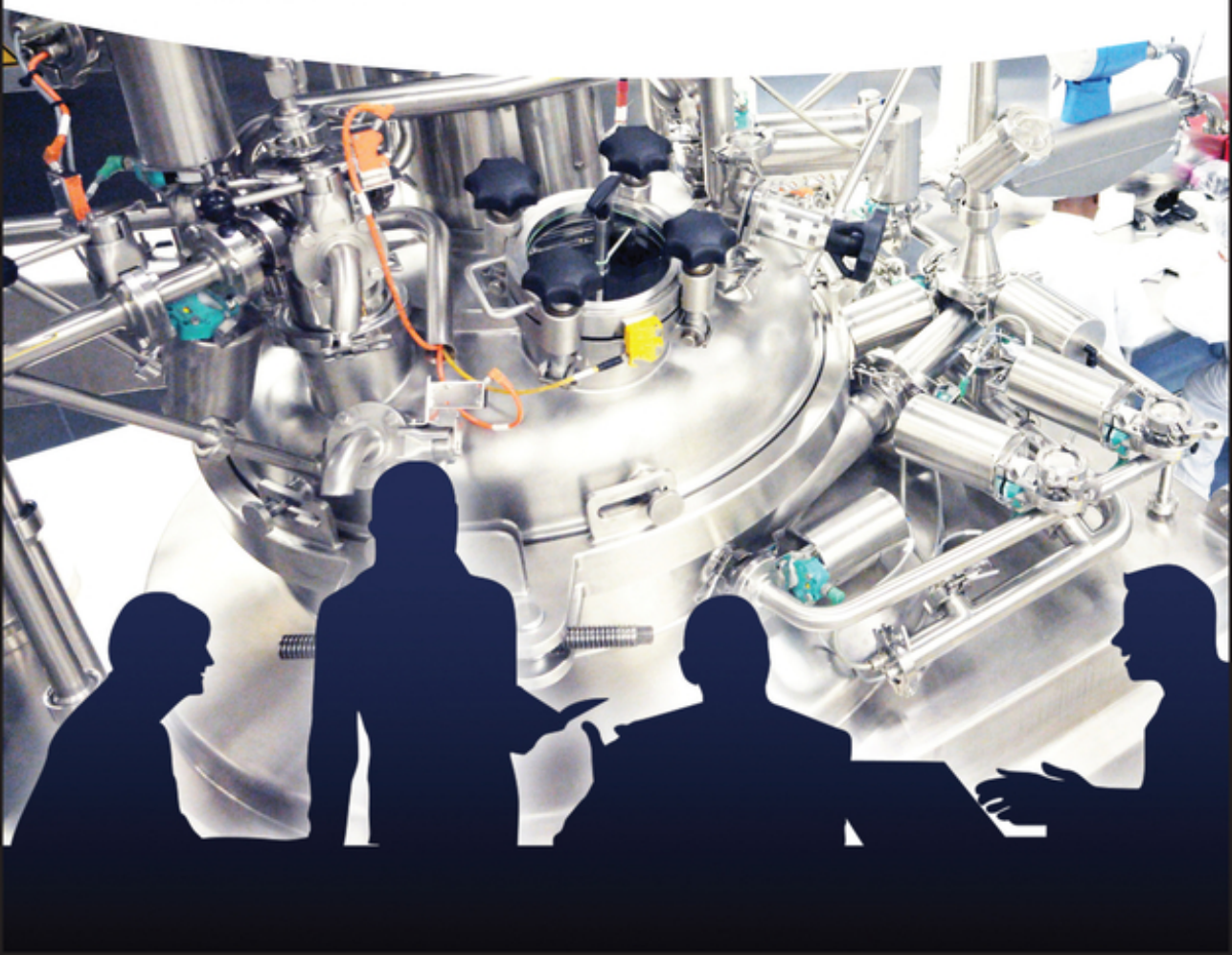


Stefan Behme

Manufacturing of Pharmaceutical Proteins

From Technology to Economy

Third Edition



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**Manufacturing of Pharmaceutical
Proteins**

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From Technology to Economy

Third Edition

WILEY-VCH

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Cover Design: Wiley

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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 on the Internet at <http://dnb.d-nb.de>.

