CONCEPTS AND STRATEGIES IN NEW DRUG DEVELOPMENT

Edited by

Peter U. Nwangwu

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Volume 4

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LIST OF CONTRIBUTORS

Sanford M. Bolton, Ph.D.
Associate Professor of Industrial Pharmacy
St. John's University

Allen Cato, M.D., Ph.D.
Head, Department of Clinical Research
Burroughs Wellcome Company

John J. Donahue, Ph.D.
Director, Research Quality Assurance
Hoffman-LaRoche, Inc.

Dr. Stanley Edlavitch
Acting Branch Chief of Epidemiology
Division of Drug Experience,
Bureau of Drugs; Food and Drug Administration

Marion J. Finkel, M.D.
Director of Orphan Drug Development
Office of the Commissioner
Food and Drug Administration

Kenneth M. Given, M.D.
Senior Director, Regulatory Affairs
Merck Sharpe and Dohme Laboratories

Richard A. Guarino, M.D., F.R.S.M.
President
Oxford Research International Corporation

Harold L. Howes, Jr., Ph.D.
Director, Regulatory and Clinical Affairs
Research and Development
Pfizer Central Research, Pfizer Inc.

Frances O. Kelsey, M.D., Ph.D.
Director, Division of Scientific Investigations
Bureau of Drugs, Food and Drug Administration

Vincent dePaul Lynch, Ph.D.
Professor of Pharmacology and Chairman, Institutional Review Board
St. John's University

Noel R. Mohberg, Ph.D.
Research Head, Biostatistics
The Upjohn Company

Peter U. Nwangwu, M.S., Pharm. D., Ph.D., R.Ph.
Associate Professor of Pharmacology and Toxicology
St. John's University

Martin O'Connell, Ph.D.
Clinical Biostatistician
The Upjohn Company

Kenneth G. Rothwell, M.D.
Vice President of Medical Affairs and Director of Clinical Research
The Purdue Frederick Company

Paul M. Worrall, M.B., Ch.B.
Department of Medical Affairs
Pharmaceutical Research and Development Division
Bristol Myers Company

PREFACE

Clinical trials of drugs play an important part in the development of new pharmacotherapeutic agents and in the advancement of medical knowledge in the prevention and cure of disease. The dire need for adequate training of more people in this rapidly growing area has been hampered by lack of such training tools as readable textbooks on the concepts and strategies employed in clinical trials of drugs. Several colleagues at different universities have expressed the difficulties they encountered in teaching a course on clinical research methodology without a readable textbook for the students. Similar difficulties were also expressed by some colleagues in pharmaceutical industries who would like to use such text for the in-house training programs they organize for their clinical research associates, clinical research monitors, and other staff and new employees involved in the clinical trials of new drugs.

This book has been written to provide an introductory text that would enable students to acquire the central principles and concepts in clinical trials of new drugs, as well as learn essential strategies and practical insights on clinical research methodology. The contributing authors are well-known and distinguished scientists involved with clinical trials and the process of new drug development in the pharmaceutical industry, government and academia.

The first chapter, "The Process of New Drug Development: Current Deficiencies and Opportunities for Improvement," provides a complete overview of the process of new drug development, beginning with current approaches in the discovery of new substances with therapeutic potential and systematically spanning the entire process of new drug development to the stage of marketing the new drug and post-marketing studies. Chapter Two, "Important Considerations for the Clinical Evaluation of Drugs," is contributed by Marion J. Finkel, M.D., Director of Orphan Drug Development, Food and Drug Administration. One of the concepts emphasized by Dr. Finkel is the need for choosing clinical trial subjects whose status approximate the intended patient population that will eventually use the drug. Quite often, new drugs are evaluated in subjects with normal liver and kidney function, and are later used on patients with liver and kidney function, and are later used on patients with liver

