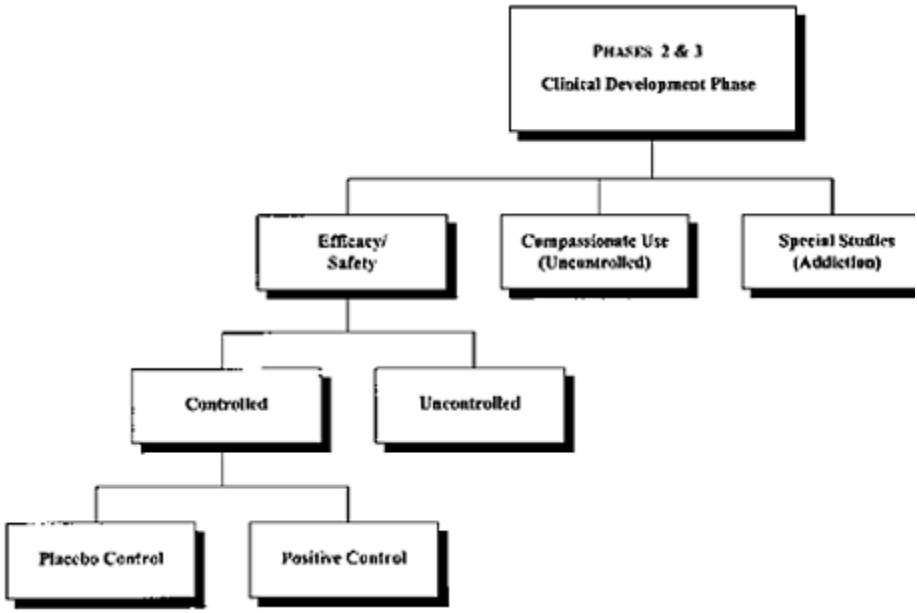

Figure 10 Investigational drug development.

situation above in the Phase I trial describes a tribulation that can occur at any point in clinical drug development. However, many issues specific to Phases II and III also must be anticipated. As seen in Fig. 10, different types of efficacy studies may be undertaken (see Chapter 6). Special studies, such as tests for addictive potential or studies allowing compassionate use of the drug (see Chapter 9), occur during these phases.

As already shown in Fig. 8, information regarding safety is collected in every study. An attempt is always made to determine any adverse events that may be caused by the drug. The process is especially difficult in patients, because illness itself is defined by a grouping of adverse events. The critical question when any adverse event occurs during a clinical trial is, “Why did it occur?” Did the event occur spontaneously, or as a result of an underlying disease, or as a result of a procedure conducted? Or was it caused by the drug?

What data are needed to answer those questions? Figure 11 depicts points along the course of a clinical trial at which data must be gathered to make an assessment. Figure 12 lists some of the numerous information points required before an accurate judgment can be made.

If Figures 11 and 12 seem unnecessarily complex and unduly detailed relative to the assessment of causality for an adverse event, consider the study of an antidepressant. A probe was made at baseline just before initiation of treatment

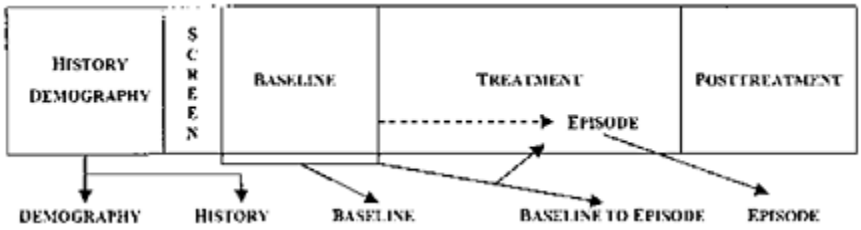

Figure 11 Information required for reporting adverse experiences.

(see Fig. 11) to determine the clinical status of the depressed individuals who were about to enter into the study. As seen in Table 4, an impressive background of complaints existed before any drug medication. In a 6-week study, multiple probes will be performed to detect adverse events. Consider, then, if headache is reported as an episode during treatment (Fig. 11), it will be extremely difficult to assign causality relative to baseline when more than half the patients reported headache at baseline.

The symptoms listed in Table 4 afflict all of us from time to time, but assessments of causality for more serious events should not require the detailed data reporting depicted in Fig. 12, right? Wrong! Table 5 lists serious adverse events not present at baseline but occurring during placebo treatment. If these events had taken place during active therapy, it would have been very difficult to avoid assigning causality to the drug (see Chapter 14).

