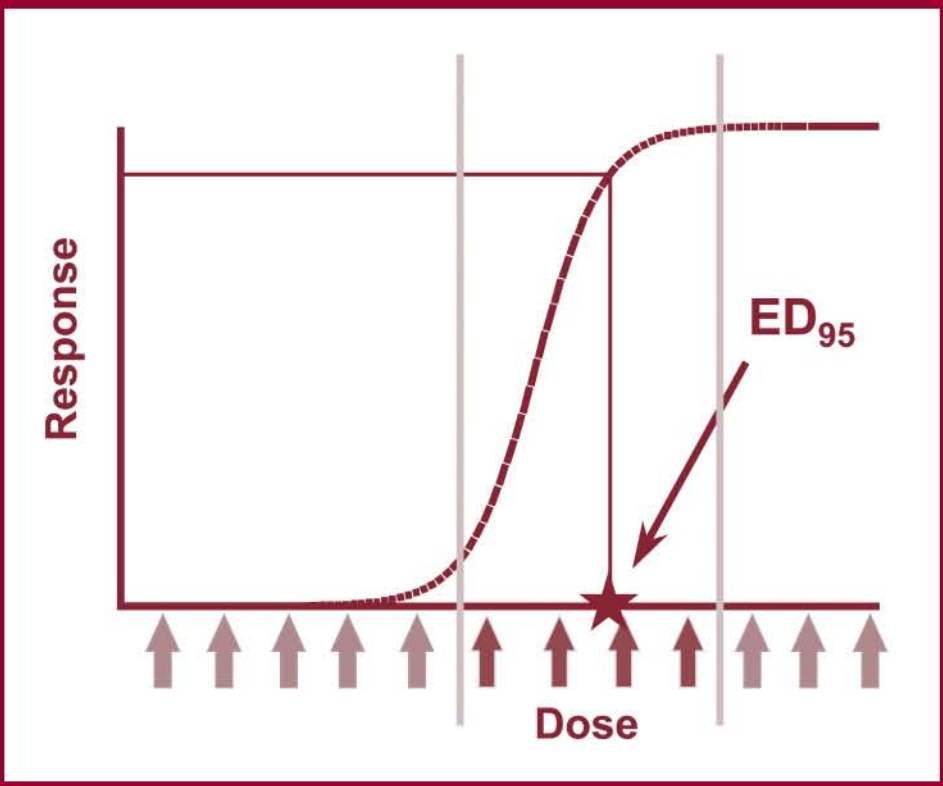
DRUGS AND THE PHARMACEUTICAL SCIENCES VOLUME 161

Dose Optimization in Drug Development



edited by
Rajesh Krishna

Dose Optimization in Drug Development

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edited by

Rajesh Krishna

Merck & Co., Inc.
Rahway, New Jersey, U.S.A.

informa
healthcare

New York London

CRC Press
Taylor & Francis Group
6000 Broken Sound Parkway NW, Suite 300
Boca Raton, FL 33487-2742

Version Date: 20130724

International Standard Book Number-13: 978-1-4200-1858-5 (eBook - PDF)

To Mom,
for always encouraging me to pursue my ambitions,
to Dad, for his strong belief that anything is achievable,
and to my wife,
for sharing and surmounting life's challenges together.

Foreword

Arguably the most difficult aspect of drug development, once proof-of-concept is achieved for a novel mechanism, is defining the "right" dose. Indeed, the question rapidly expands to right for whom? An individual? A population? A specific disease? A unique demographic? The answers can yield a dizzying array of alternatives. Yet pressures to rapidly realize the benefits of a new compound often limit time spent in early development (Phase I/II) when such questions have traditionally been explored. To more efficiently address the problem of defining the optimum dose, new approaches are being applied across the disciplines of drug development.

