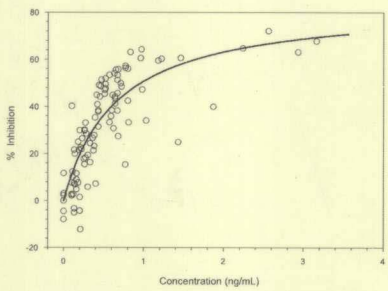
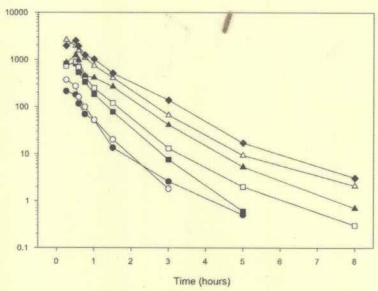
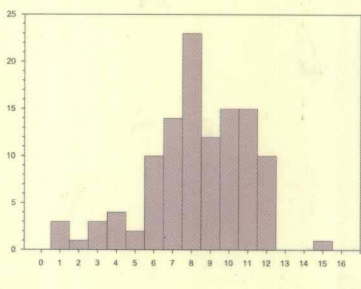
Pharmacokinetics in Drug Development:

Regulatory and Development Paradigms

Volume 2







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Pharmacokinetics in Drug Development

Volume 2: Regulatory and Development Paradigms

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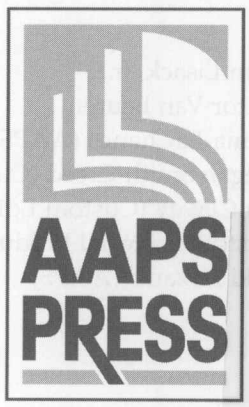

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PREFACE

Like many good ideas, the idea for this book germinated not over cocktails, but over a meal amongst friends. Many years ago, we were employed by the same company. We lamented that our graduate education had not prepared us for the expectations of industry. We knew pharmacokinetics, how to develop bioanalytical assays for drugs in biological matrices, and how to analyze data, but we had not learned how to develop drugs. How was pharmacokinetics used in drug development? What clinical studies were needed to bring a drug to market? How should data from a Phase 1 clinical study be analyzed to meet the objectives of the study and support the clinical development of the drug? These questions often get overlooked in graduate programs that favor specialized scientific endeavors.

We decided that a resource was needed that addressed pharmacokinetics' role in drug development. After organizing our ideas and assembling the outline, we realized that, to complete the project, we would require an expert team of the best people in industry to collaborate and write the book as a joint effort.

We solicited lead authors for each chapter and posed to them the question: "What practical guidance would you give a new pharmacokineticist or drug development scientist to help them understand your functional area?" The result is the product you have in your hands: the most complete guide to pharmacokinetics and its role in drug development ever published. The target audience for this book is graduate-level students and scientists in the area of clinical pharmacology and pharmacokinetics.

The book is divided into two volumes. Volume 1 discusses the role that pharmacokinetics plays in selected clinical study designs. Included are first-time-in-man studies, biopharmaceutical, and special population studies. The chapters are written to provide the reader with a familiarity for scientific and operational considerations and to provide insight into the authors' practical experiences conducting these studies. Volume 1 also discusses the application of pharmacokinetic analyses techniques to drug development—from noncompartmental analysis and interspecies scaling to deconvolution and clinical trial simulation. Volume 1 closes with a discussion on the analysis of clinical safety data in pharmacokinetic studies.

In Volume 2, the authors' attentions turn toward key regulatory and development paradigms in which pharmacokinetics supplements decision-making during drug development. Pharmacokinetics' association with toxicologic assessments, bioanalysis targets and objectives, and application in preclinical programs is discussed. General discussions for rational develop-

ment and knowledge discovery schemes are presented. Specific areas of recent regulatory interest are reviewed for exposure–response relationships, and detailed overviews of regulatory considerations and review are presented for pharmacokinetics studies and clinical trial simulations. Also included in Volume 2 are reviews of topics of special development consideration for pharmacokinetics: oncology, controlled-release, transdermal, ocular, parenteral, chiral, and biologic products.

We hope you find this book interesting, thought provoking and, more importantly, useful. It was our aim to publish a book that would fill the gap between the academic science and the practical application of that knowledge in drug development. We believe we have succeeded.

We would like to personally thank all of the authors who contributed to the book. We could never have assembled this book without you. A number of individuals need to specifically be acknowledged: Victor Van Beuren at AAPS Press, who gave us the support and encouragement needed to undertake the project; the Publications Committee at AAPS; Diana LaChance at AAPS Press, who patiently waded through each chapter, catching editorial items we missed; and Megan Smith-Creed and Jan Clavey at Custom Editorial Productions for their help in producing these books.

We would like to dedicate this book to our families for their love, encouragement and support.

