DRUGS AND THE PHARMACEUTICAL SCIENCES VOLUME 30

New Drug Approval Process

Clinical and Regulatory Management

edited by
Richard A. Guarino

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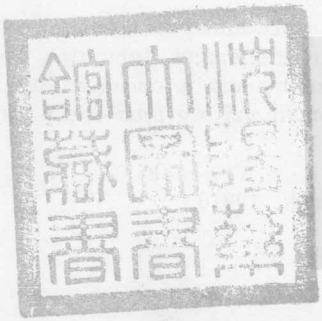

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New Drug Approval Process

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A Series of Textbooks and Monographs

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Additional Volumes in Preparation

In memory of my beloved wife, Valjean. Her love, encouragement, and understanding will always be a part of my life and my world. To my daughters Hilary and Heather, thank you for your precious love and support.

Preface

". . . to help reduce the time required for a new drug or antibiotic to gain marketing approval."

Managing a new chemical entity through regulatory channels calls for the diverse and interdependent contributions of many highly skilled individuals. This text represents the work of eleven authors and coauthors with extensive experience in seeking approval of new drugs. Its chapters provide a number of guidelines and specific references for readers interested in designing and monitoring clinical protocols and expediting the prosecution of investigational, supplemental, abbreviated and/or original new drug applications. With subjects ranging from adverse reactions to labeling requirements, from GCPs and IRBs, to suggestions and recommendations for preparing NDAs, this work cuts across a number of disciplines. These include biostatistics, toxicology, clinical study design and monitoring, regulatory liaison, and manufacturing and controls.

While virtually all of the material reflects U.S. Food and Drug Administration regulations, as promulgated by the Federal Food, Drug and Cosmetic Act or in Title 21 of the U.S. Code of Federal Regulations (CFR), many of the concerns expressed by the authors and this editor are universal themes. Of particular importance are the chapters dealing with the design and management of adequate and well-controlled clinical investigations. These represent perhaps the most costly and critical steps in the regulatory regimen. They generate adequate scientific evidence that a drug is safe and effective

for conditions prescribed, recommended, or suggested in the product's proposed labeling and consequently lead to the expeditious issuance of an approval or approvable letter for a new drug.

This volume reflects the long-awaited FDA changes on formatting, assembling, and submitting New Drug and Antibiotic Applications as published in the *Federal Register* in February 1985. These guidelines and regulations should go a long way toward facilitating the new drug approval process. Both agency and industry spokesmen, nevertheless, are still scrutinizing the "system" with an eye toward future refinements and improvements. It is essential that all personnel in this field keep abreast of proposed and implemented changes as they affect the preparation of each new submission.

The contributors to this text, reflecting a cross-section of backgrounds, present a variety of opinions. The differences—real or perceived—are healthy ones. They confirm the belief of many professionals that there is no single path to success. There are, however, some common denominators: detailed attention to all preclinical, clinical, labeling, and postmarketing procedures; and the meticulous preparation and presentation of all parts of the multifaceted new drug application to facilitate FDA review and eventually authorization to market a medication.

During the final review of Chapters 4 and 5, I was faced with the question of redundancy. Both chapters deal with the critical elements required in formulating successful protocols and plans for the clinical development of new drugs and biologicals. In spite of Dorrien Venn's and my handling of the same subject matter, I chose to recommend that both versions be published: Dr. Venn emphasizes somewhat different points of view—reflecting his many years of experience in the field. My approach varies somewhat, and is to a great extent complementary. It is my editorial opinion that the reader will benefit from back-to-back presentations reflecting the viewpoints of two practitioners and protocol designers, which are based on the successful design and management of many successful clinical research programs.

Because of the length, breadth, and importance of preparing a new drug application, Dr. Millstein's material was divided into two chapters. Chapter 11 presents general considerations, and Chapter 12, specific requirements concerning the content and format of an NDA. A comprehensive reference list and appendixes prepared by Dr. Millstein are also contained in Chapter 12.