The present volume, *Dose Optimization in Drug Development*, in the series Drugs and the Pharmaceutical Sciences, provides a timely overview of emerging knowledge in this field. This knowledge encompasses techniques for exploring individual as well as population dose optimization including the definition of dose-concentration-response relationships, modeling based on these PK/PD relationships, clinical trial simulations, and application of pharmacogenomic principles. One aspect of this research which should not be lost is the requirement for more highly integrated interactions between the clinicians, kineticists, and statisticians addressing these problems.

Dr. Rajesh Krishna, the editor of the present volume, has assembled an extraordinary group of contributors. He has succeeded in identifying the critical newly emerging capabilities in drug development as applied to dose finding and generated a volume of enormous power. The authors, for their part, address the fundamental issues of the day with respect to dose optimization—translational research, methodology development, clinical trial modeling, PK/PD simulations, biomarker identification and validation, and application of novel clinical trial designs—in a manner that is of both sufficient depth and general applicability as

to be of practical utility to the reader. This volume will become an indispensable reference work for anyone interested in applying these state of the art principles for dose optimization to the science of drug development.

Barry J. Gertz, M.D., Ph.D.
Executive Vice President
Clinical and Quantitative Sciences
Merck Research Laboratories
Rahway, New Jersey, U.S.A.

Preface

Advancements in various aspects of clinical science have resulted in remarkable improvement in scientific drug development, specifically with respect to quality of new drug applications. Despite these small and perhaps case-dependent improvements, the promise of biomarkers, new clinical methodologies and technologies, the "omic" sciences and the pharmacostatistical approaches to advanced modeling of biodynamic systems and trial simulations have all yet to significantly modulate the quality of new candidate selection, clinical optimization, and characterization, and thus profoundly reduce late stage development attrition. Fundamentally, all of these powerful tools and methodologies individually retain enormous potential to result in a better understanding of the new drug candidate's behavior in various patient populations, in understanding exposure–response relationships, and in quantitatively delineating risk versus benefit. The latter developmental aspect is a singularly worrisome gap in many drug development programs, sometimes resulting in complicated and prolonged regulatory reviews and, in rare cases, drug product withdrawals.

In considering the aspect of risk versus benefit further, one relatively underutilized concept is surprisingly the scientific basis of dose selection, focus, and optimization. It is surprising because dose selection is still largely empirical and not rationally scientific, at least to the extent that could be possible. Dose selection is hardly trivial and is intimately linked to risk versus benefit as it quantifies the therapeutic window for a given new chemical entity within the context of the disease it is being developed for.

The realities of new product development took a turn for the better when the U.S. Food and Drug Administration recently released a report entitled "Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products" on March 16, 2004, aimed at modernizing drug development. This is the first major step in recent years that a federal authority has taken to further identify the deficiencies in new drug development from a regulatory standpoint. Fortunately, this key regulatory initiative, or rather a formal recognition of a persistent

problem, has fueled considerable interest in integrating knowledge that would contribute productively to new drug development, gain a better understanding of the drug candidate's behavior in patient populations, while increasing the probability of success for new chemical entities. The emphasis on dose optimization has also encouraged research and discussion on performing more innovative Phase I/II trials to seek evidence of target engagement earlier rather than later, thereby reducing failure rates attributable to poor efficacy. These considerations have played a central role in the conceptualization and development of this book.

The theme of this volume is dose selection and optimization, specifically as they relate to new drug development. When conceptualizing this volume, the editor identified those specific areas that contribute to the rational scientific basis for dose selection. Those areas leverage the first principles of pharmacokinetics and pharmacodynamics, which in the editor's opinion are fundamental to drug development. The concepts presented here are intentionally somewhat advanced and may appeal favorably to those who are familiar with basic pharmacokinetics and clinical pharmacology. The book is not designed as a formal study course textbook, but more along the lines of presenting perspectives from expert scientists drawn from the pharmaceutical industry, academia, and regulatory agencies. The perspectives are intended to be thought-provoking and designed to elicit sustained interest and discussions on dose selection and its broader impact on various elements of risk-versus-benefit and model-based drug development.

