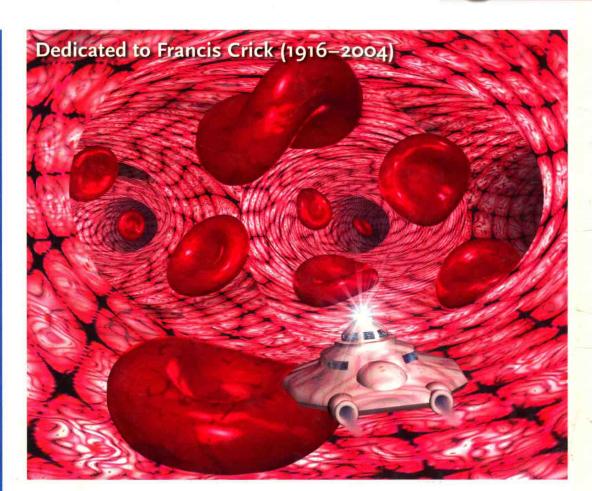


Modern Biopharmaceuticals

Design, Development and Optimization

Volume 4





Modern Biopharmaceuticals

Volume 4

Design, Development and Optimization

Edited by Jörg Knäblein



WILEY-VCH Verlag GmbH & Co. KGaA

Editor

Dr. Jörg Knäblein Head Microbiological Chemistry Schering AG Müllerstraße 178 13342 Berlin Germany All books published by Wiley-VCH are carefully produced. Nevertheless, authors, editors, and publisher do not warrant the information contained in these books, including this book, to be free of errors. Readers are advised to keep in mind that statements, data, illustrations, procedural details or other items may inadvertently be inaccurate.

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 Die Deutsche Bibliothek

Die Deutsche Bibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data is available in the Internet at http://dnb.ddb.de.

© 2005 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

All rights reserved (including those of translation into other languages). No part of this book may be reproduced in any form – nor transmitted or translated into machine language without written permission from the publishers. Registered names, trademarks, etc. used in this book, even when not specifically marked as such, are not to be considered unprotected by law.

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

Cover Tim Fonseca, www.fonsecatim.com Typsetting K+V Fotosatz GmbH, Beerfelden Printing betz-druck GmbH, Darmstadt Bookbinding J. Schäffer GmbH, Grünstadt

ISBN-13 978-3-527-31184-2 ISBN-10 3-527-31184-X

Jörg Knäblein (Ed.)

Modern Biopharmaceuticals

Further Titles of Interest

Gary Walsh

Biopharmaceuticals
Biochemistry and Biotechnology

2003 ISBN 0-470-84326-8

Gary Walsh

Proteins

Biochemistry and Biotechnology

2001 ISBN 0-471-89907-0

Rodney J.Y. Ho, Milo Gibaldi

Biotechnology and Biopharmaceuticals

Transforming Proteins and Genes into Drugs

2003 ISBN 0-471-20690-3

Chi-Huey Wong (Ed.)

Carbohydrate-based Drug Discovery

2003 ISBN 3-527-30632-3 Oliver Kayser, Rainer H. Müller (Eds.)

Pharmaceutical Biotechnology Drug Discovery and Clinical Applications

2004 ISBN 3-527-30554-8

Rainer Fischer, Stefan Schillberg (Eds.)

Molecular Farming
Plant-made Pharmaceuticals and Technical
Proteins

2004 ISBN 3-527-30786-9

Martin Schleef (Ed.)

DNA-Pharmaceuticals
Formulation and Delivery in Gene Therapy
and DNA Vaccination

2005 ISBN 3-527-31187-4

Rolf D. Schmid, Ruth Hammelehle

Pocket Guide to Biotechnology and Genetic Engineering

2003 ISBN 3-527-30895-4

Contents

Volume 1

Prologue XXV

Dedication XXIX

Foreword XXXI

Foreword XXXV

Quotes XXXVII

Executive Summary XLI

List of Contributors CXXIII

Introduction

Current Status of Biopharmaceuticals: Approved Products and Trends in Approvals 1

Gary Walsh

Part I Biopharmaceuticals Used in Molecular Medicine

From Genome to Clinic - Correlation Between Genes, Diseases and Biopharmaceuticals 37

- 1 Beginning to Understand the End of the Chromosome 37
 Thomas R. Cech
- The Role of Pharmacogenetics/Pharmacogenomics in Drug Development and Regulatory Review: Current Status 49
 Shiew-Mei Huang and Lawrence J. Lesko

Modern Biopharmaceuticals. Edited by J. Knäblein Copyright © 2005 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim ISBN: 3-527-31184-X

Co	и	to	n	+
CU	rı	LE	rı	ν.

