The Clinical Research Process in the Pharmaceutical Industry
DRUGS AND THE PHARMACEUTICAL SCIENCES

A Series of Textbooks and Monographs

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The Clinical Research Process in the Pharmaceutical Industry

edited by

Gary M. Matoren

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This book is dedicated to
the memory of

Steven J. Eisner
1904–1980

whose interest in the clinical research process provided the inspiration
and encouragement for me to undertake the development of this book

and to

my loving wife Susan and darling children Bonnie Lisa and Debbie Lynn

for their patience, support, and understanding while this book was
being developed
Physicians and scientists participating in drug development are in a unique situation because they have the potential for improving the health of millions of individuals worldwide. In contrast, physicians in private practice or in an academic milieu can be directly responsible for helping limited numbers of patients in their immediate geographic locations. It is profoundly satisfying to be involved in developing new, clinically important therapeutic agents. Furthermore, it is essential for industrial, academic, and government researchers to share the responsibility for drug development in order to achieve success.

Most drugs introduced over the past 25 years have been developed primarily by the pharmaceutical industry in cooperation with academia and government. Twenty years ago the cost in dollars and time to develop a new chemical entity was relatively low, compared to recent estimates of approximately $70 million and 10 years to develop a drug from synthesis to final approval of a New Drug Application. Clinical research represents a significant portion of these expenditures. Since clinical research is an important part of this overall process, a reference work on the clinical research process in the pharmaceutical industry is necessary to promote mutual understanding and appreciation among clinical investigators in industry and academia and those individuals involved with the regulatory process (both in industry and government). In general, this book should be useful to anyone involved in the drug development process.

Major changes have occurred in the pharmaceutical industry as a result of the 1962 Kefauver-Harris Amendments to the Food and Drug Administration Act, when efficacy (as well as safety) became a requirement for drug approval. Moreover, other requirements and guidelines have surfaced to reflect advances in the medical and pharmaceutical sciences, including pharmacokinetic profiling, bioavailability, drug interactions, differences in metabolic fate of drugs in healthy vs. ill subjects, and in the old and the young. In many instances, this information is beneficial and useful; at times acquiring it is not justified and at times may border on being unethical.
The authors of this book have attempted to address contemporary issues such as ethics in clinical research, institutional review boards, medical devices, postmarketing surveillance, contract research organizations, and "orphan" drugs, as well as the monitoring and investigation of clinical researchers themselves.

Because of the changes in the clinical research process that have occurred in the past two decades, potential investigators should be aware of the joys and advantages of conducting clinical studies of potential new drugs or marketed drugs, as well as the disadvantages that may be encountered. Such an awareness will aid investigators to avoid the pitfalls and frustrations that result from inadequate attention to details. A reference work should be available to point out the necessity for careful preparation of protocols, subsequent adherence to the protocols, and accurate record-keeping.

In addition, the recognition that various personnel collaborate in team-oriented research is of paramount importance for the overall success of drug development. These individuals include scientists involved with clinical pharmacology, clinical trial monitoring and execution, pharmaceutical formulation, statistics, computer analysis, drug disposition, and those who have not only an in-depth knowledge of the regulatory process, but, more important, know how to deal with it effectively to achieve the desired goal.

Because individuals from multiple disciplines are involved in the development of new drugs for the prevention and cure of disease, as well as for the palliation of pain and suffering, this text is most welcome. It should be enlightening to individuals already committed to the field as well as those planning to enter this exciting and socially important discipline.

Louis Lemberger
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and
Professor of Pharmacology, Medicine, and Psychiatry
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My twenty years of experience in administration and planning in the pharmaceutical industry, academia, government, and the health care field provided the foundation and impetus for undertaking the development of this comprehensive book on the clinical research process in the pharmaceutical industry.

This book examines the sequence of events and methodology in the clinical research process. This book is devoted to the industrial clinical research process as it relates to the organization and administration of clinical research programs; clinical project coordination; research quality assurance; project management; monitoring process; drug regulatory affairs; legal, moral and ethical problems; clinical information systems including computer applications; biometric and study design; education and career development; market research and the clinical research process; health economics; postmarketing surveillance; drug disposition; drug safety evaluation; the role of the Food and Drug Administration; the history of clinical research; the future; recent trends, and many other exciting topics. This list serves to provide you with a sampling of the scope of this book.

In documenting the industrial clinical research process, the authors look at the sequence of events leading to the development of new therapeutic agents. Intertwined with the methodology and sequence of events is the conceptual framework involving the philosophical, economic, political, historical, regulatory, planning, and marketing aspects of the clinical research process. Support functions involved in the industrial clinical research process, including preclinical activities, are presented to show their relationship to the whole.

This book will serve as a reference source for the multidisciplinary personnel engaged in the industrial clinical research process. Readers will become familiar with the internal and external forces surrounding the flow of events in the clinical research milieu. The rapid development of information in this field makes keeping abreast of developments at once obligatory and difficult. Since the methodology of the industrial clinical research process is constantly evolving, this book is designed to provide readers with a ready source of background information as well as a preview of things to come.
This book will serve to provide personnel involved in the industrial clinical research process with information on the latest state of the art. Clinical monitors, planners, clinical information scientists, clinical study coordinators, drug regulatory personnel, biometricians, computer scientists, medical writers, clinical research associates, clinical investigators, institutional review board members, research administrators, project management personnel, quality assurance staff, pharmaceutical scientists, market research staff, personnel and financial administrators, educators, governmental regulators, clinical scientists, and students of the health professions will find this book to be a valuable reference tool.

I believe this book will serve as a catalyst for colleges of pharmacy, medical schools, undergraduate and graduate programs in the medical sciences, and nursing and allied health programs to develop courses in the clinical aspects of drug development. I hope that this book will serve as a learning tool for the many students in the health professions embarking on a career in the pharmaceutical industry, in particular, in clinical research. Also, the book is ideal for in-service education programs conducted by pharmaceutical corporations, professional organizations, and government agencies. I intend to utilize this book for a new course I have developed, entitled: The Clinical Research Process in the Pharmaceutical Industry.

I believe this book will provide the pharmaceutical industry, academia, government, clinical investigators, physicians, pharmacists, and all personnel mentioned earlier with a long-overdue comprehensive source of information on the clinical research process in the pharmaceutical industry.

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ACKNOWLEDGMENTS

I would like to acknowledge the inspiration provided by the late Steven J. Eisner, whose interest in the clinical research process motivated me to undertake the development of this comprehensive book. The renaissance in the drug development process in my professional milieu, coupled with my background in academia, government, health care, and the pharmaceutical industry, added to the impetus for creating this book. My role in clinical as well as in research and development project coordination gave me an appreciation of the need for such a book. Coupled with this was my desire to bring to fruition a book to document the clinical research process; provide a reference source on methodology and sequence of events; and stimulate the development of courses and curricula in clinical aspects of drug development in pharmacy colleges, medical schools, and graduate programs in the basic medical sciences, nursing, and allied health care fields.

The outstanding response from my colleagues in academia, government, and the pharmaceutical industry in accepting my invitation to participate is evidenced by this outstanding book on the clinical research process. I want to express my sincere appreciation to these authors, who took time from pressing professional responsibilities to contribute to this work. They were recruited because of their international reputation in the drug development process. To them, I owe an eternal debt of gratitude.

I would like to express my appreciation to Professor Janet Landau and to Marion Weinreb for proofreading and for developing the index entries for several chapters.

I am deeply indebted to Linda Da Silva and Sharon A. Duritzo-Spocinski for the significant amount of time they devoted to proofreading the entire manuscript and developing and compiling the subject index. Finally, Linda and Sharon spent many hours integrating and typing the completed index. Their attention to detail and perfection are sincerely appreciated.
This book would have not been possible without the encouragement of the staff of Marcel Dekker, Incorporated. In particular, I want to express my sincere appreciation to Dr. Maurits Dekker and Mr. Marcel Dekker.

Finally, I would like to express my eternal gratitude to my loving wife Susan and two darling children, Bonnie Lisa and Debbie Lynn, for their patience, understanding, and support while this book was being developed.
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INTRODUCTION

Over the years, the process of new drug discovery has evolved and matured from the days of sporadic but important or astute observations made by individuals on the therapeutic benefits of certain naturally occurring medications or substances with desirable pharmacologic activity to the present state of a highly developed art and science in which a concerted effort is made, particularly in the pharmaceutical industry, to discover, develop and bring to the marketplace new drugs for the treatment of a wide variety of disease states in human beings. While some medications from the "good old days" certainly were effective or contained truly active ingredients (e.g., cinchona bark for the treatment of malaria; foxglove in the treatment of cardiac arrhythmia), undoubtedly many purported therapeutic agents and nostrums were, in fact, ineffective. Indeed, a certain number of such preparations must have contributed toxicity rather than efficacy and likely exacerbated the disease state, increased morbidity, or shortened life. Biological science, whether we like it to be so or not, is a rather inexact science because of the inherent variability among individual animals. Such differences are really not surprising when one considers the incredible array of biological processes that are ongoing at any given moment in the human body, including, but not limited to, variability in blood flow, digestive processes, intestinal function, enzymatic levels in tissues, presence of stimuli or inhibitors, transfer of oxygen through the lung, etc. The biochemical sciences developed along a quantitative path some time ago and the sciences of animal pharmacology and toxicology have also been brought to a rather high state of reproducibility in the recent past, particularly through the use of inbred animals and careful control of environmental conditions. Because of the inherent complexity involved in conducting truly controlled studies in human beings, however, the process of clinical assessment of drug effects has lagged behind experimental laboratory processes and has been brought to a reasonably high state of control only in the recent past.