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Print ISBN: 978-3-527-34947-0

ePDF ISBN: 978-3-527-83379-5

ePub ISBN: 978-3-527-83380-1

oBook ISBN: 978-3-527-83381-8

Typesetting Straive, Chennai, India
Printing and Binding

Printed on acid-free paper

10 9 8 7 6 5 4 3 2 1

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Contents

Preface to Third Edition *xvii*

Preface to First Edition *xix*

List of Abbreviations *xxi*

Part I Introduction *1*

| | | |
|----------|--|----------|
| 1 | Biopharmaceutical Production: Value Creation, Product Types, and Biological Basics Introduction | 3 |
| 1.1 | Role of Production in Pharmaceutical Biotechnology | 3 |
| 1.1.1 | Relationship Between Production and Development | 6 |
| 1.1.2 | Relationship Between Production and Marketing | 8 |
| 1.2 | Product Groups | 10 |
| 1.2.1 | Vaccines | 12 |
| 1.2.2 | Pharmaceuticals from Blood and Organs | 12 |
| 1.2.3 | Recombinant Therapeutic Proteins | 13 |
| 1.2.4 | Cell and Gene Therapeutics | 13 |
| 1.2.5 | Antibiotics | 16 |
| 1.3 | Basics of Biology | 16 |
| 1.3.1 | Cells and Microorganisms | 16 |
| 1.3.1.1 | Structure and Types of Cells | 17 |
| 1.3.1.2 | Metabolism | 19 |
| 1.3.1.3 | Reproduction and Aging | 21 |
| 1.3.1.4 | Viruses and Bacteriophages | 22 |
| 1.3.1.5 | Protein Biosynthesis | 23 |
| 1.3.2 | The Four Molecular Building Blocks of Biochemistry | 25 |
| 1.3.2.1 | Proteins | 25 |
| 1.3.2.2 | Nucleic Acids | 29 |
| 1.3.2.3 | Polysaccharides | 30 |
| 1.3.2.4 | Lipids | 31 |

Part II Technology 33

| | |
|----------|---|
| 2 | Manufacturing Process 35 |
| 2.1 | Role of the Manufacturing Process in Biotechnology 35 |
| 2.2 | Process Schematic and Evaluation 37 |
| 2.2.1 | Drug Substance Manufacturing 38 |
| 2.2.2 | Drug Product Manufacturing 40 |
| 2.2.3 | Key Factors for Process Evaluation 41 |
| 2.3 | Cell Bank 43 |
| 2.3.1 | Expression Systems 43 |
| 2.3.2 | Microbial Systems 44 |
| 2.3.2.1 | Mammalian Systems 45 |
| 2.3.2.2 | Transgenic Systems 46 |
| 2.3.3 | Manufacturing and Storage of the Cell Bank 46 |
| 2.4 | Fermentation 48 |
| 2.4.1 | Basic Principles 48 |
| 2.4.1.1 | Cell Growth and Product Expression 49 |
| 2.4.1.2 | Comparison of Batch and Continuous Processes 50 |
| 2.4.1.3 | Sterility and Sterile Technology 53 |
| 2.4.1.4 | Comparison of Fermentation with Mammalian Cells and Microorganisms 55 |
| 2.4.2 | Technologies and Equipment 56 |
| 2.4.2.1 | Fermentation in Suspension Culture 56 |
| 2.4.2.2 | Adherent Cell Cultures 57 |
| 2.4.2.3 | Transgenic Systems 60 |
| 2.4.3 | Raw Materials and Processing Aids 61 |
| 2.4.3.1 | Nutrient Media 61 |
| 2.4.3.2 | Water, Gases, and Other Processing Aids 62 |
| 2.4.4 | Overview of Fermentation 63 |
| 2.5 | Purification 64 |
| 2.5.1 | Basic Principles 65 |
| 2.5.1.1 | Basic Pattern of Purification 65 |
| 2.5.1.2 | Types of Impurities 68 |
| 2.5.1.3 | Principles of Separation Technologies 71 |
| 2.5.2 | Technologies for Cell Separation and Product Isolation 73 |
| 2.5.2.1 | Cell Separation 73 |
| 2.5.2.2 | Cell Disruption, Solubilization, and Refolding 74 |
| 2.5.2.3 | Concentration and Stabilization 75 |
| 2.5.3 | Technologies for Final Purification 80 |
| 2.5.3.1 | Chromatographic Processes 81 |
| 2.5.3.2 | Precipitation and Extraction 89 |
| 2.5.3.3 | Sterile Filtration and Virus Removal 90 |
| 2.5.4 | Raw Materials and Processing Aids 91 |
| 2.5.4.1 | Gels for Chromatography 91 |