- 3 Large-scale Detection of Genetic Variation: The Key to Personalized Medicine 71 Joerg Geistlinger and Peter Ahnert
- 4 A Systems Biology Approach to Target Identification and Validation for Human Chronic Disease Drug Discovery 99

 Bonnie E. Gould Rothberg, Carol E. A. Peña, and Jonathan M. Rothberg
- The Development of Herceptin®:
 Paving the Way for Individualized Cancer Therapy
 Thorsten S. Gutjahr and Carsten Reinhardt

siRNA - the Magic Bullet and Other Gene Therapeutical Approaches 151

- Adenovirus-based Gene Therapy: Therapeutic Angiogenesis
 with Adenovirus 5 Fibroblast Growth Factor-4 (Ad5FGF-4) in Patients
 with Chronic Myocardial Ischemia 151
 Michael McCaman, Francisco J. Castillo, Farah Fawaz, Yasushi Ogawa, Erik Whiteley,
 Elisabeth Lehmberg, Mei Tan, Jacob Kung, Bruce Mann, Erno Pungor Jr.,
 and Gabor M. Rubanyi
- 7 MIDGE Vectors and dSLIM Immunomodulators:
 DNA-based Molecules for Gene Therapeutic Strategies 183
 Manuel Schmidt, Barbara Volz, and Burghardt Wittig
- 8 Nonprotein-coding RNAs and their Potential as Biopharmaceuticals 213 Maciej Szymanski, Jan Barciszewski and Volker A. Erdmann
- 9 Double-stranded Decoy Oligonucleotides as new Biopharmaceuticals 229
 Andreas H. Wagner and Heiko E. von der Leyen
- Rational siRNA Design for RNA Interference:
 Optimizations for Therapeutic Use and Current Applications 243
 Anastasia Khvorova, Queta Boese, and William S. Marshall

Mobilis in Mobile - Human Embryonic Stem Cells and Other Sources for Cell Therapy 269

- 11 The First Cloned Human Embryo: An Unlimited Source of Stem Cells for Therapeutic Cloning 269 Woo Suk Hwang, Byeong Chun Lee, Sung Keun Kang, and Shin Yong Moon
- 12 Myocardial Regeneration Strategies using Human Embryonic Stem Cells 283

 12 Izhak Kehat, Oren Caspi, and Lior Gepstein 283
- 13 Gene and Cell-based Therapies for Cardiovascular Disease 305
 Abeel A. Mangi

14	Spheramine®: A Cell Therapeutic Approach to Parkinson's Disease	325
	Elke Reissig, Hermann Graf, and Friedrich-Joachim Kapp	

15 Applying Human Cells to Organogenesis and Transplantation 353 Benjamin Dekel and Yair Reisner

Volume 2

Part II Biopharmaceuticals and Their Mode of Action

Quid pro Quo - Lysis vs. Coagulation in the Fine-tuned Balance of the Clotting Cascade 377

- 1 Mechanisms of Serine Proteinase Activation: Insights for the Development of Biopharmaceuticals for Coagulation and Fibrinolysis 377 Rainer Friedrich
- 2 Application of the Principle of Polyvalency to Protease Inhibition 395 Luis Moroder
- A New Technology Standard for Safety and Efficacy in Factor VIII Replacement Therapy: 3 Designing an Advanced Category rFVIII Concentrate 419 Norbert Riedel and Friedrich Dorner

Errare Humanum Est - What Causes Cancer and How to Selectively Fight Tumors 451

- Biopharmaceutical Drugs from Natural Sources 451 4 David J. Newman, Gordon M. Cragg, and Barry R. O'Keefe
- 5 Biopharmaceuticals as Targeting Vehicles for In situ Radiotherapy of Malignancies 497 Raymond M. Reilly
- 6 New Directions in Tumor Therapy -Amino Acid Deptetion with GlutaDON® as Treatment for Cancer 537 Rolf Kalhammer and Natarajan Sethuraman