Although certain well-meaning, albeit uninformed groups argue vociferously that new drugs and therapeutic modalities can be developed
and their true value proven in small mammals and lower animals, all informed and experienced research investigators and physicians know only too well that this is a laudable objective that, at the present state of knowledge, represents only wishful thinking. The only way that one can truly establish the efficacy of a new drug or a new treatment regimen in man is to study that drug or treatment regimen in human beings and to study it adequately and by properly controlled methods. To this end, a truly impressive science has developed in the recent past in which careful attention to the design of protocols, selection of patients, randomization techniques, collection of data and large-scale computerized analyses of results has led to an improved quality of new drug development, albeit at a price in both out-of-pocket costs and time. As the cost of the development of a new therapeutic agent escalates into the multimillions of dollars (some estimates putting this cost as high as $70 million per drug brought to the marketplace), the pharmaceutical industry, the government, and society in general must strive to be certain that effective and safe drugs reach the patient at the most rapid, safe pace possible. The medical profession, the government, the pharmaceutical industry and society must strive more diligently than ever before to set the standards against which "benefit-to-risk" will be measured. It is, in my opinion, reprehensible to delay, withhold, or abandon an effective therapeutic agent that can provide significant amelioration of morbidity or, better yet, cure of disease because a decision cannot be made whether the associated toxicity (of which there always will be some) justified the therapeutic benefit. Society has accepted the concept of risk in everyday life (e.g., auto accidents, smoking, swimming) and it must be educated to the fact that all agents with high pharmacological activity must be expected to show some types of side effects in some patients.

While the ultimate measure of efficacy is the double-blind, controlled clinical trial, academicians, government regulators, and pharmaceutical scientists must all wrestle with the question of when the use of a double-blind, controlled study may lead to ethical problems on the one hand or to an unnecessary drain on limited and precious resources on the other.

Because of the magnitude of the importance of these problems to society, it is imperative that we attempt to answer them with an evolving standard of performance that has, as one of its objectives, assurance of the forward motion of new drug development while, at the same time, giving equal assurance of protection to the experimental subject or patient ultimately receiving the drug. Throughout this process, clinical and preclinical research scientists in the pharmaceutical indus-
try will play an intimate role. Hopefully, the contents of this book will assist those professionals who must deal with such weighty problems in formulating both the questions and the decisions that must be reached.

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1

PHARMOGENOLOGY: THE INDUSTRIAL NEW DRUG DEVELOPMENT PROCESS

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I. PHARMOCENY

The era of drug discovery, development, and application to patient care of these past 50 years has had profound, positive effects on humanity. This era is shared by rapid advancement in communications, transportation, agriculture, and other technological changes, of which all cannot be held in the same esteem as the salutary contributions of the pharmaceutical industry.

Economic forces together with growing regulatory requirements have so modulated the talented efforts of industrial pharmaceutical scientists that a special system or process of drug research and development has evolved. This chapter and much of this book deals with pharmogeny, the genesis or origin of drug products. As such, this text is one of pharmogenology, the study of the process involved in the genesis of new drug products. It is not surprising that these neologisms have not yet attained complete acceptance, as they violate a basic principle of English, namely, that all roots of a word should derive from the same language. However, perhaps violation of tradition in this case makes these terms even more appropriate—for, in fact, what is referred to as pharmogenology is a great mélange of sciences and technologies and represents a unique interdisciplinary amalgam of scientific efforts that may well deserve to be designated by a word which is itself a hybrid.

Patients who benefit from a drug encounter a dosage form and recognize it only as a medicine prescribed by their physician. The medical consumer has become accustomed to having a wide variety of medicines available to treat the signs and symptoms of their diseases. These drug products are the basis for a business called the pharmaceutical industry.

As in all other aspects of commerce, drug products must compete for the customers' attention and selection. For the pharmaceutical industry, the physician is the customer. Those drugs that meet the needs and wants of the physician who acts on behalf of patients will be prescribed and purchased and so achieve an increasing market share and become economic successes. Those drug products that do not satisfy the needs of the physician and patient will soon lose their market share. Since the aim of business is to continue to attract and progressively satisfy more customers, it behooves the pharmaceutical company to clearly identify its targets both qualitatively and quantitatively.

II. MARKET PLANNING

It may come as a surprise to some readers to find that this overview of the industrial new drug development process begins by first addressing the concept of market planning. This may be related to the mispercep-
tion generally shared by the public that a better product, or one with new attributes, will automatically compete successfully with available products with lesser attributes.

Without proper promotion and marketing this does not usually happen. In medicine, where the busy and preoccupied physician is the customer, it is often quite difficult to convince him to change prescribing habits from that with which he is comfortable and confident. Indeed, success of a new drug product is much more likely if it is the first such product available for a given indication. When this is not the case, market research can indicate where a need exists for new drug products which better meet the patient's needs and better satisfy the physician's wants with respect to the benefits provided by the product and the risks attendant to it (1).

Market research groups have a variety of techniques of market analysis which help to define those therapeutic areas in which more effective or safer drugs are needed. This identification is really the first step in the industrial new drug development process. While several pharmaceutical companies may recognize similar opportunities, the history of the firm, its present drug product profile and mix, the nature of its sales force and technical representatives, and corporate strategic planning all contribute holistically to the selection of the areas to which research and development (R&D) resources should be applied.

If, however, R&D is to produce totally novel or unique modes of therapy, it is less appropriate to defer to market analysis for direction. This is because market research tends to be historic in nature and can measure only the existing markets and the trends seen in them. Medically oriented industrial research personnel are in a better position to recognize therapeutic discontinuities, heterogeneity of disease states requiring more specific therapeutics, and opportunities for drug product applications that are innovative. Once such an innovative approach is identified, an in-depth market analysis should be done to attempt to assess the concept's commercial feasibility.

A spirit of joint enterprise and a mutual appreciation of the roles and capabilities between the R&D community and the marketing community is essential if potential new drugs are to be translated into articles of therapeutic commerce. In the well-managed pharmaceutical company, such collaboration will allow both for the generation of new drug products in response to technical market analyses and for a major commitment to new and unique approaches to disease. For instance, market analysis of the agents used to treat glaucoma might not have predicted the major success of timolol maleate solution, and the sales of therapeutics for peptic ulcer might not have identified a billion dollar market following the introduction of cimetidine hydrochloride.

Just as market planning groups must be staunch advocates of their proposals based on sound analytical techniques, so also the industrial scientists and managers must champion their novel approaches or goals if major advances are to be realized. In the end, the enthusiasm of
both groups must be aroused and all within the pharmaceutical company must be persuaded of the soundness of the direction chosen. As the research process moves forward and as Chemical Lead Compounds advance to Biological Lead Compounds, thence to Clinical Candidates, Investigational New Drugs (INDs), and finally to an approved drug product for commerce, the challenge of convincing the physician-customer that a better drug product is now available is prodigious and equal in effort to all of that which preceded it in its development.

The final step in the industrial new drug development process is to convince the medical community to prescribe the new medication for the patients for whom it is intended. This difficult task is eased if the marketing organization has participated in the drug development process from the beginning.

III. DRUGS ARE CHEMICALS

A well-organized and operated R&D community can usually attain the desired goals of a carefully constructed marketing plan. Providing they are reasonable goals, it is not really a question of whether these goals will be attained but rather when. The journey for a new drug from the chemist's bench to the physician's prescription pad is one that requires some 10 years and presently costs about $70 million. Of each 10,000 compounds synthesized by the scientists in the search for totally new drug products, only one has the biological, pharmaceutical, and clinical attributes to survive all the way to the marketplace (2).

The drug development process is a terribly expensive one; its costs inexorably increase as governments require progressively more preclinical and clinical studies to assure the safety of new drugs. There is no such thing as a totally safe drug. Drugs are chemicals that manifest desirable biological and therapeutic attributes, but they also have concomitant and attendant undesirable attributes, designated "side effects" or "toxicity."

A good drug has a favorable ratio of benefit (or therapeutic effect) to risk (or adverse effect) for the desired clinical situation. A drug is a highly sophisticated instrument which can be used correctly and effectively, or poorly and with adversity. Greater increases in testing will not make these potent chemicals safer. Only their proper use by well-informed clinicians who monitor their patients' responses to them can provide reasonable safety. Unfortunately, the rare and unanticipated anomalous adverse effects usually could not have been discovered even by excessively large batteries of premarketing studies and testing. Their discovery remains in the domain of postmarketing surveillance by a vigilant medical community and epidemiologists (3). Despite these facts, governments continue to require growing numbers of extensive and expensive preclinical and clinical studies in an attempt
1. **Pharmogenology**

to diminish risks attendant to new drug development. This has resulted in the extraordinary costs of basic research and subsequent development which are comparatively greater in the pharmaceutical industry than in other technologically oriented businesses. An obvious tenet of a research-based pharmaceutical company is that it must make sufficient profits to pay for R&D and other costs of business. This is accomplished by the introduction into therapeutic commerce of a continuum of profitable new drug products.