| | | |
|----------|---|------------|
| 2.5.4.2 | Membranes for TFF | 93 |
| 2.5.5 | Overview of Purification | 94 |
| 2.6 | Formulation and Filling | 96 |
| 2.6.1 | Basic Principles | 96 |
| 2.6.2 | Freeze-Drying | 98 |
| 2.7 | Labeling and Packaging | 99 |
| 3 | Analytics | 103 |
| 3.1 | Role of Analytics in Biotechnology | 103 |
| 3.2 | Product Analytics | 105 |
| 3.2.1 | Identity | 107 |
| 3.2.2 | Content | 107 |
| 3.2.3 | Purity | 109 |
| 3.2.4 | Activity | 109 |
| 3.2.5 | Appearance | 112 |
| 3.2.6 | Stability | 112 |
| 3.2.7 | Quality Criteria of Analytical Methods | 114 |
| 3.2.8 | Analytical Methods | 115 |
| 3.2.8.1 | Amino Acid Analysis | 116 |
| 3.2.8.2 | Protein Sequencing | 116 |
| 3.2.8.3 | Peptide Mapping | 117 |
| 3.2.8.4 | Protein Content | 117 |
| 3.2.8.5 | Electrophoresis | 118 |
| 3.2.8.6 | Western Blot | 120 |
| 3.2.8.7 | HCP Enzyme-Linked Immunosorbent Assay (ELISA) | 122 |
| 3.2.8.8 | Analytical Chromatography | 123 |
| 3.2.8.9 | Infrared (IR) Spectroscopy | 125 |
| 3.2.8.10 | UV/Vis Spectroscopy | 125 |
| 3.2.8.11 | Mass Spectrometry | 126 |
| 3.2.8.12 | Glycoanalytics | 127 |
| 3.2.8.13 | PCR | 127 |
| 3.2.8.14 | DNA/RNA Sequencing | 128 |
| 3.2.8.15 | Endotoxins and Pyrogen Testing | 129 |
| 3.2.8.16 | Bioburden Test | 130 |
| 3.2.8.17 | Virus Testing | 130 |
| 3.2.8.18 | TEM | 131 |
| 3.2.8.19 | Circular Dichroism | 131 |
| 3.2.8.20 | Differential Scanning Calorimetry | 131 |
| 3.3 | Process Analytics | 132 |
| 3.3.1 | Fermentation | 132 |
| 3.3.2 | Purification | 133 |
| 3.3.3 | Formulation and Packaging | 134 |
| 3.4 | Environmental Monitoring | 135 |
| 3.5 | Raw Material Testing | 137 |
| 3.6 | Product Comparability | 138 |