Mundus Vult Decipi - High Mutation Rates of HIV and New Paradigms for Treatment 549

- 7 AIDS Gene Therapy: A Vector Selectively Able to Destroy Latently HIV-1-infected Cells 549 Francisco Luque Vázquez and Ricardo Oya
- 8 Combinatorial RNA-based Therapies for HIV-1 569 Kevin V. Morris and John J. Rossi

Part III Improving the Development of Biopharmaceuticals

Citius, Altius, Fortius - Acceleration by High Throughput and Ultra-HT 583

- 1 Design of Modern Biopharmaceuticals by Ultra-high-throughput Screening and Directed Evolution 583 Markus Rarbach, Wayne M. Coco, Andre Koltermann, Ulrich Kettling, and Manfred Eigen
- Learning from Viruses: High-throughput Cloning using the Gateway® System 2 to Transfer Genes without Restriction Enzymes 605 Jonathan D. Chesnut

In Vivo Veritas - Early Target Validation in Knock-out Mice and More 621

- 3 Target Validation: An Important Early Step in the Development of Novel Biopharmaceuticals in the Post-genomic Era 621 Christoph P. Bagowski
- Genetically Modified Mice in Medical and Pharmaceutical Research 649 4 Cord Brakebusch
- 5 An NIH Model Organism for Biopharmaceutical and Biomedical Research: The Lower Eukaryote Dictyostelium discoideum 661 Thomas Winckler, Ilse Zündorf, and Theodor Dingermann

Revolution by Evolution - Rational Design for Desire and Scientific Art of Optimization 695

- 6 Releasing the Spring: Cofactor- and Substrate-assisted Activation of Factor IXa 695 Hans Brandstetter and Katrin Sichler
- 7 Accelerating Diagnostic Product Development Process with Molecular Rational Design and Directed Evolution 703 Harald Sobek, Rainer Schmuck, and Zhixin Shao

Volume 3

Part IV Production of Biopharmaceuticals

The Industry's Workhorses – Mammalian Expression Systems 723

1 Manufacture of Recombinant Biopharmaceutical Proteins by Cultivated Mammalian Cells in Bioreactors 723 Florian M. Wurm

- 2 Alternative Strategies and New Cell Lines for High-level Production of Biopharmaceuticals 761 Thomas Rose, Karsten Winkler, Elisabeth Brundke, Ingo Jordan and Volker Sandig
- 3 PER.C6[®] Cells for the Manufacture of Biopharmaceutical Proteins 779 Chris Yallop, John Crowley, Johanne Cote, Kirsten Hegmans-Brouwer, Fija Lagerwerf, Rodney Gagne, Jose Coco Martin, Nico Oosterhuis, Dirk-Jan Opstelten, and Ahraham Bout
- 4 Use of the Glutamine Synthetase (GS) Expression System for the Rapid Development of Highly Productive Mammalian Cell Processes 809 John R. Birch, David O. Mainwaring, and Andrew J. Racher

Vivat, Crescat, Floreat - A Ripe and Blooming Market for Transgenic Animals and Plants 833

- 5 Biopharmaceuticals Derived from Transgenic Plants and Animals 833 Iulio Baez
- Production of Recombinant Proteins in Plants 893 6 Victor Klimyuk, Sylvestre Marillonnet, Jörg Knäblein, Michael McCaman, and Yuri Gleba
- 7 Humanized Glycosylation: Production of Biopharmaceuticals in a Moss Bioreactor 919 Gilbert Gorr and Sabrina Wagner
- ExpressTec: High-level Expression of Biopharmaceuticals in Cereal Grains 931 8 Ning Huang and Daichang Yang
- Biopharmaceutical Production in Cultured Plant Cells 949 9 Stefan Schillberg, Richard M. Twyman, and Rainer Fischer
- 10 Producing Biopharmaceuticals in the Desert: Building an Abiotic Stress Tolerance in Plants for Salt, Heat, and Drought 967 Shimon Gepstein, Anil Grover, and Eduardo Blumwald
- 11 The First Biopharmaceutical from Transgenic Animals: ATryn® Yann Echelard, Harry M. Meade, and Carol A. Ziomek

Alea Non lacta Est - Improving Established Expression Systems 1021

Producing Modern Biopharmaceuticals: The Bayer HealthCare Pharma Experience 12 with a Range of Expression Systems 1021 Heiner Apeler