The editor recognizes that there are two key interfaces in new drug development: first, the transition from preclinical to Phase I clinical development (so-called early or translational development), and second, the transition from establishing pharmacological proof-of-concept in Phase IB/IIA development to pivotal efficacy Phase IIB/III trials (so-called late development). The interplay of biomarkers, novel clinical trial designs, pharmacogenomics, and new technologies overlapping these two transition events will be emphasized. Aspects of dose adjustment necessitated by both intrinsic and extrinsic considerations will also be discussed, although this is not the focus of this volume. The volume is intentionally not all-encompassing, focusing only on those opportunities which in the editor's perspective, if leveraged successfully, will positively influence drug development dose decisions.

It is hoped that the book will appeal to drug development scientists, particularly those who are clinical pharmacologists, pharmacokineticists, clinicians, and regulators. Advanced students of medicine, pharmacy, and allied health sciences may also benefit if their primary interests lie in new drug development. The book will appeal to anyone who would like to appreciate how integration of sciences facilitates meaningful changes in delineating risk versus benefit and ultimately in the selection of safe and effective doses.

Rajesh Krishna

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Contributors

James Bolognese Departments of Clinical Pharmacology and Biostatistics and Research Decision Sciences, Merck Research Laboratories, Merck & Co., Inc., Rahway, New Jersey, U.S.A.

Stephan Chalon Lilly Research Laboratories, Eli Lilly & Company, Indianapolis, Indiana, U.S.A.

Lois M. Freed Division of Neurology Products, Center for Drug Evaluation and Research, United States Food and Drug Administration, Silver Spring, Maryland, U.S.A.

Jogarao V. S. Gobburu Pharmacometrics, Office of Clinical Pharmacology and Biopharmaceutics, United States Food and Drug Administration, Silver Spring, Maryland, U.S.A.

Mathangi Gopalakrishnan Department of Mathematics and Statistics, University of Maryland, Baltimore, Maryland, U.S.A.

Peter H. Hinderling Office of Clinical Pharmacology and Biopharmaceutics, Center for Drug Evaluation and Research, United States Food and Drug Administration, Silver Spring, Maryland, U.S.A.

Rajesh Krishna Department of Clinical Pharmacology, Merck Research Laboratories, Merck & Co., Inc., Rahway, New Jersey, U.S.A.

Patrick J. Marroum Office of Clinical Pharmacology and Biopharmaceutics, Center for Drug Evaluation and Research, United States Food and Drug Administration, Silver Spring, Maryland, U.S.A.

Markus Müller Department of Clinical Pharmacology, Medical University of Vienna, Vienna, Austria

Vladimir Piotrovsky Clinical Pharmacology and Experimental Medicine, Johnson & Johnson Pharmaceutical Research & Development, Beerse, Belgium

Diether Rueppel Global Metabolism/Pharmacokinetics, Sanofi-Aventis Deutschland GmbH, Frankfurt, Germany

John-Michael Sauer Elan Pharmaceuticals, Inc., South San Francisco, California, U.S.A.

Wolfgang M. Schmidt Department of Clinical Pharmacology, Medical University of Vienna, Vienna, Austria

Jun Shi Clinical Pharmacology and Drug Dynamics, Forest Laboratories, Inc., Jersey City, New Jersey, U.S.A.

Paolo Vicini Department of Bioengineering, University of Washington, Seattle, Washington, U.S.A.

John A. Wagner Department of Clinical Pharmacology, Merck & Co., Inc., Rahway, New Jersey, U.S.A.

Willi Weber Global Metabolism/Pharmacokinetics, Sanofi-Aventis Deutschland GmbH, Frankfurt, Germany

Jennifer W. Witcher Lilly Research Laboratories, Eli Lilly & Company, Indianapolis, Indiana, U.S.A.

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Introduction to Dose Optimization in Drug Development

Rajesh Krishna

Department of Clinical Pharmacology, Merck Research Laboratories, Merck & Co., Inc., Rahway, New Jersey, U.S.A.

