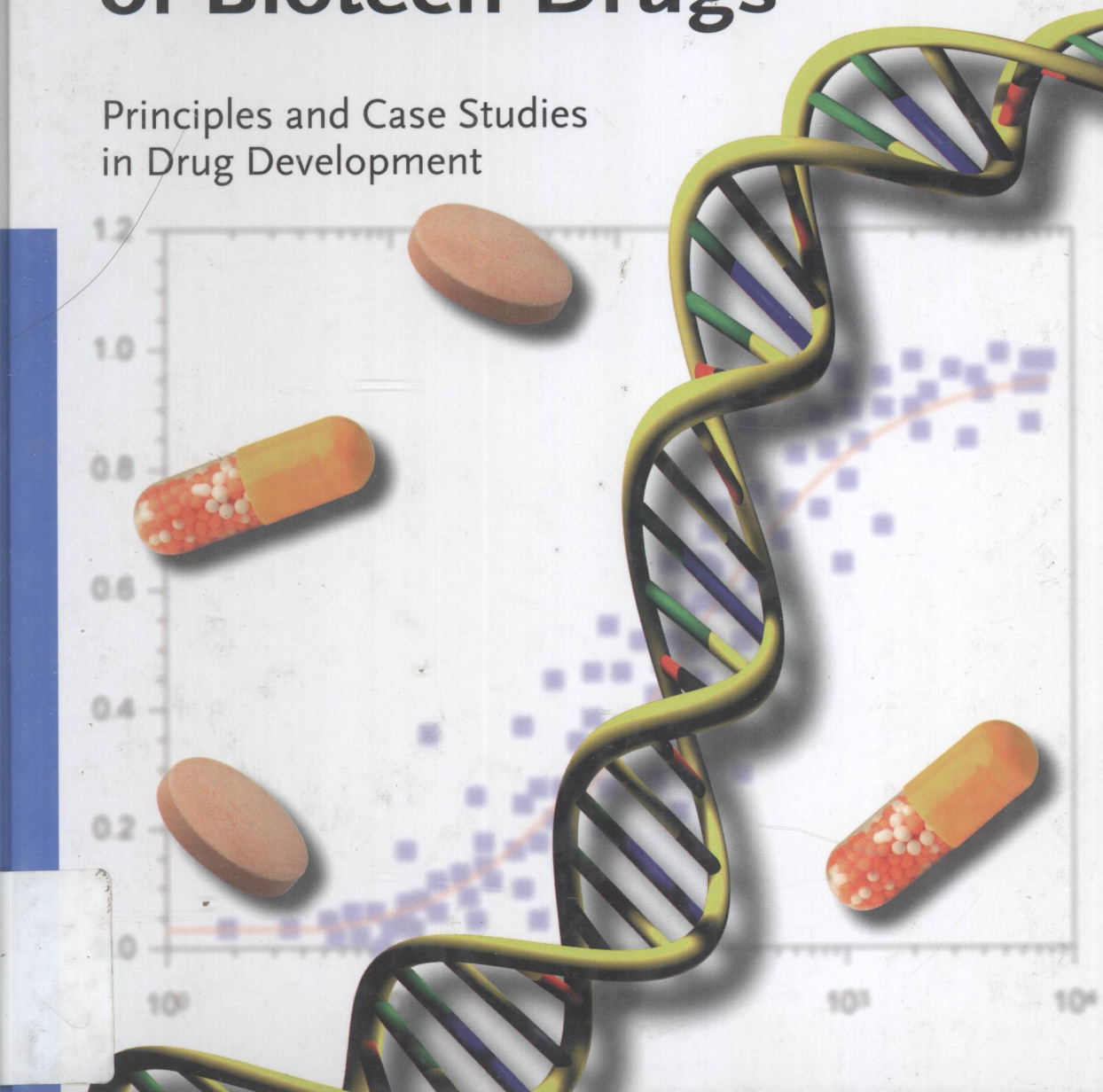
Edited by Bernd Meibohm

WILEY-VCH

Pharmacokinetics and Pharmacodynamics of Biotech Drugs

Principles and Case Studies in Drug Development



Pharmacokinetics and Pharmacodynamics of Biotech Drugs

Principles and Case Studies in Drug Development

Edited by
Bernd Meibohm

WILEY-VCH Verlag GmbH & Co. KGaA

The Editor

Prof. Dr. Bernd Meibohm
University of Tennessee
Health Science Center
Department of Pharmaceutical Sciences
College of Pharmacy
874 Union Ave. Suite 5p
Memphis, TN 38163
USA

Library of Congress Card No.: applied for

British Library Cataloguing-in-Publication Data:
A catalogue record for this book is available from the British Library

Bibliographic information published by the Deutsche Nationalbibliothek
The Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data are available in the Internet at http://dnb.d-nb.de.

Composition ProSatz Unger, Weinheim
Printing Strauss GmbH, Mörlenbach
Bookbinding Litges & Dopf Buchbinderei GmbH, Heppenheim

Printed in the Federal Republic of Germany
Printed on acid-free paper

ISBN-13: 978-3-527-31408-9
ISBN-10: 3-527-31408-3

Pharmacokinetics and Pharmacodynamics of Biotech Drugs

Edited by
Bernd Meibohm

Related Titles

M.S. Chorghade (Ed.)

Drug Discovery and Development

2 Volumes

2006. ISBN 0-471-39846-2

J. Knäblein (Ed.)

Modern Biopharmaceuticals

4 Volumes

Design, Development and Optimization

2005. ISBN 3-527-31184-X

M. Schleef (Ed.)

DNA-Pharmaceuticals

Formulation and Delivery in Gene Therapy, DNA Vaccination and Immunotherapy

2005. ISBN 3-527-31187-4

O. Kayser, R.H. Müller (Eds.)

Pharmaceutical Biotechnology

Drug Discovery and Clinical Applications