- Advanced Expression of Biopharmaceuticals in Yeast at Industrial Scale: 13 The Insulin Success Story 1033 Asser Sloth Andersen and Ivan Diers
- 14 Baculovirus-based Production of Biopharmaceuticals using Insect Cell Culture Processes 1045 Wilfried Weber and Martin Fussenegger
- 15 Robust and Cost-effective Cell-free Expression of Biopharmaceuticals: Escherichia Coli and Wheat Embryo 1063 Luke Anthony Miles

When Success Raises its Ugly Head - Outsourcing to Uncork the Capacity Bottleneck 1083

16 Contract Manufacturing of Biopharmaceuticals Including Antibodies or Antibody Fragments 1083 J. Carsten Hempel and Philipp N. Hess

Part V Biopharmaceuticals used for Diagnositics and Imaging

From Hunter to Craftsman - Engineering Antibodies with Nature's Universal Toolbox 1105

- 1 Thirty Years of Monoclonal Antibodies: A Long Way to Pharmaceutical and Commercial Success 1105 Uwe Gottschalk and Kirsten Mundt
- 2 Modern Antibody Technology: The Impact on Drug Development 1147 Simon Moroney and Andreas Plückthun
- 3 Molecular Characterization of Autoantibody Responses in Autoimmune Diseases: Implications for Diagnosis and Understanding of Autoimmunity 1187 Constanze Breithaupt

Find, Fight, and Follow - Target-specific Troika from Mother Nature's Pharmacopoiea 1211

- 4 Molecular Imaging and Applications for Pharmaceutical R&D 1211 Joke G. Orsel and Tobias Schaeffter
- 5 Design and Development of Probes for In vivo Molecular and Functional Imaging of Cancer and Cancer Therapies by Positron Emission Tomography (PET) 1243 Eric O. Aboagye
- 6 Ligand-based Targeting of Disease: From Antibodies to Small Organic (Synthetic) Ligands 1271 Michela Silacci and Dario Neri

7 Ultrasound Theranostics: Antibody-based Microbubble Conjugates as Targeted In vivo Contrast Agents and Advanced Drug Delivery Systems 1301
Andreas Briel, Michael Reinhardt, Mathias Mäurer, and Peter Hauff

Getting Insight - Sense the Urgency for Early Diagnostics 1325

- 8 Development of Multi-marker-based Diagnostic Assays with the ProteinChip®

 System 1325

 Andreas Wiesner
- 9 Early Detection of Lung Cancer: Metabolic Profiling of Human Breath with Ion Mobility Spectrometers 1343 Jörg Ingo Baumbach, Wolfgang Vautz, Vera Ruzsanyi, and Lutz Freitag

Volume 4

Part VI Advanced Application Routes for Biopharmaceuticals

Getting Inside - Quest for the Best and How to Improve Delivery 1361

- 1 Advanced Drug Delivery Systems for Biopharmaceuticals 1361 Gesine E. Hildebrand and Stephan Harnisch
- 1.1 Introduction 1362
- 1.2 Challenges for the Administration of Biopharmaceuticals 1363
- 1.3 Drug Delivery Strategies 1366
- 1.4 Outlook 1384

Pathfinder - New Ways for Peptides, Proteins and Co 1393

- Poly(ethylene) Glycol Conjugates of Biopharmaceuticals in Drug Delivery 1393 Michael D. Bentley, Mary J. Bossard, Kevin W. Burton, and Tacey X. Viegas
- 2.1 Introduction 1394
- 2.2 The Polymer 1394
- 2.3 Safety and Disposition of PEG 1396
- 2.4 PEG Reagents and Conjugation 1397
- 2.5 Biopharmaceutical Conjugates 1400
- 2.6 PEGylation of Peptides 1407
- 2.7 Formulations of PEGylated Biopharmaceuticals 1408
- 2.8 Analysis of PEG-conjugates 1411
- 2.9 Summary and Future Outlook 1415
- Novel Vaccine Adjuvants Based on Cationic Peptide Delivery Systems 1419
 Karen Lingnau, Christoph Klade, Michael Buschle, and Alexander von Gabain
- 3.1 Vaccines and their Importance in the Fight against Human Diseases 1420

