DRUGS AND THE PHARMACEUTICAL SCIENCES VOLUME 190

FIFTH EDITION

New Drug Approval Process

edited by
Richard A. Guarino, M.D.

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Oxford Pharmaceutical Resources, Inc.
Totowa, New Jersey, USA

informa
healthcare

New York London

Informa Healthcare USA, Inc.
52 Vanderbilt Avenue
New York, NY 10017

Printed in the United States of America on acid-free paper
10 9 8 7 6 5 4 3 2 1

International Standard Book Number-10: 1-4200-8849-1 (Hardcover)
International Standard Book Number-13: 978-1-4200-8849-6 (Hardcover)

Library of Congress Cataloging-in-Publication Data

New drug approval process / edited by Richard A. Guarino. – 5th ed.
p. ; cm. – (Drugs and the pharmaceutical sciences ; 190)
Includes bibliographical references and index.
ISBN-13: 978-1-4200-8849-6 (hardcover : alk. paper)
ISBN-10: 1-4200-8849-1 (hardcover : alk. paper) 1. Drug approval –United States. 2. Drugs–Testing–Standards. 3. Drugs–Testing–Government policy–United States. 4. New products–Government policy–United States. I. Guarino, Richard A., 1935- II. Series: Drugs and the pharmaceutical sciences; v. 190.
[DNLM: 1. Drug Evaluation–standards–United States. 2. Clinical Trials as Topic–standards–United States. 3. Drug Approval–United States. W1 DR893B v. 190 2009 / QV 771 N5318 2009]
RS189.N476 2009
615′.1–dc22

2009007532

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My sincere gratitude goes to our armed forces and my family members who sacrifice their lives to protect our nation's freedom and the principles that make America a world leader in giving mankind equal rights in their pursuit of endeavors.

Preface

Global registration of pharmaceutical drug, biologic, and device products is now the way pharmaceutical development and marketing are strategically planned. Since the publication of the fourth edition of *New Drug Approval Process*, there have been many changes in the regulations, requirements, and recommendations for international registration and approval of new products.

New Drug Approval Process, Fifth Edition offers, in detail, the necessary and vital information on how to develop and submit the research and the documentation required by worldwide agencies to obtain new pharmaceutical product approvals. The topics include a comprehensive as well as a pragmatic approach in addressing all aspects of clinical research development including statistical methodologies, global regulatory requirements for pharmaceutical product applications, and the mechanics necessary to understand and implement Good Clinical Practices (GCP), Good Laboratory Practices (GLP), and Good Manufacturing Practices (GMP).

Each contributing author is an expert in their respective field and has the knowledge and experience to educate the readers on the technical as well as the regulatory requirements for each topic presented. In addition, they also give a practical approach to resolve problems that might occur during product development. They impart their years of successes and failures in a way that the readers can take advantage of this information and apply it to their research practices and job descriptions, and can have a clear understanding of the scientific and legal responsibilities required to bring new pharmaceutical products to market.

The approach and format for assembling the specific data necessary to gain new product approvals globally have drastically changed in the past four years. The Investigational New Drug (IND) Application is still well accepted by the US FDA and will soon require to be submitted in electronic form. The same information, due to the implementation of the European Directives, is now expected in the countries belonging to the European Union and is contained in an Investigational Medicinal Product Dossier (IMPD). The New Drug Application (NDA) information is now in the format of the Common Technical Document (CTD) and is submitted to the regulatory agencies electronically termed an eCTD. These submissions as well as Biologic License Applications (BLAs), Abbreviated New Drug Applications (ANDAs), Supplemental New Drug Applications (SNDAs), and 505(b)(2) Applications are detailed. In addition, the essential components of the non and preclinical and clinical development comprising the safety and efficacy of products are presented and are integrated with the regulatory requirements necessary to expedite new product approvals. The Chemistry, Manufacturing, and Controls (CMC),

pertaining to, the Quality section of the CTD, is one of the most important parts of any new product application and will be given special attention.

All aspects of Good Clinical Practices (GCP) as regulated by the US Code of Federal Regulations (CFR), the EU Directives, and the ICH Guidelines are addressed extensively in the section on Global Application of Good Clinical Practices (GCP). Investigators, Sponsors, and Monitors legal obligations for conducting clinical research are not only comprehensively covered but insights are also given on how to ensure that these disciplines can work together to expedite clinical trials. Institutional Review Boards (IRBs), Independent Ethics Committees (IECs), and Informed Consent (IC), as governed by the Declaration of Helsinki, are discussed fully. The Health Insurance Portability and Accountability Act (HIPAA) and the Privacy Laws are detailed and coordinated with how they must be considered in the Recruitment, Identification, PreScreening, Retention, Handling of Patient Data, and Use of Existing Databases of subjects participating in clinical research.

The *New Drug Approval Process, Fifth Edition*, is not only a text to educate people who plan to work in the areas of new pharmaceutical product development but also acts as a reference and guide for those personnel who have questions in specific areas of their expertise. The book addresses and details all the most recent regulations, guidelines, and procedures necessary for global registrations of new pharmaceutical products. The contributors of this book approach every topic with a practical understanding of the subject matter based on their experience gained by working in their fields of expertise. Readers will gain insights and ideas of how to apply their research and regulatory capabilities in order to bring pharmaceutical products to market more efficiently, expeditiously, and economically.

I would like to sincerely thank all the contributors who have given of their talents, time and effort in the preparation of this new edition of *New Drug Approval Process*. Again, special thanks go to my assistants, Patricia Birkner and Barbara Cannizzaro, for their perseverance in assembling this edition.

