# Pharmacokinetics and Pharmacodynamics of Biotech Drugs

Principles and Case Studies in Drug Development

*Edited by*
*Bernd Meibohm*


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## Foreword

Pharmacokinetics and pharmacodynamics (PK/PD) have become essential disciplines in drug research and development. Rational use of PK/PD allows for better decision making and streamlines dose optimization. In the past, PK/PD concepts have been primarily been applied to the development of small drug molecules. However, in recent years more and more drug candidates come form the field of biotechnology and are larger molecules. Pharmacokinetics and Pharmacodynamics of Biotech Drugs gives an excellent overview of the state of the art of applying PK/PD concepts to large molecules.

After a comprehensive introduction, the basic PK/PD properties of peptides, monoclonal antibodies, antisense oligonucleotides and gene delivery vectors are reviewed. In the second part, the book covers a number of challenges and opportunities in this field such as bioanalytical methods, bioequivalence and pulmonary delivery. The text finishes with a detailed presentation of some real-life examples and case studies which should be of particular interest to the reader and integrate many of the concepts presented earlier in the text.

The book was written by a group of international expert scientists in the field. It is well-structured and easy to follow. The book is of great value for everybody working in this area.

*Hartmut Derendorf, Ph.D.*
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# Preface

In recent years, biotechnologically-derived drugs (biotech drugs) including proteins, peptides, monoclonal antibodies and antibody fragments, as well as antisense oligonucleotides and DNA preparations for gene therapy, have been a major focus of research and development (R&D) efforts in the pharmaceutical industry, and biotech drugs constitute already a sizable fraction of the medications used in clinical practice.

Pharmacokinetic (PK) and pharmacodynamic (PD) concepts impact every stage of the drug development process starting from lead optimization to the design of Phase III pivotal trials. PK and PK/PD evaluations are widely considered cornerstones in the development of new drug products and are usually deeply embedded in the discovery and development plan. The widespread application of PK/PD concepts in all phases of drug development has repeatedly been promoted by industry, academia, and regulatory authorities, most recently through FDA's Critical Path to New Medical Products initiative and the concept of integrated model-based drug development.

An understanding of PK and PD and the related dose-concentration-effect relationship is crucial to any drug – including biotech products – since it lays the foundation for dosing regimen design and rational clinical application. While general PK and PD principles are just as applicable to biotech agents as they are to traditional small molecule drugs, PK and PK/PD analyses of biotech agents frequently pose extra challenges related to factors such as their similarity to endogenous molecules and/or nutrients and their immunogenicity.

This textbook provides a comprehensive overview on the PK and PD of biotech-derived drug products, highlights the specific requirements and challenges related to PK and PK/PD evaluations of these compounds and provides examples of their application in preclinical and clinical drug development. The impetus for this project originated from the notion that at the time of its initiation there was no comprehensive publication on the market that specifically addressed this topic.

Following a short introduction, the book is structured into three sections: The 'Basics' section discusses individually the pharmacokinetics of peptides, monoclonal antibodies, antisense oligonucleotides and gene delivery vectors. The subsequent 'Challenges and Opportunities' section includes more detailed considerations on selected topics, including technical challenges such as bioanalytical

methodologies, noncompartmental data analysis and exposure-response assessments. It furthermore discusses biopharmaceutical challenges as exemplified by the delivery of oligonucleotides and of peptides and proteins to the lung, and provides insights into the opportunities provided by chemical modification of biotech drugs and the regulatory challenges related to follow-on biologics. The third and final section provides examples for the 'Integration of Pharmacokinetic and Pharmacodynamic Concepts into the Biotech Drug Development Plan', including the preclinical and early clinical development of tasidotin, and the clinical development programs for cetuximab and pegfilgrastim.

The book addresses an audience with basic knowledge in clinical pharmacology, PK and PD, and clinical drug development. It is intended as a resource for graduate students, postdocs, and junior scientists, but also for those more experienced pharmaceutical scientists that have no experience in the PK and PD evaluation of biotech drugs and wish to gain knowledge in this area.

I would like to express my gratitude to all contributors of this project for providing their unique array of expertise to this book project which allowed us to compile a wide variety of viewpoints relevant to the PK and PK/PD evaluation of biotech drugs and derived products. In addition, I would like to thank Dr. Romy Kirsten and Dr. Andrea Pillmann at Wiley-VCH for their assistance in producing this book and Ms. Faith Barcroft for her invaluable text editing.

Finally I would like to dedicate this book to my family for their patience, encouragement and support during this project.