Part III Pharmacy 141

- 4 Pharmacology and Drug Safety 143**
 - 4.1 Action of Drugs in Humans 144
 - 4.1.1 Pharmacokinetics 145
 - 4.1.2 Pharmacodynamics 149
 - 4.1.2.1 Principles of Phenomenological Effects 149
 - 4.1.2.2 Parameters of Drug Effects 150
 - 4.2 Routes and Forms of Administration 152
 - 4.3 Drug Study 153
 - 4.3.1 Pre-Clinical Study 155
 - 4.3.2 Clinical Study 157
 - 4.3.2.1 Phases of Clinical Studies 157
 - 4.3.2.2 Design and Conduct of Clinical Trials 160
 - 4.4 Path of the Drug from the Manufacturer to Patients 162
 - 4.5 Drug Safety 164
 - 4.5.1 Causes and Classification of Side Effects 165
 - 4.5.2 Methods for Supervising Drug Safety (Pharmacovigilance) 167
 - 4.5.3 Measures upon Incidence of Adverse Reactions 168

Part IV Quality Assurance 171

- 5 Fundamentals of Quality Assurance 173**
 - 5.1 Basic Principles 173
 - 5.2 Benefit of Quality Assurance Activities 174
 - 5.3 Quality Management According to ISO 9000 175
 - 5.3.1 Fields of Activity 176
 - 5.4 Structure of Quality Management Systems 178
 - 5.5 Quality Management System Components in the Pharmaceutical Area 180
 - 5.5.1 Documentation 180
 - 5.5.2 Failure Prevention and Correction 181
 - 5.5.3 Responsibility of Management and Training of Personnel 186
 - 5.5.4 Audits 186
 - 5.5.5 External Suppliers 187
 - 5.5.6 Contract Review 188
 - 5.6 Quality Assurance in Development 189
- 6 Quality Assurance in Manufacturing 191**
 - 6.1 GMP 191
 - 6.1.1 Personnel 196
 - 6.1.2 Premises and Equipment 198
 - 6.1.2.1 Measures to Avoid External Contamination 198

| | | |
|---------|---|-----|
| 6.1.2.2 | Measures to Avoid Cross-Contamination and Product Confusion | 201 |
| 6.1.3 | Equipment Qualification | 203 |
| 6.1.4 | Process Validation | 206 |
| 6.1.5 | Computer Validation | 208 |
| 6.1.6 | Documentation | 209 |
| 6.2 | Operative Workflows under GMP Conditions | 210 |
| 6.2.1 | Product Release and Deviation Management | 211 |
| 6.2.2 | Changes in the Manufacturing Process | 213 |
| 6.3 | Production of Investigational Drugs | 216 |

Appendix A Case Study Part IV: Warning Letters by FDA 219

Part V Pharmaceutical Law 223

| | | |
|----------|--|------------|
| 7 | Pharmaceutical Law and Regulatory Authorities | 225 |
| 7.1 | Fields of Pharmaceutical Law | 225 |
| 7.2 | Bindingness of Regulations | 226 |
| 7.3 | Authorities, Institutions, and Their Regulations | 227 |
| 7.3.1 | FDA | 228 |
| 7.3.2 | EMA | 230 |
| 7.3.3 | German Authorities | 233 |
| 7.3.4 | Japanese Authorities | 234 |
| 7.3.5 | Authorities of Growth Markets | 235 |
| 7.3.5.1 | China: National Medical Products Administration (NMPA) | 236 |
| 7.3.5.2 | Brazilian Agência Nacional de Vigilância Sanitária (National Health Surveillance Agency, ANVISA) | 236 |
| 7.3.6 | Other Important Institutions | 236 |
| 7.3.6.1 | US Pharmacopoeia | 236 |
| 7.3.6.2 | ICH | 237 |
| 7.3.6.3 | ISO | 237 |
| 7.3.6.4 | WHO | 237 |
| 7.3.6.5 | PIC/S | 237 |
| 7.3.6.6 | ISPE | 239 |
| 7.3.6.7 | PDA | 239 |
| 7.4 | Official Enforcement of Regulations | 239 |
| 7.5 | Drug Approval | 241 |

Appendix B Case Study Part V: Clinical Trials for Protein Products 243

| | | |
|-------|--|-----|
| B.1 | Mabthera®/Rituxan® | 243 |
| B.2 | Enbrel® | 244 |
| B.2.1 | Adult Patients with Rheumatoid Arthritis | 244 |
| B.3 | Remicade® Infiximab | 245 |