IV. **PRIORITIZATION**

Applied or directed science requires targets that are clearly identified and of sufficient temporal longevity. Unclear or ephemeral or moving targets are counterproductive and demoralizing to the R&D organization. The planning function of a company must have its positions and recommendations carefully analyzed and critiqued by the company executive body. The endorsed or revised plans and positions are subsequently communicated fully and clearly to the R&D management. Failure to do this has led to inappropriate allocation of R&D resources in some companies with much loss of time and productivity.

When the process of industrial drug development is optimal, a committee to interface the marketing management and R&D management regularly addresses the corporate drug product needs and opportunities in a clear and precise manner. That body should be convened several times yearly to address expectations or required changes in priorities as a function of changes in business or findings of the R&D programs. The existence of such a mechanism is an important component of the industrial drug development process, as the committee provides the needed direction for optimal resource utilization by R&D management. The prioritization and program review process does not preclude innovation or creativity by the R&D community. It does, however, specify where that community should be heading. How R&D gets there—and explicitly how to define "there"—is a task given to the research community. For instance, if a market planning group and the company executive management stated their desire for a new drug approach to the prophylaxis and treatment of bronchospastic diseases, the scientists of the R&D community might suggest a biological and chemical program around:

1. Cyclic nucleotide phosphodiesterase inhibitors
2. $\beta_2$-Adrenergic agonists
3. Modulators of airway hyperreactivity
4. Inhibitors of the release of mast cell mediators
5. Leukotriene synthesis inhibitors or leukotriene antagonists

or other approaches. In any R&D community resources are limited and the choosing of one or possibly two approaches to the therapeutic target
V. SCREENING

Ever since its origin in antimicrobial research, there has been a great emphasis on the screening approach to drug discovery in industry. This route appears to have first been taken in a systematic way by Paul Ehrlich, who recognized the principle of selective toxicity. He demonstrated that certain vital stains, such as trypan red, were antiprotozoal, and he subsequently screened long series of chemicals and stains for their activity against spirochetes and protozoa. This led to his synthesis, in 1907, of the organoarsenical arsphenamine (Salvarsan) (4). This revolutionized the medical treatment of syphilis and introduced the concept of chemotherapy. It also established a paradigm for drug discovery wherein a biological model is used to facilitate the study of the biological effects of large numbers of chemicals. Indeed, practically all antibacterial, antiprotozoal, anthelmintic, and antifungal drugs have been discovered by this time-honored screening procedure. In more recent times, the screening approach to drug discovery has been held in lesser repute by those who believe that more sophisticated methods exist for drug discovery through fundamental approaches to the basic sciences and better understanding of biological mechanisms. While this may eventually be the case, at present and for some years to come, new drug discovery is still very much a screening process.

It is axiomatic that pharmacological actions are observed as alterations in the function of cells, tissues, organs, or entire organisms by mechanisms involving chemical interactions. The mechanism of action of most drugs appears to be at the enzymatic, coenzymatic, or prothetic group level, and they function at receptor sites through their chemical affinity and intrinsic activity. While screening in chemotherapy originated in a search for molecules with a greater proclivity for intoxicating invading microbial cells rather than host cells (selective toxicity), screening in other aspects of drug discovery led to a search for compounds which affect enzymes, membranes, or receptor sites in vitro, or tissue and organ models relevant to various states of pathophysiology or disease processes.

Many medicinal agents have survived from antiquity; their genesis, no doubt, lies in the random search by the scientifically naive for natural substances with the ability to heal or ameliorate pain. A meaningful pharmacopoeia of primitive but nonetheless useful medicines characterizes every historical culture (5). Each pharmacognosy reflects the environmental opportunities and the prevalence of certain diseases. Some medicaments appear to have been discovered and used in antiquity,
then lost to subsequent civilizations, only to be rediscovered at later times. The point is that the random screening process has led to drug discovery through the ages and still contributes importantly today.

This is not to say that all is chance in drug discovery. It clearly is not. But chance and serendipity do indeed each play an important role in new discovery. Discovery of the unanticipated by the prepared mind contributes more than some of us impressed with the elegant and theoretical methods of science would like to admit. For this reason, the biological scientist must always be alert to the unexpected and be prepared to grasp an opportune finding. Scientific pragmatists will, as did Paul Ehrlich, follow up chemical leads like the special affinity of certain dyes for microorganisms. But they will also study the effects of other unique chemical structures on the system in question in an attempt to discover yet another approach to the same goal.

The first procedure is designated "biologically directed chemical synthesis and screening," or lead following; the second is nondirected "random screening," or lead seeking. Because of the enormous growth of our understandings of mechanisms involved in biological systems, the contemporary approach to industrial drug discovery involves, primarily, the biologically directed chemical approach. The astute medicinal chemist will still request broad screening of molecules that are intermediates in the sequence that leads to the biologically directed target compound. A very real part of the drug discovery process is an appreciation for and acceptance of scientific discoveries made fortuitously. The retrospective integration of such events into a sophisticated rational plan for discovery is one of the pleasures of the drug development aficionado.

VI. LEAD FOLLOWING

The use of the more common biologically directed chemical synthesis approach is most likely to result in yet another drug with many properties in common with others already known or being developed in competitive laboratories. This is because of the use of relatively similar batteries of biochemical and pharmacological test systems among contemporary laboratories. New drugs are sometimes discovered by introducing into these same screens compounds (such as the chemical intermediates) whose structures suggest no reason (based on the medicinal chemistry literature) for them to demonstrate the desired biological properties. Indeed, when this happens a novel chemical lead is found and further structural modification may result in a therapeutic agent with some different and possibly more useful properties.

It was in a manner akin to this that Dr. L. Sternbach of Hoffmann-La Roche discovered the activity of the precursor benzodiazepine-4-oxide structures that led to his synthesis of chlordiazepoxide (Librium)
and subsequently to diazepam Valium) (6). These drugs, whose great medical and economic successes are renowned, were discovered because a molecular rearrangement product of a substituted quinazoline-3-oxide was submitted for pharmacological screening, despite the fact that the entire series of the target compounds had thus far lacked interesting biological activity. Discovery of activity in the transformed molecule led to modifications that enhanced biological activity and greatly impacted the world of therapeutics.

Since most drugs discovered in the past 50 years are a result of the old (but very successful) modification approach, it is particularly regrettable that it is in vogue to refer to it by the pejorative term "molecular manipulation." This approach is sine qua non to the industrial new drug development process and is justified by its successes in the discovery of drugs that ameliorate the pain and suffering of millions of patients.

Now that proper honor has been paid to some earlier and still viable approaches to drug discovery, it is important to put the subject in contemporary perspective.

The design of selective, enzyme inhibitors is currently one of the most exciting approaches to the development of new drugs (7). As in all seemingly new things, a history exists for enzyme inhibition as a basis for drug action. Examples of enzyme-inhibiting drugs include allopurinal, physostigmine, penicillin, methotrexate, theophylline, digitalis, methyldopa, indomethacin, and captopril. In most situations, the fact that the drug was acting through enzyme inhibition became clear only after the fact.

Captopril is a good example of a successful attempt to moderate disease by prospective evaluation of enzyme inhibition using various natural and synthetic peptides. Angiotensin-converting enzyme (ACE) is a dipeptidyl carboxypeptidase which cleaves the C-terminal dipeptide from the nonvasoactive decapeptide angiotensin I to form the octapeptide angiotensin II, an extremely potent vasoconstrictor. An industrial drug development program directed toward finding inhibitors of ACE at the Squibb Institute for Medical Research resulted in the discovery of the important new antihypertensive agent captopril (8). The approach was based on analogy with the active site construction of a well-studied zinc-containing metalloenzyme, carboxypeptidase A. A previously reported potent inhibitor of carboxypeptidase A was used as a model for a directed chemical discovery program that eventuated first in Teprotide (a nonapeptide ACE inhibitor) and, subsequently, in the orally active antihypertensive drug captopril. This is a good example of the high degrees of selectivity and specificity that can be achieved by a program of systematic chemical structure modification using enzyme inhibition as the titrator of activity.

Industrial pharmaceutical laboratories are now approaching the search for potential therapeutic agents via chemical synthetic programs
directed at the creation of selective inhibitors of enzymes involved in metabolic processes as well as tissue regulatory substances of profound effect. For example, many laboratories have expanded their interests in prostaglandin metabolism to include all of the newly elucidated arachidonic acid metabolism. Inhibitors and modulators of lipoxygenase, cyclooxygenase, phospholipase $A_2$, thromboxane synthetase, prostacyclin synthetase, and leukotriene synthetase will likely have important roles in the therapeutics of diseases as apparently unrelated as asthma, myocardial infarction, and peptic ulcer.

Depending upon the corporate strategy for its participation in the drug market, an R&D community can establish from those enzyme models a drug discovery program aimed at lipoprotein lipase or proteolytic enzyme inhibitors affecting hypertension (ACE inhibitors or renin inhibitors), blood coagulation, or fibrinolysis. Inhibition of a protease in spermatocytes prevents their access to the ovum and represents an enzyme-based drug approach to contraception. The opportunities seem endless. The number of enzymes is vast; since enzymes are ubiquitous in the cells and tissues of an organism, inhibition of their activity can have sequelae other than might be immediately obvious from the nature of the reaction catalyzed. Thus, the study of these potent agents in vivo, to establish the extent of their effects in the presence of all other enzymes, substrates, tissues, and homeostatic mechanisms is an essential part of the drug development process. Such studies usually follow the progression: (1) in vitro enzymatic testing, (2) in vitro tissue biochemistry tests, and then (3) in vivo enzymatic and pharmacological evaluations.