2004. ISBN 3-527-30554-8

R.J.Y. Ho, M. Gibaldi

Biotechnology and Biopharmaceuticals

Transforming Proteins and Genes into Drugs

2003. ISBN 0-471-20690-3

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.
Distinguished Professor and Chairman
Department of Pharmaceutics
University of Florida

Pharmacokinetics and Pharmacodynamics of Biotech Drugs: Principles and Case Studies in Drug Development. Edited by Bernd Meibohm

ISBN: 3-527-31408-3

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

Pharmacokinetics and Pharmacodynamics of Biotech Drugs: Principles and Case Studies in Drug Development. Edited by Bernd Meibohm

ISBN: 3-527-31408-3

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*

List of Contributors

Larry Arthaud
Department of Pharmacokinetics
Genzyme Corporation
4545 Horizon Hill Blvd.
San Antonio, TX 78229
USA

Jeffrey S. Barrett
Laboratory for Applied PK/PD
The Children's Hospital of Philadelphia
Abramson Research Center,
Room 916 H
34th Street and Civic Center Blvd.
Philadelphia, PA 19104
USA

Peter L. Bonate
Department of Pharmacokinetics
Genzyme Corporation
4545 Horizon Hill Blvd.
San Antonio, TX 78229
USA

Paolo Caliceti
Department of Pharmaceutical Sciences
School of Pharmacy
University of Padua
Via Francesco Marzolo, 5
35131 Padua
Italy

Kun Cheng
Department of Pharmaceutical Sciences
University of Tennessee Health Science Center
26 S. Dunlap Street
Memphis, TN 38163
USA

Floyd E. Fox
Clinical Pharmacology
ImClone Systems Inc.
59 ImClone Drive
Somerville, NJ 08876
USA

Richard S. Geary
Pharmacokinetics and Drug Metabolism
Isis Pharmaceuticals
1896 Rutherford Road
Carlsbad, CA 92008
USA