- B.3.1 Adult Rheumatoid Arthritis 245
- B.4 Humira® 40 mg 246
- B.5 Lucentis® 247
- B.5.1 Treatment of Wet AMD 247
- B.6 Zaltrap® 247

Part VI Production Facilities 249

- 8 Facility Design 251**
 - 8.1 Basic Principles 251
 - 8.2 GMP-Compliant Plant Design 254
 - 8.2.1 Production Flow Diagram 256
 - 8.2.2 Conceptual Plant Layout 257
 - 8.2.2.1 Is the Facility Fit for the Intended Purpose? 259
 - 8.2.2.2 Is the Facility cGMP Compliant? 259
 - 8.2.2.3 Is the Facility Flexible? 259
 - 8.2.2.4 Can the Facility Be Expanded? 260
 - 8.2.2.5 Is It Possible to Separate the Core Process from the Support Functions? 260
 - 8.2.2.6 Is the Plant Capacity Optimized and Are Synergies with Existing Facilities Used? 261
 - 8.2.3 GMP Flow Analysis 261
 - 8.2.4 Zoning Concept 264
 - 8.3 Basic Concepts for Production Plants 267
 - 8.3.1 Single- and Multiproduct Plants 270
 - 8.3.2 Fractal and Integrated Configuration 271
 - 8.3.3 Flexible and Fixed Piping 273
 - 8.3.4 Steel Tanks and Disposable Equipment 274
 - 8.4 Clean and Plant Utilities 275
 - 8.4.1 Clean Utilities 275
 - 8.4.1.1 Water 275
 - 8.4.1.2 Clean Steam 282
 - 8.4.1.3 Gases and Process Air 282
 - 8.4.2 Plant Utilities 283
 - 8.4.3 Waste Management 285
 - 8.5 Equipment Cleaning 286
 - 8.6 Clean Rooms 288
 - 8.6.1 Separation of Zones by Clean Room Design 289
 - 8.6.2 Finishing of Floors, Walls, and Ceilings 291
 - 8.6.3 HVAC Installations 292
 - 8.6.4 Qualification 293
 - 8.7 Automation 293
 - 8.8 QC Laboratories 295
 - 8.9 Location Factors 295
 - 8.9.1 Cost 295
 - 8.9.2 Personnel 296

- 8.9.3 Permitting 296
- 8.9.4 Synergies with Existing Facilities or Units 296
- 8.9.5 Logistics 297
- 8.9.6 Know-How and Intellectual Property Protection 297
- 8.9.7 Other Risks 297
- 8.9.8 Market Access 297
- 8.9.9 Language and Culture 298

9 Planning, Construction, and Commissioning of a Manufacturing Plant 299

- 9.1 Steps of the Engineering Project 299
 - 9.1.1 Planning 300
 - 9.1.2 Construction 301
 - 9.1.3 Commissioning, Qualification, Validation 303
- 9.2 Project Schedules 306
- 9.3 Cost Estimates 307
- 9.4 Organization of an Engineering Project 309
 - 9.4.1 Expert Groups Involved 309
 - 9.4.2 Role and Selection of Contractors 310
 - 9.4.3 Contracts and Scope Changes 310
- 9.5 Successful Execution of an Engineering Project 314
- 9.6 Legal Aspects of Facility Engineering 315
 - 9.6.1 Health, Safety, and Environmental Law 316
 - 9.6.2 Building Law 317

Part VII Economy 319

10 Production Costs 321

- 10.1 Drug Life Cycle 321
- 10.2 Position of the Manufacturing Costs in the Overall Cost Framework 325
- 10.3 Basic Principles of Cost Calculation 327
 - 10.3.1 Nominal Accounting – Actual Accounting 327
 - 10.3.2 Cost Accounting – Profit and Loss Accounting 328
 - 10.3.3 Direct Costs – Indirect Costs 328
 - 10.3.4 Fixed Costs – Variable Costs 329
 - 10.3.5 Relevant and Irrelevant Costs 330
 - 10.3.6 Cost Type, Cost Center, and Cost Unit 331
- 10.4 Costs of Biotechnological Manufacturing Processes 332
 - 10.4.1 Capital Costs 333
 - 10.4.2 Operating Costs 335
- 10.5 Accounting Methods 338
 - 10.5.1 Cost Accounting 338
 - 10.5.2 Profit and Loss Accounting 347