INTRODUCTION

On average, it now takes approximately at least 10 years of pharmaceutical research and development time and approximately $1.7 billion to bring a new molecule to bridge the gap of growing demands of unmet medical needs (1–8). It is also interesting to note that there is a failure rate of approximately 50% in Phase III late stage development in the industry (1,5,7). A schema on the drug development value chain is presented in Figure 1. Drug development proceeds in stages, as a molecule moves from preclinical to clinical development, eventually through registration and, in the process, valuable knowledge on the preclinical and clinical properties is gained that is consistent with the learning and confirming paradigm. It takes even more to keep the drug as a viable option for therapy post-approval as new information becomes available on the safety and efficacy of the drug in a wider patient population (8). As an example of post-marketing events, Table 1 lists the drugs withdrawn from the market due to safety-related reasons. The promise of new technologies that have spanned the entire breadth and width of drug development from combinatorial chemistry approaches to high throughput screens and the advances in genomic sciences appear not to have made a significant impact on the drug development statistics yet (6). This is reflected in the declining number of new molecular (or chemical) entities received by the United States Food and Drug Administration (FDA) as compared to the early 1990s (1). The scope of

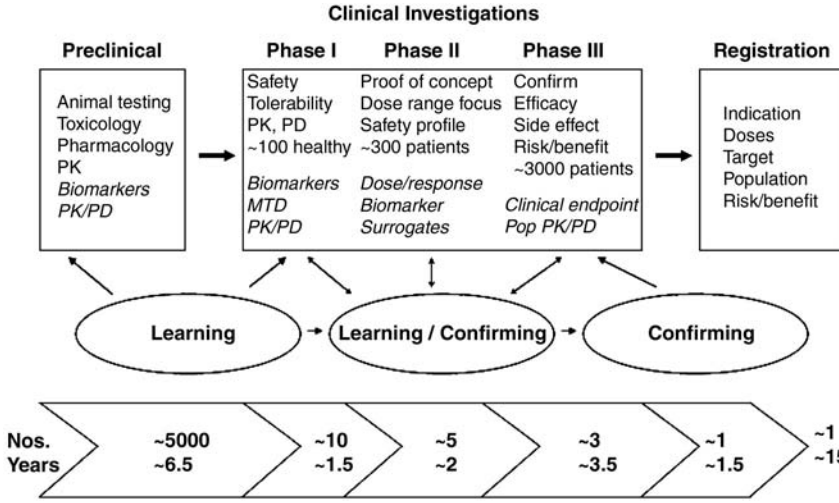

Figure 1 Drug development value chain from preclinical development through registration. The schema also illustrates compound attrition rate and development time.

knowledge-based drug development is illustrated in Figure 2, one recurring aspect of which, namely dose optimization, is the theme of this book.

CHANGING FACE OF REGULATORY ENVIRONMENT

The regulatory environment has also been rapidly changing as new information on the safety of an approved molecule arises from the wider patient population and additionally as long-term outcome trials on risk factors for disease dictate drug development and approval. This has had particular impact on drug withdrawals from the market in the past decade or two. Brewing in the midst of this cycle of innovation and stagnation, two schools of thought have emerged. One aims to critique the drug development as being too slow in bringing promising medical breakthroughs to the care of patients who deserve them faster than currently is the case, while the other aims to critique that the current drug development trials are insufficient to generate adequate safety and efficacy data to support a new molecule's broader use in a patient population.