Any type of adverse event must then flow through the decision filter. The tribulations associated with assessing causality can be multiplied if case report forms (CRFs) are improperly designed. Poorly designed CRFs during Phase II will compound and multiply the problems encountered in Phase III. Proper design of CRFs at the start of clinical trials will create a firm foundation for passing through the multiple decision filters on the way to new drug approval.

A type of tribulation that occurs more in Phase II, and particularly in Phase III trials, involves adherence to the drug regimen. Drug adherence is loosely described as the number of dosages actually taken by a patient compared with the number prescribed. Alas, as with most things in life, further reflection reveals a far more complex subject. Were dosage administrations properly spaced, were they taken with meals (if required) or without food (if required), were they taken with forbidden concomitant medications? With larger Phase III outpatient studies, the variability of adherence is exaggerated. Adherence is further hindered by prolonged or complex prescriptions. It can destroy the statistical validity of an otherwise carefully controlled trial.

Consider the extreme example of a 71-year-old patient who was admitted to the intensive care unit after being found unconscious at home. Because of his

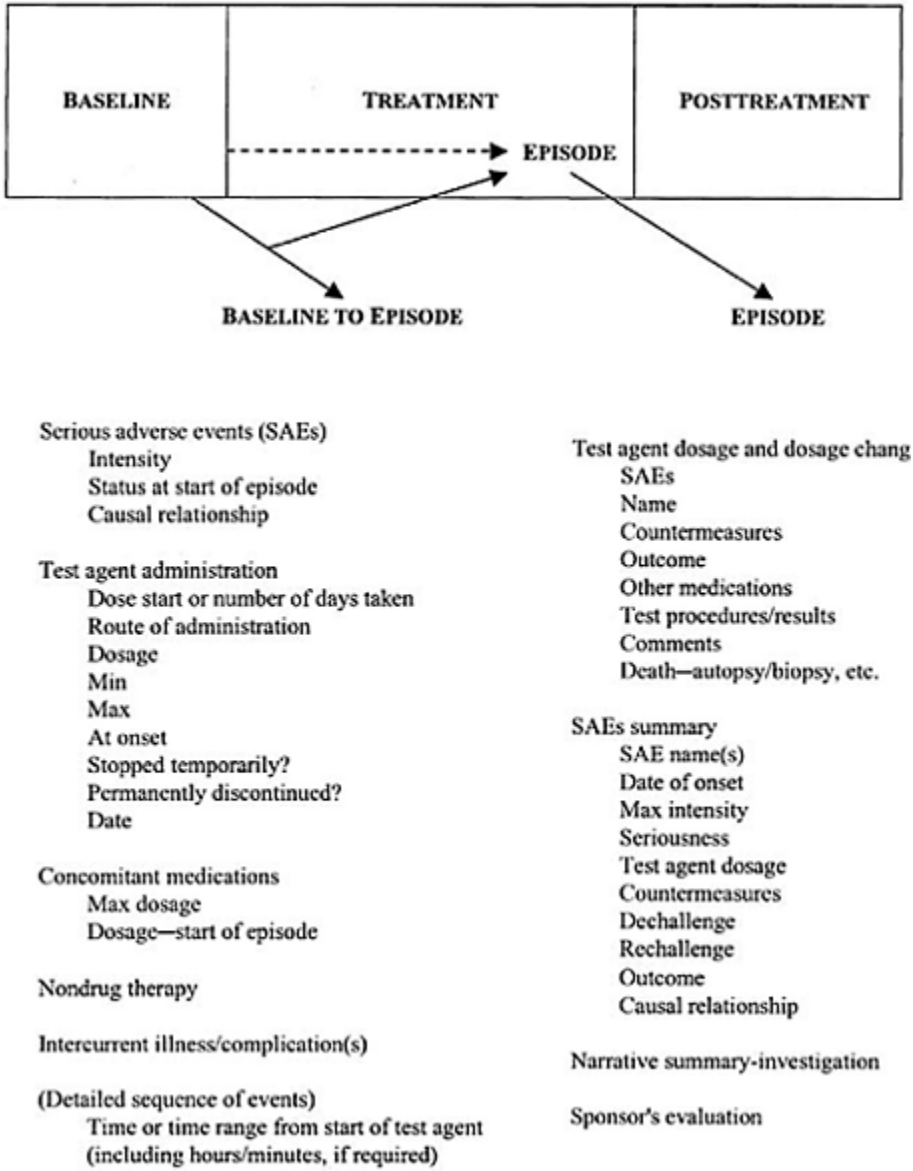

Figure 12 Information required for assessing adverse experiences.