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CONTENTS

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Drug Development and Regulatory Issues

Part I
Drug Development and Regulatory Issues

1

Drug Development: A Rational Approach

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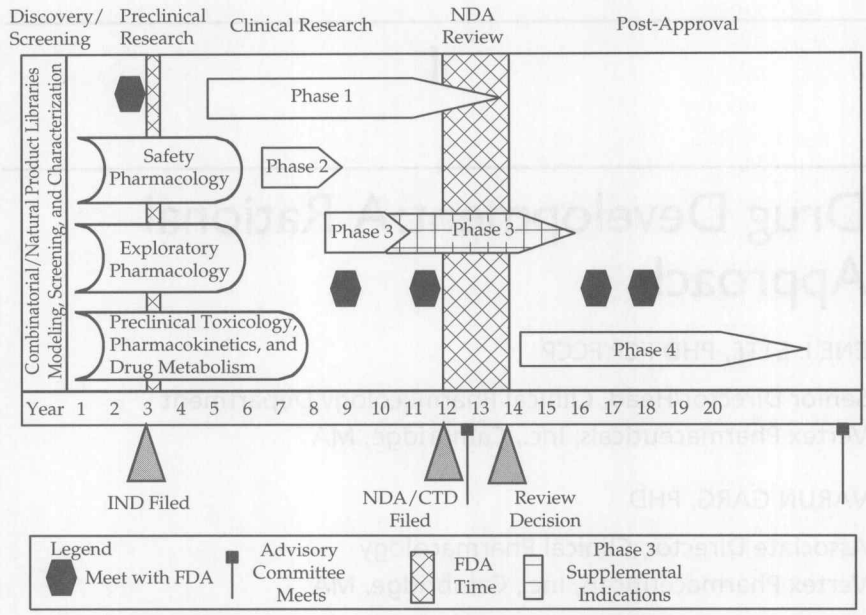
Introduction

The traditional drug development process has been a lengthy and expensive series of nonclinical and clinical studies followed by regulatory reviews (see Figure 1). Historically, the paradigm of clinical drug development has consisted of limited Phase I studies, followed by a small number of unfocused Phase II studies moving directly into numerous expensive Phase III trials. In most cases, only after evidence of clinical efficacy was demonstrated in large clinical trials did drug developers study the science of the drug in order to elucidate its basic properties: mechanism of action, pharmacokinetics, pharmacodynamic (PD) activity, and metabolism. In a survey of drugs approved during 1994 and 1995, it was noted that a typical drug spent more than seven years in development and required greater than sixty clinical trials (Peck, 1997). It was observed that, for the drug approved with the least number of clinical trials, twenty-three studies were executed with only two adequate, well-controlled confirmatory trials in Phase III; the remainder of the trials in that new drug application (NDA)



Note: IND review time is exaggerated. Actual review time is 30 days. NDA review time may vary. The median review time for a standard application in 2000 was 15 months and 6 months for a priority review.

Figure 1 The drug development process.

were clinical pharmacology trials. It was also observed in the survey that 25% of all drugs required ≥75 clinical studies and that the greatest number of studies for a drug exceeded 150 (Peck, 1997).

Indeed, the complexity of drug development and clinical testing procedures keeps increasing. The success rate of new chemical entities (NCEs) is anything but stellar (Kleinberg and Wanke, 1995). In 1987, the cost of bringing a new drug into the market was $237 million as opposed to $802 million in 2000 (Connolly, 2001). By the end of 1999, 21% of the NCEs with investigational new drug applications (INDs) filed from 1981 to 1992 had been approved for marketing in the United States (DiMasi, 2001). Of those that failed in the period from 1987 to 1992, 38% of the NCEs failed because of efficacy (e.g., activity too weak, lack of efficacy), 34% on economics (e.g., commercial market too limited, insufficient return on investment), 20% because of safety (e.g., human or animal toxicity), and 9% for nonspecific reasons (DiMasi, 2001). What is becoming increasingly clear is that traditional drug development approaches are unlikely to succeed in the future given the economics of drug development: a low probability of success coupled with increasing product development times means decreased sales time after market launch and lower return on investment for pharmaceutical companies.

To speed drug development, sophisticated new technologies and approaches in the discovery and design of new drugs are replacing the traditional methods of discovery. The use of project management techniques to control finances during development, plus portfolio review of compounds that should be discontinued from development to maintain an adequate risk–benefit ratio, are all being applied in an effort to streamline and improve the drug development process. Increasingly, however, a pharmacokinetically guided approach is being applied to drug development. Using pharmacokinetics as a surrogate for exposure, as a means to find the optimal dose, or as a means to identify important subpopulations that may require dosing adjustments are just some of the areas in which pharmacokinetics may play a role. The pharmacokineticist is taking on an increasingly important role in drug development, and it is important to have a basic appreciation of the process early in one's industrial career.

To provide an understanding of the development of an NCE, the following sections discuss the various aspects of the science of drug development including drug discovery, the role of preclinical pharmacokinetics, the phases of drug development, the use of biomarkers, practical issues regarding drug development, and the basics of the regulatory side of drug development and drug evaluation.

Learn–Confirm–Learn Paradigm of Drug Development

Sequential drug development—from discovery to preclinical through Phase I to Phase III and beyond—has traditionally been the approach taken to address the question of which compound should be selected for development and how it should be dosed. Sheiner (1997) recently characterized this information-gathering process as two successive learn–confirm cycles for drug development. Traditionally, Phases I and IIa (which will be discussed later) of clinical drug development (the first cycle) comprise learning what dose is tolerated in healthy volunteers and confirming that this dose produces some desired effect in the target patient population. A positive answer at this first cycle provides the grounds for larger and more costly Phase IIb and III learn–confirm cycles. In the latter cycle, the learning Phase II studies focus on how to use the drug in representative patients to maximize benefit and minimize risk. The objective of Phase III studies is to confirm acceptable benefit to risk in a larger patient population. In reality, learning and confirming are components of every trial—some studies may have learning as a primary objective with confirming as a secondary objective and vice-versa. Consequently, we have modified the learn–confirm paradigm in drug development into the learn–confirm–learn paradigm.

Learning and confirming are parts of each clinical trial, although the relative emphasis changes as the drug progresses toward approval.