VII. FEEDBACK

Just as the biochemistry laboratories must feed information back to the medicinal chemists to help in directing their plans for further synthesis, so also must the pharmacologists contribute to the feedback process in some very important ways. For instance, we still lack meaningful enzyme models for many diseases or for the modulation of organ function. In such situations, there is no substitute for measuring effects of the new compounds on isolated tissues. In addition, pharmacology can define the selectivity of the effect, measure the magnitude of the effect in a dose-response relationship, evaluate the effect in animal models of the disease (e.g., the genetically hypertensive rat as a model for human hypertension), and study general behavioral effects. The significance of the general behavior evaluation is obvious when one considers that feedback from the biochemists might lead the chemists to believe that they have a structure with good potency and activity as, for example, an ACE inhibitor; perhaps pharmacological data showed selectivity and potency in the spontaneously hypertensive
rat test. However, if the drug also caused animals to become lethargic, it might then not have been as attractive as it might have seemed before this fact was known. In the industrial drug development process, the pharmacologist complements the biochemist in providing to the medicinal chemist a more complete picture of the biological properties of a new drug candidate in animals as whole organisms, with reflexes and compensating homeostatic mechanisms in place. For instance, the pharmacologist will advise the chemist as to whether a compound is absorbed by the indicated route of administration, and such information puts the activity and potency in proper perspective.

The specific tests performed in isolated tissues, organ systems, or in whole animals are, of course, a direct reflection of the pharmaceutical company's therapeutic goals as earlier delineated. This is a most important concept which often eludes the uninitiated. The discovery of interesting and possibly therapeutically significant biological activity is a summation and evaluation of selected studies or tests done in the departments of microbiology, biochemistry, endocrinology, and pharmacology. These studies, tests, and screens are established to determine whether the molecules synthesized by the medicinal chemist have activity that will make them of interest for further study or for chemical synthetic analoging. However, this information is, of necessity, restricted by the nature of the biological tests, and these tests are restricted to the expressed areas of therapeutic interests and capabilities of the individual pharmaceutical company.

VIII. RESOURCES

Few (if any) pharmaceutical R&D communities have all of the resources required to do all that the scientists wish to do in the vast panorama of biomedical opportunity. Under responsible R&D managements, resources are allocated and used to support a program of drug discovery and development specifically in the areas of interest agreed upon with the company marketing people and executive management. Therefore, it is not uncommon in the pharmaceutical industry to have biological screening and study restricted to a single or just a few areas of therapeutics. If, for example, a given company's defined interests are in the field of cardiovascular and gastrointestinal therapeutics, it could be that molecules passing through their screens might be the best possible drug for mental depression, or glaucoma, or systemic fungal infection, or psoriasis, or viral infection, but they will remain undiscovered for these uses. Because of this exposure, it is not uncommon in the industrial drug development process for companies to set up contract agreements to put into their screens compounds made by another company's chemists and vice versa. This is done, of course, when the two companies have different immediate therapeutic market goals and,
therefore, a qualitatively different spectrum of biological screens. Such agreements usually include a licensing or perhaps a codevelopment option. Arrangements of this nature have resulted in drug discovery and are a testimonial to the continued value of broad random screening. They provide as well a further value to the involved firms and eventually to the broader medical community.

IX. THE CHEMIST

Success or failure in the industrial new drug discovery and development process very much depends upon the competence of the firm's medicinal chemists. Such chemists vary greatly in their imagination, creativity, industriousness, perseverance, and understanding of biological data. The pharmaceutical company with innovative, goal-oriented medicinal chemists who can function with a team in a collaborative approach toward a difficult or long chemical synthesis, for example, is in a favorable position to achieve its goals.

Medicinal chemists are, of necessity, interdisciplinary people who must be conversant with the biological implications of their structures as well as needing to be expert in organic chemistry and intimate with the literature of medicinal chemistry. The capacity of such chemists to propose new structures and areas of proposed synthesis always transcends, by far, their abilities to prepare these compounds at the bench. To have notebooks full of ideas of compounds for synthesis provoked by conversations, consultants, the literature, and a fecund imagination is the characteristic indicator of excellence in medicinal chemistry. A good medicinal chemistry management allows for a reasonable exercise of this individuality in a synthetic program that might be addressed communally. The most productive chemistry management maintains a complete sense of the specific goals at hand, and, with a restraining maturity derived from earlier goal attainment and collaborative experience, keeps its team focused on the accepted targets.

Communication of screening results back to the medicinal chemists by the biological scientists may be the weakest point in many pharmaceutical new drug development programs. This is particularly unfortunate in that the very success of drug development is directly proportional to the openness, intensity, and timely nature of this communication. Expressed another way, the failure of the industrial new drug development process is assured by inadequate, tardy, and desultory communication of test results by the biological scientists to the chemists.

The medicinal chemist initially prepared 1-4 g of a new compound for biological screening and then goes on to another synthetic project. If there is any activity of interest, within about 4 weeks he may be asked to prepare an additional 5-25 g of the material. The significance
of the biological data derived from the first few grams must be completely conveyed to him by the biologists to allow for informed communication with his management as well as for medicinal chemistry communal evaluation of the possible meanings of that activity from the perspective of chemical structure. These intellectual exercises in coupling variations of chemical structure with biological activity (referred to as structure-activity relationships, SAR) are of immense value to systematizing drug development (9). They allow the chemist to connect the present experience with all former experience of which he and his colleagues are aware in such a way as to suggest the most reasonable changes that should be made on subsequent synthetic compounds in order to enhance or otherwise appropriately modify the biological activity. Often, but not invariably, this exercise results in the preparation of more active or more potent compounds and sometimes in less toxic drugs. To make it happen, however, the ongoing communication of biological findings and their interpretation must be received and considered by the chemist.

X. THE PRECLINICAL TRAIL

A compound with activity of sufficient interest to warrant a request for resynthesis is usually considered a Chemical Lead Compound and forms the basis for an SAR chemical program and drafting a formal document entitled "Record of Invention." In the desirable case where biological evaluation of a member of the SAR family suggests it is an important compound which, when studied in full pharmacological depth, continues to be of high interest, it is considered to be a Biological Lead Compound. Biological Lead Compounds stimulate the patent application process, which is based on the original Record of Invention referred to above. Such compounds are prepared by both radio-labeled synthesis for drug disposition studies and cold synthesis, in at least a 600-g quantity, by a separate scale-up chemistry group in order to do drug safety studies and for preliminary pharmaceutical evaluations. This very desirable situation, the formal identification of a Biological Lead Compound, is not as common an event as a pharmaceutical company management might like. It can happen only as a consequence of and in proportion to the availability of resources to support the broad scope of required effort.

A Biological Lead Compound is advanced to a Clinical Lead Compound status when satisfactory results are obtained in radioisotope drug metabolism studies, preliminary animal safety studies, and when an adequate analytical chemistry and pharmaceutical profile is available. Procedures vary among companies. Most will propose to advance a Clinical Lead Compound to the subject of an Investigational New Drug Application (IND) when the complete biological profile is consistent with
the desired therapeutic activity and potency and when at least 2 weeks of toxicological studies with full histopathology is available from two animal species. More conservative firms await 30-day (interim sacrifice) histopathology results from rat and dog studies together with 90-day clinical observation of those two species in an adequate study done in compliance with the Good Laboratory Practices (GLP) regulations. The advantage of the latter drug safety evaluation program lies in the greater confidence that the firm, the initial clinical investigators, and the volunteers or patients can have in the safety of the new drug. It can also permit the drug to be given for several weeks to volunteers in the Phase I and II clinical studies and for up to 3 months administration when the 90-day animal studies are completed. For many clinical indications up to 3 months of exposure in patients is adequate to indicate the utility of the new drug and the degree of its tolerance and safety. Such a clinical exposure is usually a sufficient basis upon which to make management judgments with respect to the extremely costly, long-term animal safety studies that are required. These may include carcinogenicity studies in animals and segments I, II, and III reproduction studies. This judgment is made by the R&D management community and is implemented with executive management approval.

XI. THE BIOLOGIST

The Biological Lead Compound becomes the subject of intense investigation by the scientists in the drug disposition and metabolism disciplines. The use of a radiolabeled compound in animal studies at an early stage in development of the Biological Lead Compound facilitates an early and economical appreciation of the degree and rate of absorption of the drug and an indication of possible metabolism (10). An elimination or balance study is done in the rat and the dog and is designed to determine the comparative extent and routes of drug elimination after oral and intravenous administration of labeled compound. The amount of radioactivity eliminated in the urine and feces, as well as respiratory $^{14}\text{CO}_2$, is determined. An estimate can be made of the degree of oral absorption of the compound by comparing the radioactivity detected in the urine of animals dosed intravenously or dosed orally. Using radiolabeled drug, the distribution of radioactivity in the various tissues of animals after oral administration of compound is also commonly studied. This distribution is measured at various periods of time after dosing to determine the tissue elimination kinetics of radiolabel and to determine whether radioactivity (unchanged drug and its metabolites) is concentrated in any tissue.

An ABLE (absorption, blood level, elimination) study is also commonly done in the dog as part of the early drug development process.
This study determines blood concentrations of total radioactivity and the extent and routes of elimination of radiolabeled compound after oral and intravenous administration. The amount of radioactivity eliminated in urine and feces is determined. From data in studies with animals dosed orally compared to similar data from animals dosed intravenously, an estimate of the degree of gastrointestinal absorption can be determined, both by comparison of urinary excretion of radiolabeled drug and by comparison of the blood radioactivity concentration-time curves (serum or plasma concentration plotted with respect to time after dosing) for total radioactivity.