of organ dysfunction on the activity of the drug. The subject of "Resolving Ethical and Moral Problems in Clinical Trials," is addressed in Chapter Three by Vincent dePaul Lynch, Ph.D., Professor of Pharmacology and Toxicology, St. John's University, New York. One of the many points skillfully developed by Professor Lynch is that clinical trials are subservient to man; therefore no goal of human experimentation, no matter how high or noble, should be placed above human dignity and welfare. Harold L. Howes, Jr., Ph.D., Director, Regulatory and Clinical Affairs, Pfizer Central Research, contributes a chapter on "Coping with Regulations and Legal Aspects of Clinical Trials." Dr. Howes describes the elaborate network of laws, regulations and guidelines which control the drug development process. Although these regulatory interventions are often redundant and sometimes unnecessary, he argues that they can be coped with and provides several practical guidelines for effectively coping with government regulations in the process of new drug development. In Chapter Five, Allen Cato, M.D., Ph.D., Head, Department of Clinical Research, Burroughs Wellcome Company, covers the subject of "Practical Insights on Designing the Correct Protocol—Phase I, II, III, IV." Problem areas of protocol drafting discussed by Dr. Cato included: study rationale, objective, study design, test drugs and dosages. Specific problems in study design, such as controls, number of subjects, recording of adverse events, and dosage titration are discussed, as well as problems with patient compliance and the clinical trial material.

The subject of "Important Statistical Considerations in Clinical Trial Design" is addressed in Chapter Six by Martin O'Connell, Ph.D., Clinical Biostatistician, The Upjohn Company. Aspects covered included study objective specification, patient population determination, reduction in observational bias, common statistical designs, power and sample size considerations. A chapter on "The Logistics of Clinical Trials" is contributed by John Donahue, Ph.D., Director, Research Quality Assurance, Hoffman-LaRoche. Dr. Donahue emphasizes that successful logistics of human clinical drug trials requires good management practices, effective planning, organization and communication. Practical strategies in effecting these were discussed by Dr. Donahue in detail.

Frances Kelsey, M.D., Ph.D., Director, Division of Scientific Investigations, Office of Drugs, National Center for Drugs and Biologics, is the author of Chapter Eight, "Volunteer Studies and Human Pharmacology (Phase I Clinical Trials)." Dr. Kelsey discusses the requirements of volunteer studies and human pharmacology in detail, and provides practical perspectives on

conducting these studies. "Clinical Trials—Phase II and III," is discussed in Chapter Nine by Kenneth Rothwell, M.D., Vice President of Medical Affairs and Director of Clinical Research, The Purdue Frederick Company.

The subject of "Practical Concepts on Optimizing Data Collection and Analysis," is discussed in Chapter Ten by Noel Mohberg, Ph.D., Research Head, Biostatistics, The Upjohn Company. Dr. Mohberg considers the relationships between data collection and optimal results employing a definition of optimality, and arrives at a set of principles that are conducive to improving results from a clinical trial.

Kenneth M. Given, M.D., Senior Director, Regulatory Affairs, Merck Sharpe and Dohme Laboratories, contributes Chapter Eleven, "Effective Adverse Reaction Monitoring." Concepts relating to protocol design for adverse reaction studies, including eliciting adverse reaction information and the importance of controlled studies, as well as strategies in design of case report forms are covered in detail.

A chapter on "Essentials of Bioavailability Studies" is contributed by Sanford Bolton, Ph.D., Associate Professor of Industrial Pharmacy, St. John's University, New York. Current bioavailability and bioequivalence regulations and a practical, systematic method of developing the bioavailability study protocol, conducting the study, preparing the statistical analysis and report, and monitoring studies on bioavailability are covered in detail. Paul M. Worrall, M.D., Senior Director, Department of Medical Affairs, Pharmaceutical Research and Development Division, Bristol Myers Company, is the author of Chapter Thirteen, "How to Prepare Effective IND (Notice of Claimed Investigational Exemption for a New Drug) and NDA (New Drug Application)." Much practical insight on important elements of IND and NDA is skillfully outlined by Dr. Worrall. Helpful step-by-step strategies on IND and NDA preparation are developed.

Chapter Fourteen, "Practical Perspectives on Postmarketing Surveillance—Phase IV," is written by Stanley Edlavitch, Ph.D., Branch Chief of Epidemiology Development, Division of Drug Experience, National Center for Drugs and Biologics.

In the final chapter of the text, Richard Guarino, M.D., F.R.S.M., President of Oxford Research International Corporation discusses "Practice and Application of Good Clinical Practices." The chapter emphasizes the practice and application of all the major concepts and strategies developed by all the authors of the previous chapters in the book.