Gregory E. Hardee
Quality Assurance
Isis Pharmaceuticals
1896 Rutherford Road
Carlsbad, CA 92008
USA

Pharmacokinetics and Pharmacodynamics of Biotech Drugs: Principles and Case Studies in Drug Development. Edited by Bernd Meibohm

ISBN: 3-527-31408-3

Jeffrey R. Hughes
Pharmaceutical Sciences
College of Pharmacy
University of Florida
Box 100494, JHMHC
Gainesville, FL 32610
USA

Charlotte Kloft
Department of Clinical Pharmacy
Faculty of Pharmacy
Martin-Luther-Universität
Halle-Wittenberg
Wolfgang-Langenbeck-Strasse 4
06120 Halle
Germany

Katharina Kuester
Department of Clinical Pharmacy
Institute of Pharmacy
Freie Universität Berlin
Kelchstrasse 31
12169 Berlin
Germany

Andreas Kovar
Clinical Pharmacology
and Pharmacokinetics
Merck KGaA
Frankfurter Strasse 250
64293 Darmstadt
Germany

Jean W. Lee
Pharmacokinetics and Drug
Metabolism
Protein Labs
Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320
USA

Arthur A. Levin
Isis Pharmaceuticals
1896 Rutherford Road
Carlsbad, CA 92008
USA

Ram I. Mahato
Department of Pharmaceutical
Sciences
College of Pharmacy
University of Tennessee Health
Science Center
26 S. Dunlap Street
Memphis, TN 38163
USA

Bernd Meibohm
Department of Pharmaceutical
Sciences
College of Pharmacy
University of Tennessee Health
Science Center
874 Union Avenue, Suite 5p
Memphis, TN 38163
USA

Martin Meyer
Department of Pharmaceutics
College of Pharmacy
Box 100494, JHMHC
University of Florida
Gainesville, FL 32610
USA

Arno Nolting
Clinical Pharmacology and
Pharmacokinetics
Merck KGaA
Frankfurter Strasse 250
64293 Darmstadt
Germany

Gururaj Rao
Department of Pharmaceutics
College of Pharmacy
Box 100494, JHMHC
University of Florida
Gainesville, FL 32610
USA

Ke Ren
Department of Pharmaceutics
College of Pharmacy
Box 100494, JHMHC
University of Florida
Gainesville, FL 32610
USA

Lorin K. Roskos
Pharmacokinetics and Toxicology
Amgen Inc.
6701 Kaiser Drive
Fremont, CA 94555
USA

Katherine Stephenson
Department of Pharmacokinetics
Genzyme Corporation
4545 Horizon Hill Blvd.
San Antonio, TX 78229
USA

Arthur B. Straughn
Department of Pharmaceutical
Sciences
College of Pharmacy
University of Tennessee Health
Science Center
874 Union Avenue, Suite 5p
Memphis, TN 38163
USA

Mohammad Tabrizi
Pharmacokinetics and Toxicology
Amgen Inc.
6701 Kaiser Drive
Fremont, CA 94555
USA

Lisa Tang
Department of Pharmaceutical
Sciences
College of Pharmacy
University of Tennessee Health
Science Center
874 Union Avenue, Room 105p
Memphis, TN 38163
USA

Lloyd G. Tillman
Pharmaceutical Development
Isis Pharmaceuticals
1896 Rutherford Road
Carlsbad, CA 92008
USA

Francesco M. Veronese
Department of Pharmaceutical
Sciences
School of Pharmacy
University of Padua
Via Francesco Marzolo, 5
35131 Padua
Italy

Bing-Bing Yang
Pharmacokinetics and Drug
Metabolism
Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320
USA

Rosie Z. Yu
Department of Pharmacokinetics
Isis Pharmaceuticals
1896 Rutherford Road
Carlsbad, CA 92008
USA

Contents

Pharmacokinetics and Pharmacodynamics of Biotech Drugs: Principles and Case Studies in Drug Development. Edited by Bernd Meibohm

ISBN: 3-527-31408-3