By application of analytical tools, such as thin-layer chromatography, on the urine obtained from rats and dogs dosed with radiolabeled drug, a metabolite profile in these species is available for subsequent comparison with that seen in urine from humans dosed with the drug. This may help identify the animal species which has a metabolite profile most similar to the human. Such data are sometimes useful in determining the proper species for long-term animal drug safety studies. It is rational to choose to do long-term studies in a species which has a drug metabolism similar to that of man. The situation is complicated by judgments as to whether the metabolite patterns should be similar in urine or serum and by concern with the respective quantities of the common metabolites and possible species-associated differences in kinetics. Other elimination and ABLE studies in yet different species are sometimes necessary in order to find animals with humanlike metabolite profiles and so attempt to support the choice of species selected for drug safety studies if they are other than the rat and the dog. For the most part, 2-year chronic studies are practically always done in the mouse and rat despite these sophisticated approaches.

Plasma protein binding may play an important role in the disposition of a compound especially where renal and/or hepatic dysfunction exists. The drug development process requires evaluations to determine the extent of protein binding, to determine whether it plays an important role in therapeutics, and to evaluate whether interactions with drugs might occur through the protein-binding mechanism. Other important drug disposition studies include investigations of the effect of chronic dosing on drug half-life (enzyme induction), the isolation and structural identification of metabolites, and the correlation between the serum concentration of drug and pharmacological effect (pharmacodynamics). More detailed aspects of the contributions of drug disposition studies in the drug development process are covered elsewhere herein by E. C. Schreiber (see Chapter 14).

The development of an analytical assay for the new drug in biological fluids is an extremely important and significant part of the drug development process. The assay method should have sufficient selectivity and sensitivity to define with confidence compartment (serum, urine, etc.) drug concentrations as a function of dose
and time after dosing. Automating the analytical method facilitates industrial drug development by allowing for the efficient and cost-effective analysis of literally thousands of blood and urine samples from patients under many different conditions of investigation. This activity constitutes one of the most important ongoing interfaces between preclinical and clinical scientists in the pharmaceutical industry drug development process. This interface, like that between the biologists and chemists, can be rife with problems that challenge and perplex the most competent of research managers. It is absolutely essential to the success of the drug development process, however, that functional systems be established that reasonably satisfy both biological and clinical scientists. While clinical pharmacology studies can be and often are done in the absence of drug analyses in biological fluids, such studies are clearly of greater value to all concerned when drug concentration values are available. Similarly, drug disposition scientists do extensive and very important development work in which they compare metabolite profiles and kinetics of a drug in animals with that of humans.

Increasing numbers of basic scientists are joining the contemporary clinical pharmacology department, and because of their training they are quite comfortable and conversant with pharmacokinetic calculation, biopharmaceutical mathematics, and statistical techniques. They prefer to have the raw analytical data from biological fluids of volunteers dosed in their studies returned to them for processing and reduction to findings. The drug disposition scientists, however, do not lightly accept a role of reference analytical testing laboratory without proprietary interest in the data. Thus, research managers commonly experience a polarization between the disciplines of drug disposition and clinical pharmacology which have been quite compatible historically. This not uncommon situation is now frequently being resolved by delegating full responsibility for the processing of data acquired by clinical pharmacologists from volunteers and patients to that department. It is not uncommon for a separate section created within the drug disposition discipline to now service clinical pharmacology, drug safety, and even drug disposition scientists when the great volume of analytical samples requires highly sophisticated "crank-turning" by someone. In this case, drug disposition scientists "maintain ownership" of the processing of bioanalytical data from all species save Homo sapiens. The latter data are reserved for the clinical pharmacologists, who have the prerogative of collaborating with other well-trained and competent drug disposition scientists or moving the drug forward separately. The industrial pharmaceutical development process requires a sensitive and vigilant research management, and awareness of this drug disposition/clinical pharmacology interface is an excellent opportunity to facilitate the success of the process.
While drug disposition scientists develop the isolation and identification processes that allow for analyses in biological fluids, a different group of chemists have earlier established the chemical and analytical procedures used to define the bulk drug substance and its dosage forms. These analytical chemists work very closely with the medicinal chemists on one aspect of the drug development process and with the pharmaceutical development scientists on another quite different part of the process (11).

Scientists in analytical chemistry have the responsibility of establishing, without equivocation, the elemental composition of a new compound, its purity, and its chemical configuration or absolute spatial structure. By use of techniques such as high-pressure liquid chromatography, the analytical chemist can isolate the new drug in an ultimate state of purity. With an armamentarium of tools from the basic infrared spectrometer through more advanced devices such as the mass spectrometer, nuclear magnetic resonance spectrometer, and optical rotary dispersion spectrometer, the analytical chemist proves the chemical nature of the drug. Through x-ray diffraction crystallography, the structure of drug substances can be certified to the most skeptical of colleagues. These chemists develop analytical profiles as well as analytical methods for new drug substances. Since this methodology must be stability-indicating, it must be established that the assay method is specific for the drug entity intended to be measured and does not include in the measurement any of the degradation or decomposition products of the new drug. This requires the isolation and identification of decomposition products from degradation studies done on the new drug.

As all synthetic substances made by a sequence of chemical reactions contain traces of reactants from the earlier steps, analytical chemists must also develop, define, and establish an impurity profile of the new drug. In order to better understand the new drug, they do a series of physicochemical studies which include solubility and stability (as a function of oxygen, water, heat, light, and pH), pKa, partition coefficients, decomposition profile, thermal effects, crystal properties (e.g., polymorphism), and kinetic studies of degradation processes. The analytical chemists prepare and report raw material specifications and establish the first certified reference standard for the new drug. As the development process moves forward, they test and release bulk drug for the preparation of clinical supplies as well as for animal safety studies. They also later test and release the first batch of product intended for clinical evaluation.

In collaboration with pharmaceutical scientists, analytical chemists conduct comprehensive stability studies of bulk drug as well as samples from developmental batches of clinical drug product supplies. Analytical
chemistry maintains an important presence throughout the entire drug development process, for it must test and release all subsequent batches of active ingredient and formulations. It seems obvious—but it is far too important to go without saying—that all of these detailed tests and studies in analytical chemistry, as in all of the collaborating sciences in this industrial drug development process, must prepare regular, rigorous, and timely reports on every aspect of their work. These reports form a "paper trail" that allow any scientist, manager, or regulatory investigator to trace back to its origin any material or data and to be satisfied that the work was done professionally, that the material is exactly as represented, and that the data are unequivocally accurate, reliable, and true.

In the past, some R&D managements have experienced great difficulty and embarrassment by failing to establish the lineage of the data in regulatory filings. Open and clear communication of data, with statements of their significance, replication of results, and validation of methodology is not only part of the drug development process but it integral to all science. Any disregard shown to so basic a tenet of science can only imperil the goal of the entire drug development process.

XIII. BIOPHARMACEUTICS

At one time the pharmacy in a drug firm was a place where powders were converted into tablets or capsules and that was all. Now, with a better understanding of biopharmaceutical concepts, an area with an enormous recent literature, the contributions of the pharmaceutical scientist are looked on with much appreciation. It is now accepted that the actions of a new drug substance depend not only upon its intrinsic pharmacological and biochemical properties but also very much upon its ability to reach target sites in the body. "Biopharmaceutics is the study of the factors influencing the bioavailability of a drug in man and animals and the use of this information to optimize pharmacologic or therapeutic activity of drug products in clinical applications"(12). Drug delivery systems are now designed and formulated not only to enhance the amount of administered drug that reaches the systemic circulation but to target the drug more specifically to its site of action. In approaching the optimal formulation and drug product presentation, the pharmacist now considers:

- Solubility at various pH values and in a variety of solvents
- Stability in the dosage form
- Dissociation constant (pK_a)
- Crystalline properties (polymorphs)
- Dissolution rate
- Partition coefficients
Biological transmembrane permeability
Enzymatic stability
Gastrointestinal drug interactions
Hepatic first-pass effects
among other variables.

The research pharmacist or pharmaceutical scientist works in close collaboration with many disciplines. Not only does pharmacy interface with analytical chemists on the stability evaluation, but it also interacts with marketing, process chemistry, medicinal chemistry, drug disposition, drug safety, scale-up chemistry, clinical pharmacology, clinical research scientists, biometricians, and electronic data processing people.

An example of optimizing the absorption of an insoluble compound is the work done with the antifungal antibiotic griseofulvin (13). In an early application of biopharmaceutical intervention, it was shown that serum concentrations of the antibiotic were doubled by preparing capsules of this insoluble drug from bulk materials ground to very small particle size. Since only the drug which reaches the general circulation has a chance to exert its intrinsic desirable biological effects, it was then possible to use capsules with finely ground drug at half the dose of original antibiotic of larger particle size. The literature is now rich with examples wherein reduction in particle size has augmented drug absorption and hence bioavailability.

The concept is not one that can be considered routine, as there are compounds which also accrue undesirable properties by micronization, such as loss of wettability or increased electrostatic charge resulting in consequent handling difficulty. Besides altering particle size to affect the degree and rate of absorption of the drug substance, modulation may be achieved by proper selection of crystal form or salt derivative.