Since this book is designed to be a teaching text for students and scientists new to the field of clinical trials of drugs, the authors have not attempted to provide a complete exposition of all problems encountered in clinical research, or the process of new drug development. Although the book was designed especially for students and those new to clinical trials, established and experienced scientists and administrators in this field will find the book most stimulating and useful.

Peter U. Nwangwu, Pharm. D., Ph.D.
New York, New York

ACKNOWLEDGMENTS

The preparation of this book began several years ago when the editor realized there were no suitable textbooks on the subject matter for the Pharm. D. students in his course on Clinical Research Methodology at Florida A&M University. After completing the first chapter, however, and because of the urgency and universality of the need for such a book, it was decided that several colleagues involved in various aspects of clinical research should be invited to contribute to the development of the book. Subsequently, a national symposium on the subject matter was planned and developed simultaneously with the book.

I wish to acknowledge the kind cooperation of our distinguished authors who developed and sent the manuscripts on their respective chapters. Without their enthusiastic support, this book would not have been developed so rapidly.

The national symposium at which each author discussed the subject of their respective chapters was sponsored by St. John's University, New York and the American Federation for Clinical Research, in cooperation with the Pharmaceutical Manufacturers Association. The invaluable assistance of Peter J. Rubino with the logistics of the symposium, and the kind guidance of Dr. Andrew J. Bartilucci, Vice President for Health Professions at St. John's University, and Dr. Joseph Aterno, Vice President for Drug Regulatory Affairs and New Product Planning at Pfizer Laboratories, are gratefully acknowledged.

Finally, I wish to thank Michael Fisher, Barbara Leffel, Raymond Kanarr, and Susan Goodman Alkana, editors at Praeger Publishers, for their fine professional services and the promptness with which they handled the development of this book.

CONTENTS

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THE PROCESS OF NEW DRUG DEVELOPMENT: CURRENT DEFICIENCIES AND OPPORTUNITIES FOR IMPROVEMENT

Peter U. Nwangwu

PROCESS OF NEW DRUG DEVELOPMENT

Discovering New Drugs

New drugs are discovered from many different sources. Serendipity and careful observations by alert investigators have led to the development of some important drugs. A classic example is the discovery of penicillin by Fleming who in 1928 noticed that a stray mold (genus Penicillium) which contaminated the plate culture of staphylococci he was working with had inhibited the growth of the bacteria. Dr. Fleming's curiosity about this accidental event was the beginning of antibiotic therapy. Although chance discoveries are still made today, they occur infrequently; most new drugs available today are the products of the research and development efforts of the large pharmaceutical companies. Current approaches in the discovery of new drugs include systematic screening of synthetic chemicals and natural products, exploitation of observed side-effects of existing drugs, and the rational design of substance to fulfill a particular biological role.

Natural Products

The investigation of natural products for potentially useful agents is ordinarily carried out by a relatively simplified procedure of extracting a sample of the material and testing the extract in a biologic system. The approach is time-consuming since large numbers of compounds are tested for pharmacologic activity. For example, thousands of samples of soil may be tested in search

for a new antibiotic.[1] This seemingly inefficient approach, coupled with advances in modern synthetic chemistry resulted in decreased attention for several years in natural products. In discussing this decreased interest and the delay until 1947 for the discovery by Western science of such an ancient remedy as Rawolfia, De Ropp remarked:

> This situation results, in part at least, from the rather contemptuous attitude which certain chemists and pharmacologists in the west have developed toward both folk remedies and drugs of plants origin. . . . They further fell into the error of supposing that because they had learned the trick of synthesizing certain substances, they were better chemists than Mother Nature who, besides creating compounds too numerous to mention, also synthesized the aforesaid chemists and pharmacologists. Needless to say, the more enlightened members of these professions have avoided so crude an error, realizing that the humblest bacterium can synthesize, in the course of its brief existence, more organic compounds than can all the world's chemists combined.[2]

At the present time, however, there seems to be a renewed interest in the investigation of natural products and herbal medicine for their active ingredients.[3]

Synthetic Chemicals

The greatest number of new drugs originate from screening synthetic chemicals for pharmacological activity. In the empiric approach, the screening process may involve evaluating a new chemical with several screening methods to determine the total pharmacologic profile of the chemical. Alternatively, groups of chemically related compounds may be put through a limited number of screening tests designed to reveal a specific type of pharmacological effect.