Table 4 Observed Adverse Events at Baseline

Event	Percent of patients

Insomnia	92
Tiredness/fatigue	74
Anorexia	59
Headache	54

deteriorating condition, he had been prescribed 13 different medications at one time or another, but no one had ascertained whether he had adhered to his dosage regimen. The ambulance staff found 46 bottles containing 10,685 tablets for 13 different medications in his room (6)!

III. THE FUTUR

Although the search for new chemical entities or natural product extracts to treat diseases is likely to continue for years to come, changes are underway that will have a profound impact on how we diagnose and treat disease. The identification of various active entities such as cytokines and delineation of their functions has already led to a new class of molecular therapies. This process is going to take a quantum leap forward now that the entire genetic code of a human being is accessible on the Internet.

One new area generating interest and huge investment is called pharmacogenomics—an attempt to identify therapy targeted to an individual's specific genetic composition. The desired result would enhance efficacy, or minimize toxicity, or both. A consequence of deciphering the human genetic code is the increasing number of blood tests that can reveal disease-gene mutations and pre-

Table 5 Serious Adverse Events Not Present at Baseline and Occurring During Therapy with Placebo

Marked EKG changes
Grossly abnormal EEG
Acute renal failure
Seizures
Sudden death

dict with varying degrees of certainty the chances of progressing to a disease state. However, with this new technology, new tribulations immediately appear: Do you want to know that when you are 40 or 50 years of age you may be diagnosed with Huntington's disease, a degenerative brain disorder for which no treatment currently exists?

A huge knowledge gap exists between knowing a gene's structure and understanding

its function. Some functions are currently known, however, and some of these genes are the reason for the enthusiasm many hold for gene transfer, creating a permanent or semipermanent change in the human body. Many tribulations face gene transfer such as getting the gene into a cellular nucleus, having it express the necessary protein, and having the DNA remain long enough for it to do its job. Probably the first successes will be with genes that are needed only for a short time, such as those expressing for angiogenesis. Likely within a few years (not decades), advanced coronary arterial disease will be treated with gene coding. Rather than, or perhaps in concert with, coronary arterial bypass grafting, there will be an ability to grow new vessels to supply oxygen to arterial tissue that continues to be viable.

Although gene transfer may be the wave of the future, its safety and efficacy must still be satisfied through the drug development process. Regulatory scrutiny has already exceeded its previous bounds, but there continue to be areas that can reduce the time and cost of drug development. Technologically trailing only slightly behind gene transfer is electronic data capture and real-time data analysis. Once this technology is implemented, data capture and analysis times for all studies can be greatly reduced, creating substantial cost savings. The sheer tonnage of data required to pass just the clinical decision filter (Fig. 13) is enormous. If each case report form has an average of 200 data characters, with 25 pages of CRFs per patient, the total data bits required for a conservatively sized NDA of 2000 patients or volunteers would be 10 million. Information technology will help manage these data in efficient and less expensive ways.

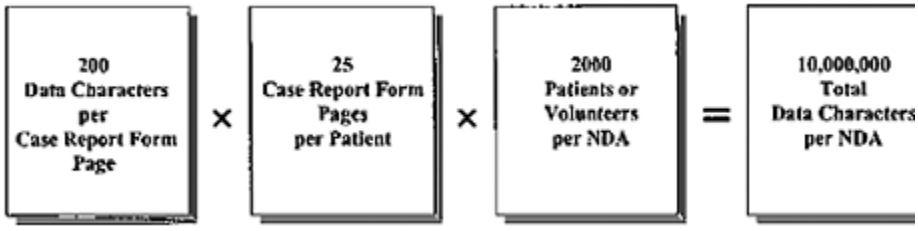

Figure 13 Quantity of clinical data characters required for an NDA.