Preformulation pharmaceutics begins with studies of the physicochemical characteristics of the new drug substance and identification of interactions with typical dosage form excipients. Close collaboration with the analytical chemists is essential here to avoid extensive duplication of effort; although generally there is significant overlap in this early work, the overlap represents a reasonable scientific control through replication of results.

In addition to studies of the stability of the drug substance at specified temperatures and humidities, its stability upon exposure to light at various conditions of pH is examined. As drug dosage form data are accumulated and evaluated, the drug substance and requisite excipients are examined for optimization in laboratory-scale processing and from the perspective of adequacy for scale-up to pharmaceutical pilot plant size batches and ability to run on large-scale, high-speed manufacturing equipment. Continuing evaluations of tablets include tests of hardness, tablet disintegration time, friability, moisture con-
tent, and dosage form uniformity. Other dosage forms require other tests to ensure their quality (e.g., clarity of solution for injection, or particle size distribution for an inhalation aerosol).

The speed in which a tablet breaks up is called its disintegration time, which is measured in a standardized test. Along with particle size, disintegration time is an important factor in the subsequent solubilization (dissolution) of the active component. Dissolution is prerequisite to absorption and thus bioavailability. A goal of the pharmaceutical scientist is to formulate the new drug substance so that absorption is optimized, with concomitant controlled increase in therapeutic action. In this pursuit, a number of apparently equivalent formulations generally become available for testing. The dissolution rate is used to screen these solid dosage formulations to decide which one is most likely to have maximal bioavailability. The ultimate test, of course, is to challenge an animal species (and optimally man) with the designed oral dosage forms and to determine, by serum concentration measurements, which formulation has the best total bioavailability and time-course profile. Very importantly, the dissolution time (from an appropriately designed procedure) can often be shown to correlate to bioavailability in humans (14). If the correlation can be well established, it is not necessary to run resource-intensive bioavailability studies on each manufactured batch of drug product. Rather, the dissolution rate test can be relied upon as an important measure upon which the bioavailability of production batches is indirectly assured.

Biopharmaceutic data and pharmaceutical technology are used to design quality into the dosage form; the modern dosage form must be bioavailable, stable, and readily and reproducibly prepared. Scale-up studies are performed to ensure that the quality which was evaluated during clinical trials will be present in the commercial dosage form. Biopharmaceutical studies not only ensure an optimal formulation for the eventual patient but also attest to and ensure the availability of the new drug substance to the tissues of animals in toxicity evaluations. Drugs are rarely distributed selectively to tissues. The same physicochemical characteristics responsible for directing a drug substance to tissues where desirable biological interactions occur also result in the distribution of the drug to other tissues where unneeded, undesirable, or adverse effects may occur. The qualitative and quantitative characterization of these effects on tissues and organs and their role in mortality in animal studies are the responsibility of drug safety evaluation scientists, a group which includes toxicologists and pathologists.

XIV. DRUG SAFETY EVALUATIONS

Of each 10,000 new compounds prepared by chemists and screened by biologists, only about 10 have sufficiently interesting activity in the
biological models of disease and are also considered sufficiently innocuous in the preclinical drug safety evaluations to advance to clinical investigation. The toxicity testing program is an animal-intensive one of very great expense. Governments and the public have worried about the possibility of another disaster to humans due to undetected toxicity ever since the thalidomide misfortune. A result of this concern has been a very substantial increase in the number, variety, and length of animal tests required to support the safety of a new drug substance.

As stated earlier in this chapter, there is no such thing as a totally safe drug. Drugs are biologically potent chemicals capable of doing much good when used properly in disease states for which they have been demonstrated to be effective. Increasingly more extensive and more stringent animal toxicity testing effectively precludes the availability of potentially useful therapeutic agents for which elucidation of minimal and idiosyncratic adverse effects requires close patient monitoring by scrupulous and meticulous clinicians. It is likely that the pattern will not change and that governments will continue to require progressively more evidence of safety before permitting full-scale clinical investigations of new drugs.

A. Acute Toxicology

The industrial drug development process encompasses a toxicity evaluation program which is founded on and coordinated with biological and pharmaceutical investigations (15). The most commonly mentioned toxicity test is the LD$_{50}$ (the estimation of a dose that is lethal to 50% of the animals in a test situation); it is also probably the least useful because it is a measure of acute single-dose toxicity and its real need is now being seriously questioned. In such an acute toxicity study a potent poison can be readily identified. Corrosive chemicals, organic solvents, and irreversible enzyme inhibitors having very low LD$_{50}$ values are rarely considered for further drug development. The acute toxicity study is usually done in two or three species and by several routes of administration; in addition to identifying frank poisons, it provides limited information about the dose ranges that might be appropriate for the toxicity evaluation of longer duration or for initial human use. An interesting ancillary use for the LD$_{50}$ is that one might obtain the first indication of the extent of gastrointestinal absorption by comparing LD$_{50}$ values after oral and parenteral administration.

After a single dose or escalating single oral doses of a drug to different rodent species or to dogs, the animals are observed for signs and symptoms of toxicity such as vomiting, sedation, tremors, ataxia, convulsions, and respiratory changes. Should any such signs be observed, they may serve as clues to the potential adversity attendant to the use of the new drug, and additional, more specific studies might
be suggested. The death of animals shortly after dosing is testimony of its potency as a biological poison. Death a day or more after dosing is also of concern because this indicates more occult organ damage induced by the drug.

The identification of target organs or tissues that are selectively sensitive to the drug under study is particularly important in understanding and assessing the toxic potential of the drug. The degree of toxicity in animal studies that is considered acceptable as well as the number and kinds of animal studies done are related to the eventual clinical indication and the treatment already available. Drugs with a low therapeutic ratio but with life-saving potential (such as certain agents used in oncology or refractory collagen diseases) may be evaluated in only animal studies of short duration (1-2 weeks or a once-weekly dosing for 6-8 weeks) as compared to the more usual drugs for which studies of 1, 3, and 6 months duration are done. The U.S. Food and Drug Administration (FDA) has prepared guidelines for animal toxicity studies that are deemed appropriate to support various kinds of clinical study (see Table 1) (16). These guidelines have provided an ordered basis for current procedures in the industrial drug development process.

B. Chronic Toxicology

The research management of pharmaceutical firms is greatly challenged during each new drug development project to determine the correct temporal sequence in which to place various aspects of the toxicological and clinical evaluations. If chronic (1- or 2-year) toxicity studies are begun too early, major commitments of personnel and funds may be lost should it be found that the new drug substance is insufficiently well tolerated in humans or that it does not have the desired therapeutic activity at clinically or economically acceptable dose levels.

Shorter (e.g., 1-month) toxicity studies may not be sufficient to detect a drug's potential for producing a serious adverse effect. If such effects are not discovered until the chronic toxicity study is ongoing or complete, a considerable investment of resources applied to the parallel clinical development is also lost and greater risks are involved in the early study patients. Thus, programming the proper sequences of drug safety studies for each drug is an exercise in risk and resource management which is an important aspect of industrial pharmaceutical new drug development.

Chronic toxicity studies in animals are classically 1 year in length and are usually conducted in rats and one nonrodent species, using male and female animals of each species. The animals are dosed via the major route to be used in patients. During this prolonged study, animals mature and grow under the stress of chronic influence of the drug, a fixed diet, and an unnatural and restraining environment. These latter effects, together with the degenerative organ changes
Table 1: Synopsis of U.S. Food and Drug Administration Guidelines for Animal Toxicity Studies

<table>
<thead>
<tr>
<th>Drug category</th>
<th>Duration of human administration</th>
<th>Clinical study phase</th>
<th>Subacute or chronic toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral or parenteral</td>
<td>Several days</td>
<td>I,II,III,NDA</td>
<td>Two species; 2 weeks</td>
</tr>
<tr>
<td></td>
<td>Up to 2 weeks</td>
<td>I</td>
<td>Two species; 2 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>II</td>
<td>Two species; up to 4 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>III,NDA</td>
<td>Two species; up to 3 months</td>
</tr>
<tr>
<td></td>
<td>Up to 3 months</td>
<td>I,II</td>
<td>Two species; 4 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>III</td>
<td>Two species; 3 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NDA</td>
<td>Two species; up to 6 months</td>
</tr>
<tr>
<td></td>
<td>Six months to unlimited</td>
<td>I,II</td>
<td>Two species; 3 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>III</td>
<td>Two species; 6 months or longer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NDA</td>
<td>Two species; 12 months (nonrodent), 18 months (rodent)</td>
</tr>
<tr>
<td>Inhalation (general anesthetics)</td>
<td></td>
<td>I,II,III,NDA</td>
<td>Four species; 5 days (3 hr/day)</td>
</tr>
<tr>
<td>Dermal</td>
<td>Single application</td>
<td>I</td>
<td>One species; single 24-hr exposure, followed by 2-week observation</td>
</tr>
<tr>
<td></td>
<td>Single or short-term application</td>
<td>II</td>
<td>One species; 20-day repeated exposure (intact and abraded skin)</td>
</tr>
<tr>
<td></td>
<td>Short-term application</td>
<td>III</td>
<td>As above</td>
</tr>
<tr>
<td></td>
<td>Unlimited application</td>
<td>NDA</td>
<td>As above, but intact skin study extended up to 6 months</td>
</tr>
<tr>
<td>Ophthalmic</td>
<td>Single application</td>
<td>I</td>
<td>Eye irritation test</td>
</tr>
<tr>
<td></td>
<td>Multiple application</td>
<td>I,II,III</td>
<td>One species; 3 weeks daily application as in clinical use</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>One species: duration commensurate with period of drug administration</td>
</tr>
<tr>
<td>Vaginal or rectal</td>
<td>Single application</td>
<td>II</td>
<td>Local and systemic toxicity</td>
</tr>
<tr>
<td></td>
<td>Multiple application</td>
<td>I,II,III,NDA</td>
<td>Two species; duration and number of applications determined by proposed use</td>
</tr>
<tr>
<td>Drug combinations</td>
<td></td>
<td>I</td>
<td>LD50 evaluations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>II,III,NDA</td>
<td>Two species; up to 3 months</td>
</tr>
</tbody>
</table>
associated with aging and endemic chronic infections, tend to confound the toxicological picture and the evaluation of tissue pathology. Considerable expertise is needed to distinguish nondrug from drug effects. The separation of nondrug effects from drug effects is aided by maintaining a control group of each species that comprises animals of both sexes. The control group is exposed to the same conditions as those of the drug-dosed animals, except for the active drug treatment. At the end of chronic toxicity studies, as is the case for the acute and subchronic studies, all animals are sacrificed and the tissues of all major organ systems are examined for gross and microscopic pathology.