Memphis, Summer 2006 *Bernd Meibohm*

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# Part I
# Introduction

# 1
# The Role of Pharmacokinetics and Pharmacodynamics in the Development of Biotech Drugs

*Bernd Meibohm*

## 1.1
## Introduction

During the past two decades, advances in biotechnology have triggered the development of numerous new drug products. This group of so-called biotech drugs is a subset of the therapeutic group of biologics. Therapeutic biologic products, or biologics, are defined by the U.S. Food and Drug Administration (FDA) as any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment or cure of diseases or injuries of man. Biologics are a subset of drug products distinguished by their manufacturing process. While classical drugs are synthesized via a chemical process, biologics are manufactured utilizing biological processes and are typically derived from living material – human, plant, animal, or microorganism. Biotech drugs can be considered as those biologics that are manufactured using biotechnology-based production processes.

The similarity in the drug development and evaluation process for biotech drugs and conventional, chemically synthesized drugs has recently been acknowledged in the FDA's 2003 decision to transfer certain product oversight responsibilities from the Center for Biologics Evaluation and Research (CBER) to the Center for Drug Evaluation and Research (CDER). The biologics for which oversight was transferred include monoclonal antibodies for *in vivo* use, proteins intended for therapeutic use, including cytokines (e.g., interferons), enzymes (e.g., thrombolytics), growth factors, and other novel proteins that are derived from plants, animals, or microorganisms, including recombinant versions of these products, and other non-vaccine and non-allergenic therapeutic immunotherapies. Classical biologics such as blood, blood components and vaccines remain under the regulatory authority of the CBER. Even under this new structure, however, the biologic products transferred to the CDER will continue to be regulated as licensed biologics – that is, a Biologic License Application (BLA) must be submitted to obtain marketing authorization as compared to a New Drug Application (NDA) which is used for traditional, chemically manufactured drug products.

For the purpose of this book, biotech drugs include not only therapeutically used peptides and proteins, including monoclonal antibodies, but also oligonucleotides and DNA preparations for gene therapy. Although oligonucleotides are, due to their chemically defined production process, classified by the FDA as classical drugs requiring an NDA prior to marketing authorization, and DNA preparations for gene therapy are regulated by the CBER, they are both included in the class of biotech drugs as their therapeutic application relies heavily on the principles of molecular biology and they are considered by analysts as biotech compounds.

## 1.2 Biotech Drugs and the Pharmaceutical Industry

In parallel with the development of the discipline of biotechnology during the past two decades, an increasing fraction of pharmaceutical R&D has been devoted to biotechnology-derived drug products. It has been estimated that more than 250 million patients have benefited from already approved biotechnology medicines to treat or prevent heart attacks, stroke, multiple sclerosis, leukemia, hepatitis, rheumatoid arthritis, breast cancer, diabetes, congestive heart failure, kidney cancer, cystic fibrosis and other diseases [1]. This number is expected to increase significantly with the introduction of new biotech drugs into the marketplace. According to a survey by the Pharmaceutical Research and Manufacturers of America (PhRMA) in 2004, 324 biotechnology medicines were in development for almost 150 diseases. These include 154 medicines for cancer, 43 for infectious diseases, 26 for autoimmune diseases, and 17 for AIDS/HIV and related conditions. These potential medicines – all of which were at the time of the survey either in human clinical trials or under review by the FDA – will enlarge the list of 108 biotechnology medicines already approved and available to patients (Fig. 1.1) [1].

Biotech and genomic companies currently perform almost one-fifth of all pharmaceutical R&D, and this figure is set to double during the next 10 years [2]. It has been suggested that over half of all the New Active Substances developed during the next 10–15 years will result from research into antibodies alone. Biotechnology products accounted for more than 35% of the 37 New Active Substances that were launched in 2001 [2]. This success in drug development is underlined by the fact that several biotech drugs have achieved blockbuster status, earning more than US$ 1 billion in annual sales, including Epoetin-α (Epogen/Procrit/Eprex), interferon-α2b (IntronA, PEG-Intron/Rebetron combination therapy), and filgrastim (Neupogen) [3].

Since the development of biotech drugs generally rests on a fundamental understanding of the related disease, their clinical development has also proven to be more successful than for conventional, chemically derived small-molecule drugs. Only 8% of the new chemical entities that entered the clinical phases of drug development between 1996 and 1998 reached the market, compared to 34% of biotech drugs (Fig. 1.2). This means that biologics have, at the time of their first-in-