| | | |
|---|---|------------|
| 11 | Investments | 351 |
| 11.1 | Basic Principles | 352 |
| 11.1.1 | Investment Targets | 352 |
| 11.1.2 | Types of Investments | 353 |
| 11.1.3 | Decision Processes | 355 |
| 11.2 | Value–Benefit Analysis | 359 |
| 11.3 | Investment Appraisal | 360 |
| 11.3.1 | Static Methods | 364 |
| 11.3.1.1 | Cost Comparison | 364 |
| 11.3.1.2 | Profit Comparison | 365 |
| 11.3.1.3 | Profitability Comparison | 365 |
| 11.3.1.4 | Static Payback Time | 365 |
| 11.3.2 | Dynamic Methods | 365 |
| 11.3.2.1 | Capital Value | 366 |
| 11.3.2.2 | Internal Rate of Return | 366 |
| 11.3.2.3 | Annuity | 367 |
| 11.4 | Dynamic Payback Time | 367 |
| | | |
| 12 | Production Concept | 369 |
| 12.1 | Capacity Planning | 369 |
| 12.2 | Dilemma of In-House Manufacturing | 372 |
| 12.3 | Aspects of Manufacturing Outsourcing | 375 |
| 12.3.1 | Types of Cooperation | 376 |
| 12.3.2 | Contractual Agreements | 377 |
| 12.3.3 | Technology Transfer | 382 |
| 12.3.4 | Time Schedules | 384 |
| 12.4 | Make-or-Buy Analysis | 385 |
| 12.5 | Process Optimization | 387 |
| 12.5.1 | Comparability of the Product | 387 |
| 12.5.2 | Operational Excellence | 390 |
| 12.5.2.1 | Lean Management | 391 |
| 12.5.2.2 | Six-Sigma | 392 |
| 12.6 | Supply-Chain Management | 396 |
| 12.6.1 | Security of Supply | 398 |
| 12.6.2 | Performance Management | 401 |
| | | |
| Appendix C Examples Part VII: Manufacturing Cost | | |
| | Calculation | 405 |
| C.1 | Introduction | 405 |
| C.2 | Basic Assumptions for Both Production Processes | 405 |
| C.3 | Step 1: Production of Product 1 in Dedicated Facility | 405 |
| C.3.1 | Cost Structure | 406 |
| C.3.2 | Product Costs | 407 |
| C.3.3 | Idle Costs | 407 |

- C.3.4 Unit Price Based on Facility Usage 407
- C.4 Step 2: Addition of a Second Product 408
- C.4.1 Costs of Products 409
- C.4.2 Evaluation of Manufacturing Options 410

**Part VIII Production Organization and
Digitalization 413**

- 13 Organization of a Manufacturing Facility 415**
 - 13.1 Functional Setup of a Manufacturing Plant 416
 - 13.2 Development of a Plant Organization 416
 - 13.3 Organizational Charts and Cooperation Pathways 421
 - 13.4 Cultural Aspects: The Human Factor 424
- 14 Digitalization 427**
 - 14.1 Operational and Digital Perspective 428
 - 14.2 Digital Maturity 435
 - 14.3 Integration and IT Architecture 440
 - 14.4 Digital Transformation 444
 - 14.5 Digital Applications in the GMP Environment 446

References 451

- Further Reading 451
- Biotechnology General 451
- Fermentation 452
- Purification 452
- Aseptic Filling and Lyophilization 452
- Bioanalytics 452
- Regulatory 453
- Pharmacy and Clinical Development 453
- Quality and Validation 453
- Good Manufacturing Practice 454
- Facility Design 454
- Clean Rooms 454
- Project Management 454
- Engineering 454
- Economy 455
- Weblinks 455