All toxicity studies in animals are done to elicit toxicity. Doses are increased sufficiently or extended over sufficient time to permit the identification of "target organs" for toxicity. These might be considered sites of selective toxic actions that occur at tissue concentrations not generally destructive but that occur only in animals which are generally debilitated because of the drug. Such selective organ toxicity is considered an amplification of the real-world animal-drug interaction and is considered only a coarse guide to the type of toxicity for which the clinical investigators of the new drug must be ever-vigilant and suspicious.

Organ changes that occur in most dosed animals in a defined cause-and-effect relationship at a dose that does not impair the general welfare of the animal are specific organotoxic effects. These uncommon organotoxic effects are worrisome and require considerable reflection by R&D managements deliberating whether to advance such a drug to clinical investigation. In such cases, it is customary to have a group of experts and consultants evaluate and deliberate the relevance and significance to the human of all animal toxicity data. Organotoxic effects are often species-specific and, not uncommonly, occur at doses that are many orders of magnitude greater than the proposed human therapeutic dose level. Nonetheless, organotoxic effects are a clinical reality whose existence must be detected early to protect and preserve the patient's welfare.

C. Reproduction Studies

The thalidomide misfortune underscored the necessity to determine a drug's potential to affect either parents or offspring during reproduction. Since no single experimental study can examine the entire reproductive process, animal reproduction studies are done in three segments, each involving a different phase of reproduction (17).

Segment I requires the drug dosing of male rats for 60-80 days prior to mating to assess spermatogenesis and general gonadal function.

Female rats are dosed for 14 days prior to pairing, and half of these are sacrificed in midpregnancy to evaluate the number and state of embryos. The other females are allowed to litter and are studied for litter size, survival of pups, and gross anomalies. Thus, Segment I studies provide information concerning drug action on the entire re-
productive process including teratogenesis, late stages of gestation, parturition, lactation, and weaning.

Segment II is the formal teratology study in which it is determined whether a drug has a potential for embryotoxicity and/or teratogenicity. For this purpose drug dosing is restricted to the period of organogenesis in pregnant mice, rats, or rabbits. The fetuses are surgically removed approximately 2 days prior to anticipated parturition and are subjected to gross examination and to special soft tissue section and skeletal examination techniques for abnormalities.

The purpose of the Segment III study is to determine if adverse effects of the drug occur when it is administered during the last third of pregnancy and through the period of lactation. This study is particularly relevant to the safety of a drug intended for chronic use in pregnancy because it delineates effects of drug on late fetal development, labor and delivery, lactation, and neonatal viability and growth.

The Segment II study and the female portion of Segment I are completed before a new drug substance may be administered to women of childbearing potential. Before Phase III clinical trials may commence, acceptable data must be made available to the FDA from all three segments of the reproduction studies.

The last drug safety evaluation done on behalf of a new drug that successfully overcomes the hurdles of clinical trials is the carcinogenicity study. This is last because currently the animals are dosed for about 2 years. As selective processes have resulted in healthier strains of mice and rats from laboratory animal vendors, it is now sometimes necessary to dose these animals for as much as 30 months to achieve a target effect on morbidity and natural "background" or control tumor incidence.

It is necessary to do a full dose-ranging study prior to selection of the dose levels used in the carcinogenicity studies. This is done to establish an upper dose that is sufficiently high as to be intoxicating yet not so great as to induce excessive mortality and thus decrease the high dose population necessary to elicit and observe the incidence of tumorigenicity. It usually requires a full year for comprehensive tissue preparation, examination, and reporting after the study is completed and the animals have been sacrificed. The histopathology studies are best performed by experts in animal pathology.

The modern industrial drug development process requires electronic data processing support and substantial statistical capability in order to evaluate and report the enormous data bases that drug safety evaluations produce. While electronic data processing support is commonly provided to the clinical operations of contemporary pharmaceutical firms, it is not generally recognized that the data base in the drug safety disciplines is equal to that from clinical studies or even greater in magnitude and requires the same sophisticated remedy.
XV. THE CLINICAL TRIAL

It has often been said in jest by those involved in the new drug clinical development process that "their product is paper." It must indeed seem so to the industrial clinical scientists involved in drafting many revisions of protocols, correspondence with principle investigators, investigators' new drug brochures, clinical study reports, summaries of the relevant literature, summaries of the full Phase I program (and Phase II and III), reports to management, comprehensive reports on clinical adverse events or reactions, and the clinical optional expanded summary for a New Drug Application (NDA). The writing is, indeed, prodigious but constitutes a most important and essential part of pharmogeny.

As most of this book deals specifically with various aspects of the clinical research process as it is employed in the pharmaceutical industry, this overview chapter will treat that aspect only briefly.

The clinical development of a new drug really begins with a formal research management decision to do so.

A. The Area Team

A number of important steps routinely precede this management decision. The recommendation to advance a Biological Lead Compound to a Clinical Lead Compound is made by a multidisciplinary scientific group. In many pharmaceutical firms such eclectic groups of scientists are assembled monthly as area teams to review and assess the laboratory findings on compounds of interest. Area teams are topical and are customarily dedicated to a specific area of therapeutics or diseases. For example, the scientists of a cardiovascular diseases area team might address themselves to novel approaches to drug discovery for hypertension during one period of years and to innovative drug treatment for the atherosclerotic diseases in a subsequent period of years. The choice, of course, is directed as described earlier by the corporate marketing strategic plan. It is the scientists of the area team that design and evaluate relevant biological screens and evaluate the data they generate. This same group identifies the Chemical Lead Compound and suggests to the chemistry department ideas for improving on that lead. The chemists who participate in the area team communicate such discussions to their own management and develop full synthetic programs responsive to their management.

The scientific area team designates a Biological Lead Compound when a critical mass of biochemical, pharmacological, and early drug safety evaluation results generates high interest in the chemical. At this point the involved scientists formalize plans for further in-depth biological study of the lead and stimulate an agenda for pharmaceutical, drug disposition, analytical chemistry, and toxicological evaluations.
that more completely defines this new agent. Area teams regularly
develop such Biological Lead Compounds, but it is much less common
when the consensus of their deliberations on the expanded preclinical
data base causes them to recommend to management that the subject
of their intense interest merits advancement to a Clinical Lead Com-

pound status. This designation is tantamount to the proposal that the
chemical be the subject of an Investigational New Drug filing (IND) and
that the research management facilitate the development of all data on
the potential new drug required for such a regulatory filing.

The details of this development process have been presented earli-
er. The area team presents its drug candidate in a formal document;
and subsequent to this promulgation a major seminar on the drug is
addressed to the company general R&D community, R&D management,
invited consultants, market planners, and executive management. The
intramural drug monograph is an anthology of all that is known about
the new agent and presents the findings of every scientific discipline.
Also described in the text is the patent status, a profile of competitive
drugs, a market plan, and an outline of the clinical operating plans
for evaluations essential to creating an approvable NDA or international
regulatory filings. If the drug monograph and the drug conference
satisfies the questions and expectations of R&D management, the de-
cision is generally made to proceed to IND preparation.

B. The "First in Man" Committee

At a defined point in the IND preparation process, a specific group
meets to consider the question: "Are there now adequate, sufficient
and appropriate data to recommend the investigation of this new drug
in man?" In some pharmaceutical firms, this is the responsibility of
a group of research managers referred to as the First in Man Com-
mittee. These physician-scientists and basic scientists who are also
professional R&D managers review the drug safety evaluation data,
as well as drug disposition, pharmacological, biochemical, chemical,
analytical, biopharmaceutical, and all other relevant data and decide
if the available data base is sufficient to advance the new drug sub-
stance to a well-defined clinical pharmacology study in volunteers.

Should the data base on the drug be found to be insufficient or to
raise some question, the First in Man Committee attempts to define the
additional preclinical studies required to satisfy the questions in order
to advance the drug to study in humans. If the committee concludes
that company data demonstrate that it is inappropriate to advance the
new drug substance for evaluation in humans under any circumstances,
the substance is deleted from further consideration and all preclinical
work with it is terminated. A positive conclusion results in the filing
of the IND.
C. Phase I Clinical Studies

When a sponsor, usually a pharmaceutical company, wishes to begin the clinical trials process in the United States, a Notice of Claimed Investigational Exemption for a New Drug, (referred to as the IND and identified as Form FD 1571) is submitted to the FDA (18). The IND requirements are summarized in Table 2. A detailed description of these requirements is contained in the Code of Federal Regulations, Title 21, Part 312.1. A plan or outline of proposed clinical investigations is required under Item 10. Phases I and II are defined as clinical pharmacology, and Phase III as broad clinical trial.