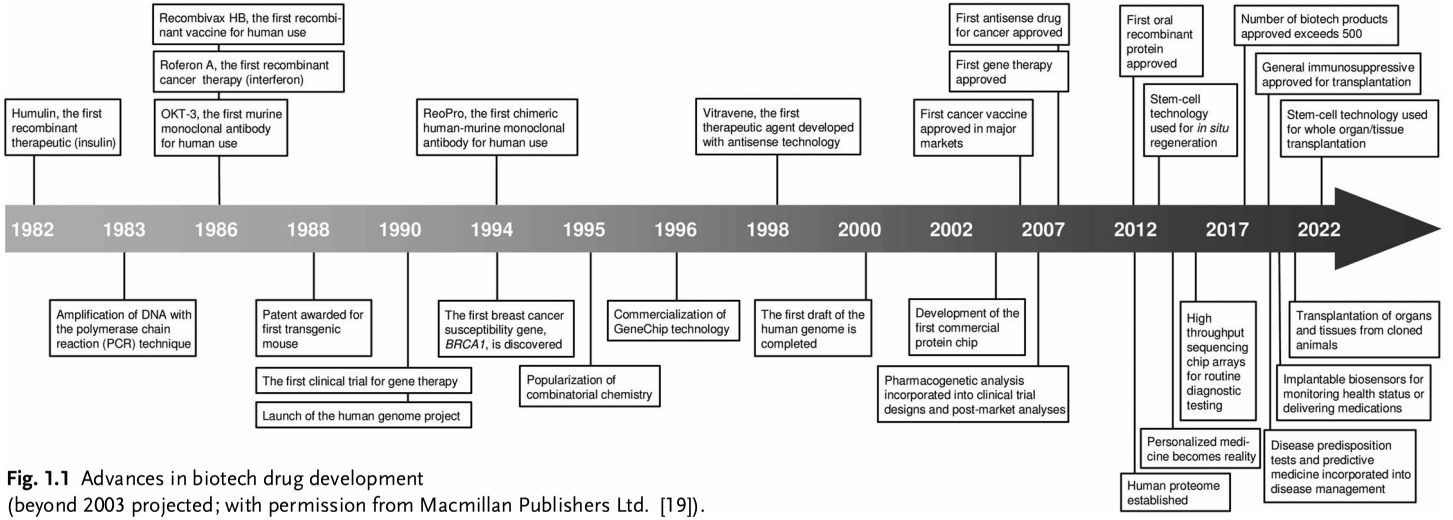


**Fig. 1.1** Advances in biotech drug development
(beyond 2003 projected; with permission from Macmillan Publishers Ltd. [19]).

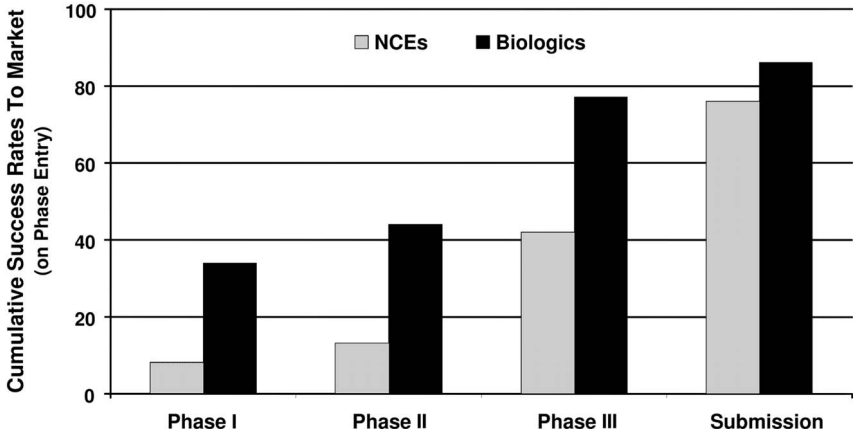


**Fig. 1.2** Success rates for clinical drug development are much higher for biologics than for traditional, chemically defined drug compounds. NCE: New chemical entity (modified from [2]).

man studies, a fourfold greater chance than traditional, chemically defined drugs of making it into the marketplace. Thus, greater use of biologics will likely reduce the attrition rate at every stage of the clinical drug development process [2]. Based on these facts, it can be predicted that biotech drugs will play a major – if not dominant – role in the drug development arena of the next decades.

## 1.3 Pharmacokinetics and Pharmacodynamics in Drug Development

The general paradigm of clinical pharmacology is that administration of a dose or the dosing regimen of a drug results in defined drug concentrations in various body compartments and fluids. These are, in turn, the driving force for the drug's desired and undesired effects on the human body that collectively constitute the drug's efficacy and safety profile. Based on this paradigm, the basis for the pharmacotherapeutic use of biotech drugs is similar to that of small molecules – a defined relationship between the intensity of the therapeutic effect and the amount of drug in the body or, more specifically, the drug concentration at its site of action (i. e., an exposure–response relationship). The relationship between the administered dose of a drug, the resulting concentrations in body fluids and the intensity of produced outcome may be either simple or complex, and thus obvious or hidden. However, if no simple relationship is obvious, it would be misleading to conclude *a priori* that no relationship exists at all rather than that it is not readily apparent [4, 5].

The dose–concentration–effect relationship is defined by the pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of a drug. Pharmacokinetics comprises all processes that contribute to the time course of drug concentrations