The declining rate in approval of new molecular entities has been a subject of debate for a number of both scientific and business forums in the understanding of why pharmaceutical innovation is on the decline. The FDA Modernization Act of 1997, implying that a single adequate and well-controlled investigation with confirmatory evidence was sufficient for drug approval, triggered additional thought and public debate (9–16). A hypothesis on this issue was presented by Carl Peck, Donald Rubin, and Lewis Sheiner, which appeared

Table 1 Partial List of Drugs Withdrawn from the Market (1971–2005) Due to Safety Reasons

Drug	Reason for withdrawal
Azaribine	Thromboembolism
Ticrynafen	Liver and kidney toxicity
Benoxaprofen	Liver toxicity
Encainide	Mortality
Nomifensine	Hemotological effects
Suprofen	Kidney toxicity
Temafloxacin	Haemolytic-uraemic syndrome
Triazolam	Psychiatric effects
Zomepirac	Anaphylactic reactions
Apa	Anaphylactic reactions
Dilevalol	Liver damage
Fenclofenac	GI and skin toxicity and carcinogenicity
Feprazone	GI toxicity
Indoprofen	GI toxicity
Indomethacin-in-OROS	GI toxicity
Metipranolol	Granulomatous anterior uveitis
Perhexiline	Peripheral neuropathy and liver damage
Terodiline	Torsades de pointes
Zimeldine	Peripheral neuropathy
Flosequinan	Increased deaths
Fenfluramine	Heart valve disease
Terfenadine	Fatal arrhythmia
Bromfenac	Liver toxicity
Mibefradil	Fatal arrhythmia
Grepafloxacin	Fatal arrhythmia
Astemizole	Fatal arrhythmia
Troglitazone	Liver toxicity
Alosetron	Ischemic colitis
Cerivastatin	Muscle damage leading to kidney failure
Rapacuronium	Severe breathing difficulty
Etretinate	Birth defects
Levomethadyl	Fatal arrhythmia
Rofecoxib	Heart attack, stroke
Valdecoxib	Skin disease

Source: Adapted from Refs. 8, 45.

in *Clinical Pharmacology and Therapeutics* in June 2003 (17). The authors argued against the perception of lowered standards for drug effectiveness and stated that drug development will be more efficient in the end with a single clinical trial with confirmatory evidence of effectiveness.

Recognizing the apparent deficiencies in drug development and regulatory approval, the U.S. Food and Drug Administration put forth a white paper on

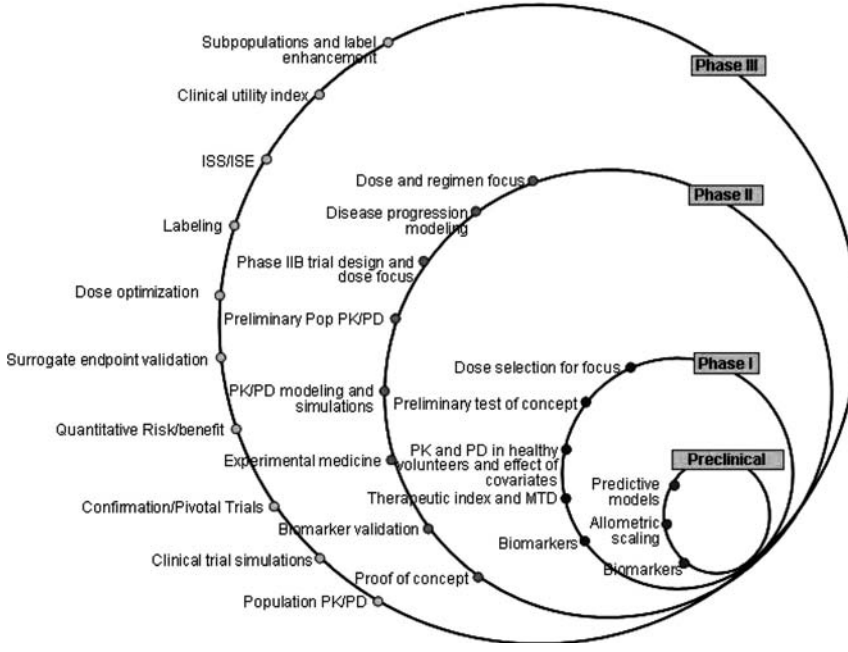

Figure 2 Scope of knowledge-based drug development (modified from the original, courtesy Dr. Jeff Barrett, University of Pennsylvania).