One approach in chemical synthesis has been to systematically modify the molecular structure of an established drug in order to develop an analog that has more desirable properties than the original compound. The aim may be to improve the margin of safety, to eliminate a particular type of side-effect, to prolong or shorten the duration of action or to improve absorption into the gastro-intestinal tract. Although once in a long while a company may be surprised by the joy of a major discovery

through this approach, in general the new agents developed by this approach offer little advantage over already available drugs; but they are frequently marketed for competitive reasons and become "me-too" drugs.

Exploitation of Side Effect

Many significant advances in modern therapy have their origin in clues provided by the observed side-effects of existing drugs. Such serendipitous clinical discovery of new uses for existing drugs is a major pathway of therapeutic progress. When sulfanilamide was first introduced as an antibacterial agent, careful clinical observation indicated that it produced a slight increase in both the volume and pH of urine. Subsequently the drug was found to inhibit the enzyme carbonic anhydrase, which in turn was found to prevent the normal acidification of the urine. Structural manipulations led to the development of more potent carbonic anhydrase inhibitors, such as acetazolamide. Although the carbonic anhydrase inhibitors have limited usefulness as therapeutic agents, they played a significant role in the elucidation of normal kidney function. Moreover, further modifications of the acetazolamide molecule produced the therapeutically important thiazide diuretics.[1]

Rational Design of a Substance

The newest and most rational form of research and development has been to design a substance to fulfill a particular biological role. At its simplest level this may entail the synthesis of a naturally occurring substance, such as a hormone or vitamin. The deliberate approach to achieve a specific pharmacologic objective has led to the development of a number of useful agents like probenecid which act by competitively antagonizing the actions of other drugs or of functionally important endogenous substances. The search for new types of drugs may also be guided by rational concepts when the biochemical or physiological abnormality underlying a disease state is revealed. The treatment of Parkinsonism, for example, was dramatically changed in the last two decades with the discovery that the major defect in the disease was a decrease in the dopamine content of certain areas in the brain. Dopamine itself could not be used effectively to correct the biochemical lesion since it does not cross the blood-brain barrier easily. However, levodopa, a precursor of the neurotransmitter dopamine, crosses the barrier readily into the brain where it is metabolically converted to dopamine; levodopa was thereby introduced as a new treatment of Parkinsonian patients with remarkable success.

Preclinical Studies

The first tests a new compound undergoes in animals are preliminary screening studies to determine whether the agent has any biologic activity of potential pharmacologic interest. Screening for specific types of pharmacologic activity may arise from clues provided by careful observation of animals administered the compound, or may be based on a particular pharmacologic activity for which the compound was developed. The screening procedure may be either organ oriented which assesses the effect of the compound on an organ, or it may be disease oriented which measures the usefulness of the compound on a disease process. The difficulty generally associated with any testing procedure, especially with the disease-oriented test, is finding or producing in animals an exact counterpart of the physiologic state or disease process seen in man.

When a compound has been found in preliminary studies to possess a significant pharmacologic effect, it is selected for step-by-step, detailed and exhaustive in vivo and in vitro studies. The aim of these preclinical studies is to obtain sufficient data on the drug's safety and efficacy clearly demonstrating that there will be no unreasonable hazard in initiating clinical trials in human beings. Studies are carried out to determine the effectiveness of the drug in several species of animals, and often the animals are sacrificed after varying intervals to assess the effects of the drug on various organ systems. At times, dosages far in excess of those anticipated for human use are employed in order to uncover potential sites of toxicity. A serious adverse effect on any organ can preclude further considerations of the compound as a therapeutic agent. The total process of gathering efficacy and safety data can take several years. The drug may be discarded at any stage of the evaluation because of inadequate effectiveness or signs of toxicity.

Regulatory agencies have set stringent requirements for the kinds of data that must be submitted in order to obtain permission for trials in human subjects. In March 1966, a scientific group organized by the World Health Organization formulated principles and guidelines for the preclinical testing of drug safety. Two broad categories of animal studies were considered: Biochemical Studies and Toxicological Studies.[4]

Biochemical Studies

Biochemical studies are designed to estimate the rate and degree of absorption, distribution, excretion, and metabolism of a drug. These are the basic factors that determine the onset