XII	Conte	nts
'	3.2	

3.2 3.3 3.4 3.5	Adjuvants: An Overview 1423 Cationic Peptides as Novel Vaccine Adjuvants 1426 Cationic Antimicrobial Peptides (CAMP) as Novel Adjuvants 1433 Cationic Peptide Delivery Systems in Combination with Other Adjuvants 1437
3.6 3.7	The Development of IC31 and Future Prospects 1440 Conclusions 1440
4	The Evolving Role of Oralin TM (Oral Spray Insulin) in the Treatment of Diabetes using a Novel RapidMist TM Diabetes Management System 1445 Pankaj Modi
4.1	Introduction 1446
4.2	Rationale for Oralin TM Development 1446
4.3	The Benefits of Oralin TM 1447
4.4	The Preparation and Pharmaceutical Properties of Oralin TM 1448
4.5	Phase II, Long-term Safety and Efficacy Study 1457
4.6	Conclusions 1460
4.0	Conclusions 1400
-	to the state of th
5	Improvement of Intestinal Absorption of Peptide and Protein Biopharmaceuticals by Various Approaches 1463 Akira Yamamoto
5.1	Improvement of Peptide and Protein Absorption 1464
5.2	Use of Protease Inhibitors 1467
5.3	Chemical Modification of Peptide and Protein Biopharmaceuticals 1472
5.4	Chitosan Capsules for the Colon-specific Delivery of Insulin 1480
5.3	Conclusion 1484
9,5	Conclusion 1464
Via Ma	lla – the Stoney Road of DNA Delivery: Back-pack, Feed-back, and Pay-back 1487
6	DNA Vaccine Delivery from Poly(ortho ester) Microspheres 1487
	Chun Wang, Herman N. Eisen, Robert Langer, and Jorge Hellen
6.1	Introduction 1488
6.1 6.2	
	Introduction 1488
6.2	Introduction 1488 Poly(Ortho Esters) 1494 Preparation and Characterization of Microspheres 1496
6.2 6.3 6.4	Introduction 1488 Poly(Ortho Esters) 1494 Preparation and Characterization of Microspheres 1496 In vivo Evaluation of Immune Responses 1500
6.2 6.3	Introduction 1488 Poly(Ortho Esters) 1494 Preparation and Characterization of Microspheres 1496 In vivo Evaluation of Immune Responses 1500
6.2 6.3 6.4	Introduction 1488 Poly(Ortho Esters) 1494 Preparation and Characterization of Microspheres 1496 In vivo Evaluation of Immune Responses 1500 Concluding Remarks 1503 Liposomal In vivo Gene Delivery 1507 Shigeru Kawakami, Fumiyoshi Yamashita, and Mitsuru Hashida
6.2 6.3 6.4 6.5	Introduction 1488 Poly(Ortho Esters) 1494 Preparation and Characterization of Microspheres 1496 In vivo Evaluation of Immune Responses 1500 Concluding Remarks 1503 Liposomal In vivo Gene Delivery 1507 Shigeru Kawakami, Fumiyoshi Yamashita, and Mitsuru Hashida Cationic Charge-mediated In vivo Gene Transfer to the Lung 1510
6.2 6.3 6.4 6.5	Introduction 1488 Poly(Ortho Esters) 1494 Preparation and Characterization of Microspheres 1496 In vivo Evaluation of Immune Responses 1500 Concluding Remarks 1503 Liposomal In vivo Gene Delivery 1507 Shigeru Kawakami, Fumiyoshi Yamashita, and Mitsuru Hashida
6.2 6.3 6.4 6.5 7	Introduction 1488 Poly(Ortho Esters) 1494 Preparation and Characterization of Microspheres 1496 In vivo Evaluation of Immune Responses 1500 Concluding Remarks 1503 Liposomal In vivo Gene Delivery 1507 Shigeru Kawakami, Fumiyoshi Yamashita, and Mitsuru Hashida Cationic Charge-mediated In vivo Gene Transfer to the Lung 1510 Asialoglycoprotein Receptor-mediated In vivo Gene Transfer to Hepatocytes 1512
6.2 6.3 6.4 6.5 7 7.1 7.2	Introduction 1488 Poly(Ortho Esters) 1494 Preparation and Characterization of Microspheres 1496 In vivo Evaluation of Immune Responses 1500 Concluding Remarks 1503 Liposomal In vivo Gene Delivery 1507 Shigeru Kawakami, Fumiyoshi Yamashita, and Mitsuru Hashida Cationic Charge-mediated In vivo Gene Transfer to the Lung 1510 Asialoglycoprotein Receptor-mediated In vivo Gene Transfer to Hepatocytes 1512 Mannose Receptor-mediated In vivo Gene Transfer to Macrophages 1513
6.2 6.3 6.4 6.5 7 7.1 7.2 7.3 7.4	Introduction 1488 Poly(Ortho Esters) 1494 Preparation and Characterization of Microspheres 1496 In vivo Evaluation of Immune Responses 1500 Concluding Remarks 1503 Liposomal In vivo Gene Delivery 1507 Shigeru Kawakami, Fumiyoshi Yamashita, and Mitsuru Hashida Cationic Charge-mediated In vivo Gene Transfer to the Lung 1510 Asialoglycoprotein Receptor-mediated In vivo Gene Transfer to Hepatocytes 1512 Mannose Receptor-mediated In vivo Gene Transfer to Macrophages 1513 Folate Receptor-mediated In vivo Gene Transfer to Cancer Cells 1515
6.2 6.3 6.4 6.5 7 7.1 7.2 7.3	Introduction 1488 Poly(Ortho Esters) 1494 Preparation and Characterization of Microspheres 1496 In vivo Evaluation of Immune Responses 1500 Concluding Remarks 1503 Liposomal In vivo Gene Delivery 1507 Shigeru Kawakami, Fumiyoshi Yamashita, and Mitsuru Hashida Cationic Charge-mediated In vivo Gene Transfer to the Lung 1510 Asialoglycoprotein Receptor-mediated In vivo Gene Transfer to Hepatocytes 1512 Mannose Receptor-mediated In vivo Gene Transfer to Macrophages 1513 Folate Receptor-mediated In vivo Gene Transfer to Cancer Cells 1515

