DRUGS AND THE PHARMACEUTICAL SCIENCES VOLUME 100

New Drug Approval Process

Third Edition

The Global Challenge

edited by
Richard A. Guarino, M.D.

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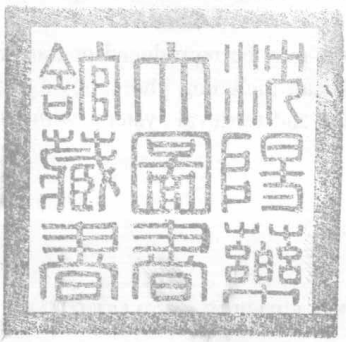

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To my family and friends,
who never left my side during good and crisis situations.
Their dedication, support, and love will remain with me always.

Preface

New drug, device, and biological product development in the United States has changed drastically since the time of the Kefauver Amendments in 1962. Regulations now demand that both safety and efficacy be evident before products can be marketed with FDA's stamp of approval. The mechanics involved in the drug approval process have had a tremendous impact on how new products are developed globally. Good Clinical Practices and ICH guidelines must be followed meticulously for FDA and other worldwide regulatory agencies to allow pharmaceutical products to be marketed bearing labels that show safety as well as efficacy. As we forge into the 21st century with the need to develop a larger array of pharmaceuticals, consideration of the rules, regulations, and guidelines in the new drug approval development process must become part of a company's strategic plan in bringing these products to market.

New Drug Approval Process, Third Edition addresses all the latest information and methodologies on the mechanics of preparing INDs and NDAs. New ways to expedite this process are detailed. The organization of this edition is very different from that of previous editions. The text is now divided into sections, each representing an essential step in the new drug development process. Our intention is to help readers identify and answer specific questions related to their areas of interest and expertise while using the text as a desk reference. Although each step of the process is considered separately, the text as a whole covers every aspect of how to bring pharmaceutical products to market.

The selection of authors to address the drug development process was based on their ability to present factual data in a manner that the reader can readily comprehend. In Part I, Regulatory Aspects of New Drug Development, the authors mesh their years of experience in IND and NDA development. The essential aspects of the nonclinical and clinical development of products are carefully considered along with the regulatory requirements necessary for regulatory agencies' approval. Having dealt with these regulations for many years, the authors are able to suggest ways to expedite the new drug approval process. Other specialized areas, such as, ELAs, PLAs, and ANDAs, that often are not addressed, are covered in this section. Special attention is given to biotechnology, manufacturing, and control requirements for NDAs and ANDAs.

Part II, Clinical Research Development, and Part III, Good Clinical Practices, detail the necessary steps in the clinical development process. The authors help the reader clearly understand and absorb the regulatory requirements. Special attention is given to IRBs, informed consents, ADR handling and reporting, and program management. Also, GCP regulations of the investigator, sponsor, and monitor obligations are approached practically and applied to clinical research. A discusion of the importance of quality assurance and its growing role in drug development as it relates to the changing industry completes these sections.

Part IV, The Orphan Drug and the Rx to OTC Switch, are addressed by specialists who have had great success getting FDA approval for products in these areas. The development of orphan drugs through biotechnology is addressed. It is inevitable that more products will undergo an Rx to OTC switch because of the changes occurring in medical care and costs globally.

The last topics in Part V, Effective Methodology in Expediting NDA Approval, present all new information not referred to in earlier editions. The changes that have occurred throughout the pharmaceutical industry in new drug development processes have added a new dimension to the marketing process. FDA liaison and data presentation for FDA submissions have given new challenges to industries developing new drug, device, and biological applications. The evolving CRO and SMO companies, as well as the "computer world haven," have influenced new product development. Again, authors of these chapters have combined information with insight on the mechanics of getting new product approvals globally.

My appreciation and thanks are extended to all the authors, who have worked diligently in the preparation of this third edition of *New Drug Approval Process*. Special thanks go to Patricia Blaine, Lisa Butkowski, Sharon Mirowsky, and Catherine Juliano for their continuous endeavors in the preparation of this book.

Richard A. Guarino, M.D.