I wish to express my appreciation to all authors for their patience, sustained interest, and cooperation in the preparation of this book. Special thanks is due to Dr. Jules J. Haberman for his willingness to take time from a busy schedule to review the material and provide some excellent recommendations.

Richard A. Guarino, M.D.

Introduction

The following guidelines for preparing a new drug application have been given by the FDA:*

The Federal Food, Drug, and Cosmetic Act (the act) provides that a new drug may not be introduced or delivered for introduction into interstate commerce unless the Food and Drug Administration has approved a new drug application for it (21 USC 355). FDA approves an application for a new drug only if the applicant demonstrates by 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 act defines substantial evidence of effectiveness as evidence consisting of adequate and well-controlled investigations, including clinical investigations that are conducted by qualified experts. Additionally, to obtain approval, an applicant is required to show that the methods used in, and the facilities and controls used for, the manufacturing, processing, and packaging of the drug are adequate to preserve its identity, strength, quality, and purity.

To obtain the evidence needed to show whether a drug is safe and effective, the applicant generally must perform studies of the drug in animals (preclinical studies) and in humans (clinical studies).

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*U.S. Food and Drug Administration, Center for Drugs and Biologics (1985). Draft Guidelines on Formatting, Assembling, and Submitting New Drug and Antibiotic Applications, Docket #85-D-0248.

The preclinical testing is conducted as an aid in assessing whether initial human studies will be acceptably safe and in predicting the drug's likely therapeutic activity. If the drug looks promising, human clinical studies are proposed in an "Investigational New Drug Application" (IND).

The IND must contain sufficient information about the investigational drug to show it is reasonably safe to begin human testing. An IND for a drug not previously tested in human subjects will ordinarily include, in addition to other information, the results of preclinical studies, the protocols for the planned human tests, and information on the drug's composition, source, and method of manufacture.

Drug testing in humans proceeds progressively through three phases (called Phases I, II, and III). Phase I includes the initial introduction of an investigational drug into humans and consists of short-term studies in a small number of healthy subjects, or patients with the target disease, to determine the metabolism and basic pharmacologic and toxicological properties of the drug, and, if possible, to obtain preliminary evidence of effectiveness. Phase II consists of larger, more detailed studies, usually including the first controlled clinical studies intended to assess the effectiveness of the drug and to determine the common short-term side effects and risks of the drug. Phase III studies are expanded controlled and uncontrolled trials. They are performed after preliminary evidence of effectiveness has been established and are designed to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for professional labeling. Regulations governing the conduct of investigational new drug studies are set forth under 21 CFR Part 312. Additionally, regulations on the protection of human subjects in clinical investigations regarding informed consent and institutional review board (IRB) review and approval are set forth in 21 CFR Part 50 and 21 CFR Part 56, respectively. The agency also has developed a series of clinical guidelines that describe how applicants may conduct studies on particular classes of drugs, so that the studies are likely to yield data which can be used to determine whether a drug is safe and effective.

The act requires that anyone who seeks to market a new drug must submit the results of investigational studies to FDA in a new drug application and obtain FDA's approval. Section 505(b) of the act requires that an application contain: (1) full reports of studies (both preclinical and clinical) to demonstrate the drug's safety and effectiveness, (2) a description of the drug's components, chemical formulation, and manufacturing controls, and (3) samples of the drug itself and of the proposed labeling. The act requires FDA either to approve the application or to issue a notice of an opportunity for a hearing on whether the application is approvable within 180 days of

its filing, unless the applicant and FDA agree to an extended time period. Regulations implementing the statutory requirements for obtaining marketing approval for new drugs and antibiotics are set forth in 21 CFR Part 314. In the *Federal Register* of February 22, 1985 (50 FR 7452), FDA published a final rule revising those regulations as part of a broader agency plan to improve the new drug approval process.

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