8	Programmed Packaging:
	A New Drug Delivery System and its Application to Gene Therapy 1521
	Kentaro Kogure, Hidetaka Akita, Hiroyuki Kamiya, and Hideyoshi Harashima
8.1	New Concept for Gene Delivery 1521
8.2	Controlled Intracellular Trafficking 1525
8.3	Transgene Expression and Gene Correction 1531
8.4	Towards Clinical Applications of Transgene Expression
	and Gene Correction 1534
Getting	Beyond – Rocket Science vs. Science Fiction 1537
9	Bionanotechnology and its Role to Improve Biopharmaceuticals 1537 Oliver Kayser
9.1	Introduction 1537
9.2	Drug and Gene Delivery 1539
9.3	Gene Delivery 1543
9.4	Biosensors 1544
9.5	Implants and Tissue Engineering 1546
9.8	Safety Aspects 1548
9.7	Conclusions and Future Trends 1550
Part VI	From Transcription to Prescription of Biopharmaceuticals
	Facit Venenum – The Therapeutic Window between Systemic Toxicity ck of Efficacy 1557
	Analytics in Quality Control and In vivo 1557
and Lad	Analytics in Quality Control and In vivo 1557 Michael Hildebrand
and Lac 1 1.1	Analytics in Quality Control and In vivo 1557 Michael Hildebrand Introduction 1558
1 1.1 1.2	Analytics in Quality Control and In vivo 1557 Michael Hildebrand Introduction 1558 Quality Control 1559
1 1.1 1.2 1.3	Analytics in Quality Control and In vivo 1557 Michael Hildebrand Introduction 1558 Quality Control 1559 Classes of Biopharmaceuticals 1560
1 1.1 1.2 1.3 1.4	Analytics in Quality Control and In vivo 1557 Michael Hildebrand Introduction 1558 Quality Control 1559 Classes of Biopharmaceuticals 1560 Analytical Methods and Specifications 1560
1.1 1.2 1.3 1.4 1.5	Analytics in Quality Control and In vivo 1557 Michael Hildebrand Introduction 1558 Quality Control 1559 Classes of Biopharmaceuticals 1560 Analytical Methods and Specifications 1560 International Guidelines on Quality Control 1571
1.1 1.2 1.3 1.4 1.5 1.6	Analytics in Quality Control and In vivo 1557 Michael Hildebrand Introduction 1558 Quality Control 1559 Classes of Biopharmaceuticals 1560 Analytical Methods and Specifications 1560 International Guidelines on Quality Control 1571 Analytics In vivo 1573
1.1 1.2 1.3 1.4 1.5	Analytics in Quality Control and In vivo 1557 Michael Hildebrand Introduction 1558 Quality Control 1559 Classes of Biopharmaceuticals 1560 Analytical Methods and Specifications 1560 International Guidelines on Quality Control 1571 Analytics In vivo 1573
1.1 1.2 1.3 1.4 1.5 1.6	Analytics in Quality Control and In vivo 1557 Michael Hildebrand Introduction 1558 Quality Control 1559 Classes of Biopharmaceuticals 1560 Analytical Methods and Specifications 1560 International Guidelines on Quality Control 1571 Analytics In vivo 1573 Conclusions 1577 Design, Development and Optimization: Crystal Structures of Microsomal Cytochromes P450 1581 Dijana Matak Vinković, Sheena Whyte, Harren Jhoti, Jose Cosme,