Phase I studies are the initial evaluations of the new drug substance in humans. In industrial drug development, it is usual to enlist normal (healthy) volunteers to participate in these early studies. The primary reason for selecting normal volunteers for Phase I studies is that the individuals selected must be healthy in all respects and clinical laboratory test results, vital signs, electrocardiograms, and whatever else is monitored must be in a normal range prior to drug treatment. Any abnormalities in these tests found subsequent to treatment with the drug can be reasonably attributed to drug effect. If the initial studies are done in patients with disease, the clinical laboratory tests and other evaluations are likely to be outside the normal range in some respect before the investigational drug is administered. Further, the effect of the drug on existing but occult organ system impairment cannot be determined in advance. It would not be obvious which of the observed effects are due to preexisting disease with concomitant organ dysfunction and which are assignable to the investigational drug.

The Phase I studies establish human tolerance to the drug, absorption and elimination kinetics, blood concentrations as a function of time after dosing, the metabolic profile, and pharmacological effects at various doses. If, however, a drug has dramatic biochemical or pharmacological effects specifically tailored to address a specific disease state, Phase I studies are done only in persons with such a disease state.

D. Phase II Clinical Studies

Phase II studies, are, of necessity, done in persons with signs or symptoms of the disease for which the drug is intended. This is because the purpose of this evaluation is to gain evidence of efficacy and to establish the proper dose and dosing interval. In this Phase II clinical program, more safety and tolerance data are acquired in patients with disease which the drug is intended to treat. Physicians expert in doing Phase I and II trials are referred to as clinical pharmacologists. Such persons must be well trained in human pharmacology, toxicology, biopharmaceutics, and pharmacokinetics and be cognizant of government regulations relating to human research.
**Table 2 Contents of an IND**

<table>
<thead>
<tr>
<th>Item</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Item 1</td>
<td>Name, chemical structures, dosage form, and route(s) of administration of the new drug</td>
</tr>
<tr>
<td>Item 2</td>
<td>List of all components of the drug entity, including reasonable alternates for inactive components</td>
</tr>
<tr>
<td>Item 3</td>
<td>Quantitative composition of the drug entity, including reasonable variations that may be expected during the investigational stage.</td>
</tr>
<tr>
<td>Item 4</td>
<td>Source and preparation of new drug substances used as components; this includes manufacturing processes for new drug substances(s) and dosage form</td>
</tr>
<tr>
<td>Item 5</td>
<td>Methods, facilities, and controls used for the manufacturing, processing, and packing of the new drug; the establishment and maintenance of appropriate standards of identity, strength, quality, and purity</td>
</tr>
<tr>
<td>Item 6</td>
<td>Preclinical pharmacology, toxicology, and drug metabolism data; available clinical data if drug used previously (e.g., in another country) or is a combination of previously investigated or marketed drugs</td>
</tr>
<tr>
<td>Item 7</td>
<td>Informational material to be provided to investigators; this includes a copy of the labels to be on the drug containers identifying the drug as investigational and a clinical monograph describing the drug, possible utility, prior investigations, and known hazards, contraindications, side effects, and precautions</td>
</tr>
<tr>
<td>Item 8</td>
<td>A statement of the training and experience required of investigators</td>
</tr>
<tr>
<td>Item 9</td>
<td>The names and credentials of the monitors and investigators' responsibilities regarding record keeping, informed consent, and supervision of subjects</td>
</tr>
<tr>
<td>Item 10</td>
<td>Outline of the clinical investigation, including specification of phase involved: Phases I and II (clinical pharmacology) or Phase III (broad clinical trial)</td>
</tr>
<tr>
<td>Item 11</td>
<td>Agreement to notify FDA if investigation is discontinued and why</td>
</tr>
<tr>
<td>Item 12</td>
<td>Agreement to notify investigators if investigation is discontinued or an NDA for the investigational drug is approved</td>
</tr>
<tr>
<td>Item 13</td>
<td>Completed only if sponsor wishes to sell rather than distribute test drug free to investigators; the reason for the need to sell must be explained</td>
</tr>
</tbody>
</table>
Table 2 (cont.)

Item 14: Agreement not to ship drug or use in humans until 30 days after receipt of IND by FDA

Item 15: An environmental impact statement when requested

Item 16: Statement that all nonclinical laboratory studies comply with Good Laboratory Practices (GLPs)

E. Phase III Clinical Studies

Phase III is the program of broad clinical trials which is needed to determine whether a drug is appropriately safe and effective and has the therapeutic attributes required to satisfy the needs expressed by the market analysis. The immense cost of pharmaceutical development is particularly evident when these large-scale clinical trials are undertaken. It is possible, albeit undesirable, of course, that the Phase III evaluations of the new drug will not demonstrate any advantage over currently available marketed drugs. Faced with this reality, a pharmaceutical company may choose to accept the loss of its significant expenditures to that point rather than to increase them by pursuing a poor competitor into therapeutic commerce. For most drug candidates there is, unfortunately, no certain path other than the Phase III experience that delineates the actual therapeutic scope or profile of a new drug. Compounding the costs even further are the completion of the full reproduction studies and the very costly carcinogenicity studies, as well as the initiatives that must be taken in chemical and pharmaceutical manufacturing, in parallel with the Phase III studies. It is no wonder that figures of the order of $70 million are cited as the average cost for each successful new chemical entity drug product approved for marketing by the FDA. By way of contrast, it is of interest to note that the average R&D cost for a new drug brought to market during the 1950s was only about $1.5 million (19).

The objective of all of the clinical trials is to produce clear and well-documented evidence that the new drug candidate is effective ("substantial proof of efficacy based on adequate and well-controlled clinical investigations") and is safe when used in the manner intended. A close collaboration between pharmacists and the company clinical monitors is essential to design rigorous methodology of "blinding" (all dosages made to look alike), packaging (bottles, blister packs, etc.) and labeling for these "well controlled" often "double-blind" clinical studies. It is not usual for thousands of patients to be involved in a massive effort to provide the required proof. The completed case report forms for each of these patients must reflect, in full fidelity,
the clinical experience of the patient throughout a clinical trial. These case report forms must be complete and their contents checked for accuracy against source documents. This last step is essential because it is only the data on the case report form that the sponsor has to digest, analyze, process, and tabulate. The assurance of complete fidelity of the clinical trial to the methodology of the protocol and monitoring of the quality of the data on the case report form is the responsibility of medical scientists in the company clinical research group. Mathematical processing of compilations of data from all involved patients as reported on case reports provides the basis of the claim for efficacy and safety of the new drug substance.

These data, together with detailed reports of chemistry, pharmacology, toxicology, biopharmaceutics, manufacturing, and quality controls, are assembled in a New Drug Application (NDA) and submitted to the FDA. It is not unusual for an NDA to be significantly greater than 100,000 pages in length and for the three copies required by the FDA to weigh half a ton or more.

XVI. PROJECT MANAGEMENT

Pharmogeny as developed and practiced in the pharmaceutical industry is characterized by manifold disciplines which contribute to the process in a rather rigorous and systematic manner. The activities and reports of many scientists and disciplines must be projected, scheduled, and coordinated in such a manner as to engender a harmonious program and efficient use of resources. When this is not done, various parts of the program are out of phase and incoherent. This results in duplication of effort, significant loss of time, and unnecessary costs. To avoid this, it is now quite common to formalize this pivotal coordinative function into the separate and distinct discipline of project management (20). The persons involved in project management are often scientists with sufficient scope of experience so as to have a good functional understanding of the contribution of all component R&D groups. The coordination of the program of studies of all disciplines results in cost and time savings and contributes greatly to the assurance of the success of multiple, concurrent drug development projects. The positive impact of good project management and dynamic project coordination is difficult to overestimate. When this function is done optimally it requires electronic data processing support and an interactive system with all participating research managers. Such use of computer technology for project management is now common in the pharmaceutical industry.
I. Pharmagenology

XVII. THE PRODUCT

The industrial new drug development process begins with sophisticated market analyses and comes full circle when an NDA is approved. It is then that the pharmaceutical company competes for the attention of the prescribing physician and attempts to make known the attributes and significance of the new drug. If the new therapeutic entity offers advantages to the patient, and the marketing arm performs well in communicating its virtues, then the business of the pharmaceutical firm will grow and prosper.

This is well, for disease is still prevalent and all R&D communities require continuing support and resources. Past successes have left only the most difficult and most challenging therapeutic needs as the remaining targets for the industrial new drug development process. These present therapeutic needs are even now stimulating the pharmageny of the future.

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13. Tagamet patients spend more days on job than placebo patients, trials show. *F.D.C. Repts.* 43(45):7 (Nov. 9, 1981).


5. Clinical data generated outside the United States and not subject to a "Notice of Claimed Investigational Exemption for a New Drug." Code of Federal Regulations 21, Section 312.20.


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4. Alfred, Lord Tennyson (1809-1892), excerpt from *Idylls of the King*.
6. Rudyard Kipling (1865-1936), excerpt from "If."