challenge and opportunity on the critical path to new medical products, in March 2004 (1). The white paper calls for an increased emphasis on methodologies that can reliably predict the safety and effectiveness of a drug and also novel clinical evaluation approaches to increase the efficiency of the so-called bottleneck of drug development, the clinical development (18). According to the white paper, the critical issue impeding successful development is the inability to predict safety and efficacy failures early in the process, such that the clinical development path (Phases I through III) is optimized for molecules with high probability of success to regulatory acceptance and approval. The FDA hopes to create new publicly accessible methodologies on modeling, simulation, biomarkers, and clinical endpoints to streamline the path to regulatory approval and has initiated a number of initiatives within and external to the agency to help make this vision a reality. A regulatory perspective is presented in Chapter 9.

NEW TECHNOLOGIES FOR DRUG DEVELOPMENT

Biomarkers

The integration of biomarkers in a drug discovery and development program provides valuable insights into a mechanism of action for a desired therapeutic intervention (19–40). These biological or biochemical markers of efficacy

and/or safety will aid in the development of appropriate exposure/response relationships and can be implemented as early as preclinical pharmacology studies are performed in the drug discovery stage. Together with allometric scaling of pharmacokinetics (PK), exposure margins from toxicological data, and prediction of drug behavior in humans, they present the first opportunity to elucidate the projected clinically relevant dose range in translational development for assessment in the first human trial.

Typically, early biomarker identification and applications involve those biomarkers that are implicated in the normal course of disease progression, such that measurement of the marker provides some understanding of the pharmacological responses to a desired effect.

It is not uncommon to use the early phase of clinical development to investigate the viability of multiple markers of disease progression and/or safety. Biomarkers are particularly useful in the transition from preclinical to clinical development and also at the interface of early clinical and late stage clinical development. Their application in translational and early clinical (Phase I) development is in the selection of doses and/or regimens to be initially assessed.

Disease progression is discussed in Chapter 2 while biomarker validation and qualification are discussed in Chapter 3. Surrogate endpoints (discussed in Chap. 6) are generally those biomarkers that are intended to substitute for a particular clinical endpoint; clinical endpoints are those that represent functional or survival attributes (21–40). Specific definitions for the terminology used have been proposed by the biomarkers definitions working group listed in Table 2 (20).

Informative biomarkers and surrogate endpoints add value to drug development not only for deciding on comparative efficacy among lead candidates and a basis for termination or continuance of a program, but they are amenable to elucidating PK/pharmacodynamic (PD) assessments, thus aiding in target validation, providing early scope for risk/benefit, dose selection, focus and optimization, and in identifying a subset of the target population who may respond to a specific treatment option more favorably. In addition, they can aid

Table 2 Terminology for Biomarkers and Endpoints

Term	Definition
Biomarker	A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.
Clinical endpoint	A characteristic or variable that reflects how a patient feels, functions, or survives.
Surrogate endpoint	A biomarker that is intended to substitute for a clinical endpoint. A surrogate endpoint is expected to predict clinical benefit (or harm or lack of benefit or harm) based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence.

Source: Adapted from Ref. 20 (Biomarkers Definition Working Group).

Table 3 Partial List of Biomarkers and Clinical Endpoints

Disease	Biomarker	Clinical endpoint
Alzheimer's disease	Entorhinal cortex volume by MRI	Cognitive testing
Asthma	Lung function tests	Respiratory distress
Cancer	Tumor size	Survival, progression
Diabetes	Fasting plasma glucose, HbA1c	Nephropathy, retinopathy
Glaucoma	Intraocular pressure	Visual acuity
Hyperlipidemia	Serum cholesterol	Myocardial infarction
Hypertension	Blood pressure	Stroke, myocardial infraction
Multiple sclerosis	Lesion incidence, volume	Neurologic manifestations
Osteoporosis	Bone mineral density	Fractures
Rheumatoid arthritis	c-reactive protein, joint space, erosion	Pain, mobility
HIV	CD4 levels, viral load	Survival
Congestive heart failure	Cardiac output, ejection fraction	Survival