and Lac 1 1.1 1.2 1.3 1.4 1.5 1.6 1.7	Analytics in Quality Control and In vivo 1557 Michael Hildebrand Introduction 1558 Quality Control 1559 Classes of Biopharmaceuticals 1560 Analytical Methods and Specifications 1560 International Guidelines on Quality Control 1571 Analytics In vivo 1573 Conclusions 1577 Design, Development and Optimization: Crystal Structures of Microsomal Cytochromes P450 1581 Dijana Matak Vinković, Sheena Whyte, Harren Jhoti, Jose Cosme, and Pamela A. Williams
and Lac 1 1.1 1.2 1.3 1.4 1.5 1.6 1.7 2	Analytics in Quality Control and In vivo 1557 Michael Hildebrand Introduction 1558 Quality Control 1559 Classes of Biopharmaceuticals 1560 Analytical Methods and Specifications 1560 International Guidelines on Quality Control 1571 Analytics In vivo 1573 Conclusions 1577 Design, Development and Optimization: Crystal Structures of Microsomal Cytochromes P450 1581 Dijana Matak Vinković, Sheena Whyte, Harren Jhoti, Jose Cosme, and Pamela A. Williams P450: The Background 1581
and Lac 1 1.1 1.2 1.3 1.4 1.5 1.6 1.7 2 2.1 2.2	Analytics in Quality Control and In vivo 1557 Michael Hildebrand Introduction 1558 Quality Control 1559 Classes of Biopharmaceuticals 1560 Analytical Methods and Specifications 1560 International Guidelines on Quality Control 1571 Analytics In vivo 1573 Conclusions 1577 Design, Development and Optimization: Crystal Structures of Microsomal Cytochromes P450 1581 Dijana Matak Vinković, Sheena Whyte, Harren Jhoti, Jose Cosme, and Pamela A. Williams P450: The Background 1581 Importance of P450s for Drug Development 1582
and Lac 1 1.1 1.2 1.3 1.4 1.5 1.6 1.7 2 2.1 2.2 2.3	Analytics in Quality Control and In vivo 1557 Michael Hildebrand Introduction 1558 Quality Control 1559 Classes of Biopharmaceuticals 1560 Analytical Methods and Specifications 1560 International Guidelines on Quality Control 1571 Analytics In vivo 1573 Conclusions 1577 Design, Development and Optimization: Crystal Structures of Microsomal Cytochromes P450 1581 Dijana Matak Vinković, Sheena Whyte, Harren Jhoti, Jose Cosme, and Pamela A. Williams P450: The Background 1581 Importance of P450s for Drug Development 1582 Variability and Drug Metabolism 1583
and Lac 1 1.1 1.2 1.3 1.4 1.5 1.6 1.7 2 2.1 2.2	Analytics in Quality Control and In vivo 1557 Michael Hildebrand Introduction 1558 Quality Control 1559 Classes of Biopharmaceuticals 1560 Analytical Methods and Specifications 1560 International Guidelines on Quality Control 1571 Analytics In vivo 1573 Conclusions 1577 Design, Development and Optimization: Crystal Structures of Microsomal Cytochromes P450 1581 Dijana Matak Vinković, Sheena Whyte, Harren Jhoti, Jose Cosme, and Pamela A. Williams P450: The Background 1581 Importance of P450s for Drug Development 1582