IV. CONCLUSION

Guiding a new chemical entity through the tribulations involved in the drug testing and approval process is a task that is exciting and rewarding as well as long and complex. Advances in gene transfer, electronic data capture, and real-time data analysis all promise to increase our chances of success. Ultimately, however, it is through dedication, skill, and lots of luck that the drug development process is successful and we can provide a new medication to the people who need it to fight the pain and suffering of illness. At those times, the camel truly has made its way home through the eye of a needle.

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Preclinical Drug Discovery and Development

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I. INTRODUCTION

The major change that has occurred in the drug development process over the last 15–20 years has been the introduction of significant advances in new technologies that expedite the design, screening, and identification of new chemical entities. A brief review of these technologies, together with a review of the various approaches used in the discovery of new chemical entities, is presented to update the readers and encourage their deeper involvement in areas pertinent to their interests. The use of these technologies has forced the drug discovery process to evolve into a rapid, integrated, and usually very targeted process. In addition, changes in regulatory requirements, as well as the introduction of International Conference on Harmonization (ICH) Guidelines, have led to new concepts for the timely and cost-efficient development of drugs for registration in world markets. The authors' experiences in interpreting these guidelines and applying them to the drug development process are presented for the readers' consideration.

II. DRUG DISCOVERY

A. Source of Molecules Used in Drug Discovery Process

Anyone interested in drug discovery must first address the issue of the source of molecules that will ultimately provide the new drugs. Some of the oldest sources

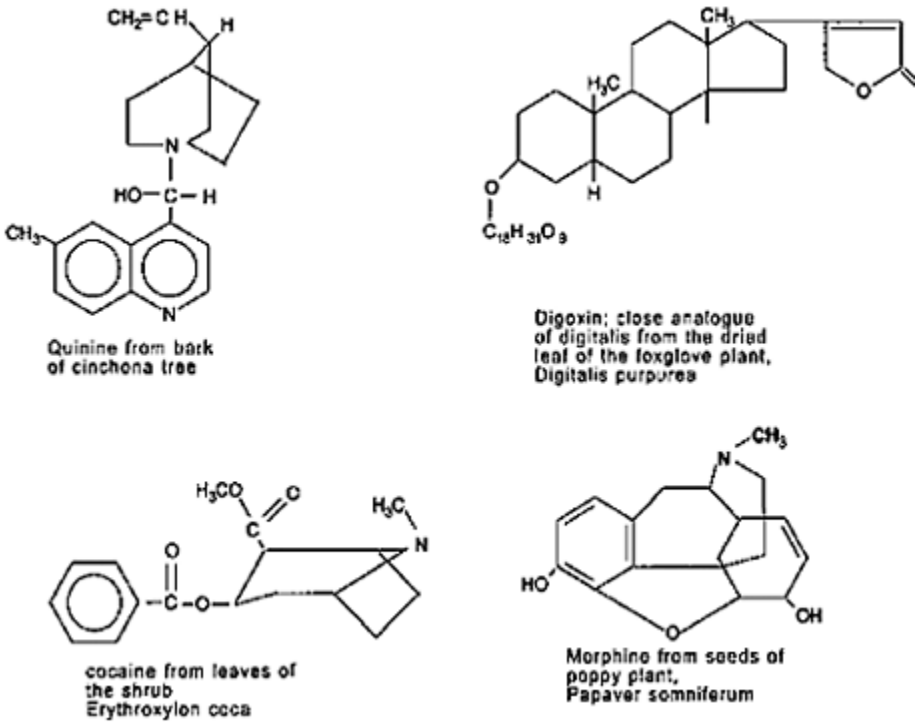

Figure 1 Structures of natural products.

of drugs have come from plants and their analogs, microbial broths containing various metabolites of microorganisms, animal cells and their extracts, animal and marine toxins, and, more recently, genetic engineering (Fig. 1).

Recent advances in technologies such as combinatorial chemistry and computer-assisted design have markedly increased the ability of the chemist to supply new chemical entities for study. However, diversity of molecules is not easily obtainable, even with the advent of these new advances in technology. In fact, high-throughput screening techniques have made the process of screening molecules so rapid that the diversity of structures available for screening has dwindled to the point that the search for natural products with their inherent diversity is now taking on additional importance.

B. Methods Used in the Drug Discovery Process

1. General Screening

Many previous drug discovery programs were based on the random screening of large numbers of chemically diverse compounds through one or more biological assays in hopes of finding a therapeutically useful property. These biological assays consisted of in vitro assays (e.g., enzymes or binding assays), assays in isolated tissues, and in vivo