Introduction

The discovery and approval of new drugs during the next millennium will revolutionize the entire health care industry. Bureaucratic agencies throughout the world are becoming more homogeneous and resourceful in their ways of accepting and approving new products that will benefit patients suffering from diseases. The increasing demands by consumers for nonprescription drugs, as a result of the rapidly changing health care programs, will stimulate the ethical companies to switch their prescription (Rx) products to over-the-counter (OTC) ones.

Pharmaceutical companies are seeking ways to meet the national and international requirements of the changing health care market. Mergers, acquisitions, and licensing all play an important role in what and how products will come to market in the next 10 to 15 years. In many instances, decisions regarding these new products will be based on economics and social demands rather than on scientific discovery. The research into new product development has made a 180-degree turn. Companies are decreasing their internal drug development staffs and are outsourcing a large part of research and development responsibilities to CROs. As a result, both CROs and SMOs have boomed in the last 10 years and have put new demands on pharmaceutical companies' management teams.

Notwithstanding these drastic changes in the philosophy of new product development, the basic rules, regulations, and guidelines remain firm and must be adhered to if manufacturers intend to get approval for their new products. Regulatory requirements throughout the world continue to include stringent regulations to confirm safety and efficacy of drugs, biologics, and devices.

The FDA and similar agencies in Europe are collaborating to bring these regulations to a global acceptance through the International Committee on Harmonization. It is hoped that these efforts will allow companies to achieve global approval of new products.

At present, in the United States, the FDA approves INDs that contain sufficient information about the investigational drug to show that it is safe for human testing. NDAs are approved only if the applicant demonstrates through adequate scientific evidence that the drug is safe and by substantial evidence

that the drug is effective for the conditions prescribed, recommended, or suggested in the product's proposed labeling. The content of the FDA/ICH regulations define substantial evidence of effectiveness and safety as that which is demonstrated by adequate and well-controlled clinical investigations. Additionally, to obtain FDA approval, an applicant must show that the methods used in manufacturing and control, processing, and packaging of the drug are adequate to preserve its identity, strength, quality, and purity. Good Manufacturing Practices (GMPs) play an important role in completing this process.

As simple and procedural as this process for an IND and NDA may seem, to achieve the final goal of bringing a new product to market, a vast amount of in-depth understanding of the drug approval process is necessary.

Good Laboratory Practices (GLPs), Good Clinical Practices (GCPs), and Investigational Review Boards (IRBs) regulations have become more precise and efficient to ensure that within new drug development, subjects enrolled in new product investigations are used wisely and safety measures are implemented to minimize risks. FDA's concentration on "orphan" drugs and the new trend to bring more prescription drugs to OTC status have put new demands on the strategic planning to implement the process.

This third edition of *New Drug Approval Process* will give an innovative prospectus to all individuals involved in new drug development. Also, the aura of the changing industry will be reflected throughout the book with the intention of recasting traditional methodologies as a basis for successful implementation of current and future new product development.

Richard A. Guarino, M.D.

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Acronyms and Initialisms

The Medical Communications Department of Oxford Pharmaceutical Resources, Inc. has been collecting acronyms and initialisms throughout the professional careers of its individual members. We have obtained about 600 items through workshops, conventions, professional publications, and the other chapters in this book. The author of two of the chapters in this book, William M. Troetel, Ph.D., graciously allowed us to merge a large list from one of his chapters into this list. We gratefully acknowledge his contribution.

The following list should be used as your reference for acronyms and initialisms throughout this book.

AAAS	American Association for the Advancement of Science
AABB	American Association of Blood Banks
AACR	American Association for Cancer Research
AADA	Abbreviated Antibiotic Drug Application (FDA) (used primarily for generics)
AAFP	American Academy of Family Physicians
AAI	American Academy of Immunologists
AAP	American Association of Pathologists
AAPP	American Academy of Pharmaceutical Physicians
AAPS	American Association of Pharmaceutical Scientists
ABPI	Association of the British Pharmaceutical Industry
ACCP	American College of Clinical Pharmacology
ACE	Adverse Clinical Event
ACIL	American Council of Independent Laboratories
ACP	Associates of Clinical Pharmacology (USA), a group that certifies clinical research associates (CRAs) and clinical research coordinators (CRCs)
ACPU	Association of Clinical Pharmacology Units
ACRA	Associate Commissioner for Regulatory Affairs (FDA)
ACRPI	Association for Clinical Research in the Pharmaceutical Industry (UK)