5.6

5.7

5.8

5.9

Content	S
3	Mettox TM : A Suite of Predictive <i>In silico</i> and <i>In vitro</i> Assays for Metabolic and Genotoxicological Profiling of Preclinical Drug Candidates 1603 Michael Murray
3.1	Issues and Economics of Early ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) Assessment 1604
3.2	Phase I Metabolism Prediction: Computational Approaches 1608
3.3	Phase I Metabolism Prediction: <i>In vitro</i> Techniques 1613
3.4	Genotoxicity Prediction 1624
3.5	Conclusions 1634
Нарру	End: Claim to Fame and Approval 1637
4	Considerations for Developing Biopharmaceuticals: FDA Perspective 1637
	Kurt Brorson, Patrick G. Swann, Janice Brown, Barbara Wilcox,
4.1	and Marjorie A. Shapiro
4.1	Introduction 1638
4.2	Regulatory Authority 1639
4.3	Overview of Product Development: CMC Perspective 1643
4.4	Chemistry, Manufacturing and Controls Considerations 1645
4.5	Quality Control and Assurance 1647
4.6	Microbial Issues Specific to Biopharmaceuticals 1650 Process Validation 1653
4.7	
4.8	Inspectional Considerations 1653
4.9	Biotech Development: Lessons Learned and Issues Overcome by Industry and FDA 1654
4.10	FDA Initiatives to Improve the Pharmaceutical and Biopharmaceutical
	Development Process 1661
5	The Regulatory Environment for Biopharmaceuticals in the EU 1669
	Axel F. Wenzel and Carina E. A. Sonnega
5.1	Introduction 1673
5.2	History and Background 1673
5.3	The Competent Regulatory Bodies 1676
5.4	What is the EU Authorities' Definition of a Biotechnological Product? 1681
5.5	The Regulatory Framework 1682

CP: The "Biotech" Procedure 1683

From Transcription to Prescription:

Conclusions and Outlook 1701

Biogenerics 1700

What is Different for Biotechnological Drugs? 1688

Part VIII From Bench to Bedside - The Aftermaths

Think Big and Dealmaking for Growth - G	llobal Changes in the Health-care Sector 1	711
---	--	-----

1	Healthcare Trends and their Impact on the Biopharmaceutical Industry:
	Biopharmaceuticals Come of Age 1711
	Alexander Moscho, Markus A. Schäfer, and Kristin Yarema

- 1.1 Introduction 1712
- 1.2 Despite Robust Demand the Industry Faces Severe Challenges 1713
- 1.3 Why Biopharmaceuticals can Succeed in Rougher Markets 1724
- 1.4 Biopharmaceutical Players Will Need to Adapt their Portfolios and Business Models 1728
- 1.5 Conclusions and Outlook 1738

News and Views - Quo Vadis, Biopharmaceuticals? 1741

- 2 mondoBIOTECH: The Swiss biotech BOUTIQUE 1741 Dorian Bevec and Fabio Cavalli
- 2.1 Introduction
- 2.2 Product Platforms 1742
- 2.3 Interferon-y + Genechip 1750
- 2.4 Bacteriophages 1751
- 2.5 Outlook for the Company 1752
- 3 G-CSF and Bioequivalence: The Emergence of Healthcare Economics 1755 James Harris, III
- Introduction 1756 3.1
- 3.2 Biogenerics and Bioequivalence 1756
- Summary and Outlook 3.3

Light at the End of the Tunnel or Back to the Roots? 1771

- Bioinformatics: From Peptides to Profiled Leads 1771 4 Paul Wrede and Matthias Filter
- 4.1 Introduction 1772
- 4.2 Basic Concepts of Virtual Drug Discovery 1773
- Pep2Lead Concept 1778 4.3
- 4.4 ADMETox Profiling 1785
- 4.5 Outlook 1798
- 5 Engineering and Overproduction of Polyketide Natural Products 1803 Martha Lovato Tse and Chaitan Khosla
- 5.1 Introduction 1804
- 5.2 Polyketide Synthases 1806

XVI | Contents

5.3 Engineering PKSs to Produce Novel Polyketides 1815

5.4 Development of Scalable Production Processes 1820

5.5 Conclusions 1825

Epilog 1833

More about the Editor 1835

Supplement CD-ROM 1837

Subject Index 1841