Richard A. Guarino, M.D.

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Introduction

The pharmaceutical industries developing drugs, biologics, and devices consider every new as well as an approved product a potential for international markets. Product applications and registrations, once difficult to achieve in many countries, are now evaluated by global agencies based on data meeting the requirements and guidelines governed by the International Committee of Harmonization (ICH). In the United States, pharmaceutical products have long been regulated by the US Code of Federal Regulations (CFR). For countries belonging to the European Union (EU), pharmaceutical product development now comes under the regulations of the European Union Directives (EUD). In Japan, the Pharmaceutical and Medical Safety Bureau governs pharmaceutical product development. Other countries that do not follow the CFR, the EUD, and Japanese regulations now adapt the ICH Guidelines, which are also reflected and used in the CFR, the EUD, and Japan. The international acceptance of new product development data, based on the ICH guidelines, has given pharmaceutical industries a more factual procedure and raised the incentive to register their products globally. This will result in accelerating better health care to world populations.

The ICH is largely responsible for the progress of new global pharmaceutical product development by diligently establishing ways for the international exchange and acceptance of scientific data. This committee not only presents guidelines and recommendations for the safety, efficacy, and quality components required for regulatory submissions of new products, but also outlines an easy-to-follow format for reporting these data. With the exception of some minor variations required by certain countries, the Common Technical Document (CTD) allows sponsors to submit their data to international regulatory agencies in a comprehensive way that is accepted and understood by all countries.

The cost of Research and Development (R&D) of new products, especially for prescription drugs, has become astronomical. Pharmaceutical companies are reluctant to embark on the clinical research of products if the outcome does not promise to gain a major market share. Even orphan drug development, notwithstanding the incentives offered to encourage the development of these drugs, is cautiously considered in relation to the cost of development compared to the economic projections for these drugs. Drug, biologic, and device companies are looking at every aspect of new product development with the objective of decreasing costs and time to bring their products to market. The inducement of knowing that data emanating from R&D required for new product applications can be simultaneously submitted in many countries has resulted in an enthusiasm for pharmaceutical companies to bring new products to market.

Time involved in R&D is probably the next consideration compared to cost. Every day that a product is delayed during the R&D phases or needs additional information from regulatory agencies, before it is launched for marketing, costs the companies millions of dollars, euros, etc. Therefore, understanding exactly how to implement the correct procedures in drug, biologic, and device new product development is not only essential but can also save time and cost in bringing products to market. Basic knowledge of how and what to do, which is gained from any text, is only a foundation. It is only from experience of trial and error and constant training can one become capable of successfully achieving product submissions and approvals.

The most important recommendation that can be advanced to anyone embarking on a pharmaceutical career in R&D is that one must love and practice detail for every aspect in the process of new product development. The intricate components of developing clinical research for safety and efficacy of products, regulatory requirements for new product applications, manufacturing practice for finished pharmaceuticals, and an understanding of assurance for every aspect of the new product approval process are keys in achieving pharmaceutical product approvals by global regulatory agencies.

The fifth edition of *New Drug Approval Process* gives the reader detailed directions and is a guide on how to accomplish the intricate steps in developing pharmaceutical products for market. Specific attention, throughout the book, is based on the requirements of Good Clinical, Good Laboratory, and Good Manufacturing Practices governed by international regulations. The contributors of these chapters have many years of experience in their specialized areas and offer information based on their trials and tribulations encountered during the process of product development. The reader learns strategic advantages in the best ways to approach each phase of product development, resulting in savings of time and money. This latest edition is a must-read for all those in the pharmaceutical and related industries, as it provides the most recent rules, regulations, and guidelines essential for the approval of new pharmaceutical products worldwide.

Richard A. Guarino, M.D.

1 Drug Development Teams

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INTRODUCTION

The drug discovery and development process requires the close interaction of a large number of scientific disciplines for as many as 10 to 12 years. Most pharmaceutical and biotechnology firms employ teams to guide the processes involved in taking a discovery lead through the various preclinical/nonclinical (or Safety) and clinical (or Efficacy) drug development stages for making the drug candidate into a therapeutic product. The responsibilities of these project teams include, but are not limited to:

1. Reviewing research results from experiments conducted by any of the various scientific disciplines.
2. Integrating new research results with previously generated data.
3. Planning research studies to further characterize and develop a drug candidate.
4. Preparing a detailed drug development plan, including designation of key points or development milestones, generating a timeline for completion of key research studies, and defining the critical path.
5. Monitoring the status of research studies to ensure that they are being conducted according to the timeline and critical path in the development plan and, if appropriate, modifying the plan as new information becomes available.
6. Comparing research results and development status and timelines with drug candidates under development by competitors.
7. Conducting appropriate market surveys to ensure that the development of a drug candidate is economically justified and continues to meet a medical need.
8. Reporting the status of the drug development program to management and making recommendations on the continued development of the drug candidate.

This chapter discusses the various types of project teams that are involved in the drug discovery and development process. Also included is a detailed example of a drug development logic plan for what many developmental pharmaceutical scientists consider to be the most difficult and time- and resource-consuming drug candidate to develop into a therapeutic product.

DRUG DISCOVERY PROJECT TEAM

A company makes a decision to enter into a new disease area or to expand an existing therapeutic area on the basis of new research findings, an unmet medical need, or marketing surveys. The responsible department, commonly a therapeutic disease group such as cardiovascular, CNS, cancer, infectious diseases, or metabolic diseases, assigns researchers to the new project—usually chemists to