Source: Adapted from Refs. 19–40.

in the design of efficient clinical trials and in the approval of new molecules, using an accelerated approval program. A good example of an accelerated approval based on a surrogate endpoint is from the infectious diseases therapeutic area (26,30,34–36). CD4 lymphocyte count is widely acknowledged and applied as a surrogate endpoint for AIDS progression. Zidovidine was first approved in 1987 based on survival data at 17 weeks. DDI, on the other hand, was approved in 1991 based on the CD4 as a surrogate endpoint for use in cases where AZT therapy failed, and ddC became the first molecule approved under the accelerated approval paradigm in 1992. Many drugs against HIV have since been approved. Based on a review of the recent accelerated approvals for drugs against HIV, the endpoint has been either the change of CD4, time-averaged change of CD4, HIV change from baseline, or HIV RNA <400 and/or <50 copies/mL. Table 3 lists the biomarkers, and surrogate and clinical endpoints for a few other disease segments. The role of pharmacogenomics in dose optimization is presented in Chapter 8.

Modeling and Simulation

PK characterization of a new molecule involves the quantitative description of the time course of a new molecule in the biological system, enabling elucidation of key PK parameters, such as half-life, volume of distribution, clearance, and so on. Similarly, PD characterization of a drug quantitatively describes the biological effects of drugs and mechanism of action. When PK is integrated with PD,

valuable information on concentration versus effect relationships can be obtained, which has important implications in drug development. Simple and empirical exposure/response relationships can guide many aspects of drug discovery and development decisions such as dose selection, effect of exposure alteration on desired pharmacological response, defining target effect concentration margins, and prediction of response for a given concentration/exposure. Notably, PK/PD models can aid in elucidating the biological plausibility of various biomarkers early in drug development while providing an opportunity to accelerate drug development when integrated with biomarkers, surrogate, or clinical endpoints (12,17,41,42).

Over the last two decades, a new dimension of PK/PD modeling has emerged, in part borrowed from advanced engineering and business decision analysis fields (42). While probably still in infancy, the emerging science of pharmacometrics offers a quantitative basis for the principles of clinical pharmacology and therapeutics to an extent perhaps greater than that which has been accomplished in the past. This involves the application of complex computational and statistical principles in development of more mechanistic exposure/response relationships, integration of population PK/PD modeling, and stochastic simulation analysis incorporating Monte Carlo simulation paradigm, which have opened doors to a more quantitative outlook on clinical pharmacology. With the available programming and simulations software, these complex modeling and simulations approaches have already begun to have a positive impact on drug development. More importantly, their core application has been in forecasting the uncertainty in attaining a desired probability of success for a given therapeutic endpoint for large Phase II–III trials, thereby adding value to the design of clinical trials and dose and regimen optimization. This is possible by modeling the time course of disease progression based on available data on the progression of disease, outcome trials, and epidemiologic database, thus providing an opportunity to assess drug effects on disease progression. Virtual trials can be performed essentially in-silico and can assess the factors that influence the PK or PD of a given molecule against the backdrop of typical events that occur in an actual trial setting. Many of these concepts are applied and presented in Chapters 10–12.

Clinical Trial Design

In recent years, clinical trial designs have been a subject of numerous discussions and scientific debates. Given the increasing number of ineffective new molecular entities, failed clinical trial outcomes, and escalating trial costs, it has become increasingly apparent that novel clinical study designs would benefit from a redesign with an aim to improve upon the efficiency of clinical trials in selecting the winners, while minimizing exposing trial subjects to ineffective treatments. In general, for the purposes of discussion, there are two types of clinical designs based on flexibility. One is a frequentist design that is a *P*-value-based fixed