Index 457

Preface to Third Edition

What started out over ten years ago as being a book focused on protein manufacturing, in the meantime has evolved into a broad introduction of many different aspects of pharmaceutical operations. All but two sections – technology and regulatory – can be applied to any pharma production, which also gives testimony to the maturity and standardization that pharmaceutical protein manufacturing has achieved by now. The third edition of this book has been amended by two new chapters about plant organization and digitalization, broadly applicable to pharma. The general, conceptual, and simplifying approach makes the book a valuable source also for those working on transferring advanced pharmaceutical technologies like cell and gene therapies into economically feasible, large-scale solutions.

The original concept of the book – keep it simple and speak through pictures and examples – has been kept alive. The concept of strong simplification has been well received by many readers over the last years. Dipping into specific chapters of interest and quickly getting familiar with basic concepts and terminology has obviously addressed the needs of readers both in industry and academia. So, I am very happy to present the third edition of this book now and thank my editor Wiley-VCH for the ongoing support.

Berlin, 23 May 2021

Stefan Behme

Preface to First Edition

This book introduces the basic knowledge of industrial manufacturing of biopharmaceuticals. It is written for those wanting to understand the landscape, interfaces, and interactions between the different disciplines relevant for production as such; aspects of technology and analytics, pharmacy, quality assurance, regulatory affairs, facility technology, and economic efficiency are illustrated. The work shall serve as a textbook and reference at the same time, and is directed toward students as well as industry-experienced engineers, pharmacists, scientists, or economists wanting to acquire a basic knowledge of biotechnological production.

My daily industrial practice has inspired this book. Manufacturing advanced drugs under good manufacturing practice conditions can indeed be a critical factor for drug development and marketing. Being part of multidisciplinary teams, it became obvious to me that the technological and economic challenges of biopharmaceutical manufacturing and its interdependencies with adjacent disciplines are not understood everywhere. Decision making in interdisciplinary teams requires communication and appreciation of the constraints on the various counterparts in order to address them efficiently in the overall program. In contrast to this, particular disciplines become more and more specialized, using their language on a level difficult to understand for the counterparts foreign to the field, sometimes flavoring modern project work with a taste of the tale of the Tower of Babel.

Facilitating communication about manufacturing issues is the goal of this book. It does so by using numerous illustrations and simplifications, making the book easy to read. Correlations between disciplines are highlighted by cross-references, and a detailed keyword index facilitates the search for special topics. After having read this book, the reader should have a high-level understanding of the roles, correlations between terminologies of the different disciplines engaged in the production of biopharmaceutical

proteins. For those wanting to dig deeper into the topics, literature recommendations and web links are provided for further reading.

I would like to thank Andrea Rothmaler and Andreas Janssen for their valuable input into the manuscript, my students at the Technical University of Dortmund for their instructive questions, and my company Bayer Schering Pharma AG for providing the opportunity to participate in exciting biotechnological projects.

I hope that my readers will enjoy reading this book as much as I have enjoyed writing it.

Berlin, October 2008

Stefan Behme

List of Abbreviations

| | |
|-------|--|
| AA | Amino Acid (= AS) |
| ADR | Adverse Drug Reaction |
| AE | Adverse Event |
| AIEX | Anion Exchanger |
| AMG | Arzneimittelgesetz |
| AMWHV | Drug and drug manufacturing Regulation |
| AP | Aqua Purificata |
| API | Active Pharmaceutical Ingredient |
| APR | Annual Product Review |
| AR | Adverse Reaction (= ADR) |
| AR | Annual Report |
| ATP | Adenosine Triphosphate |
| AUC | Area Under the Curve |
| AVP | Aqua Valde Purificata |
| BAS | Building Automation System |
| BDS | Bulk Drug Substance |
| BLA | Biological License Application |
| BOD | Basis of Design |
| BP | Basen Pair |
| BPMN | Business process model and notation |
| BR | Batch Record |
| BRR | Batch Record Review |
| BSE | Bovine Spongiforme Encephalopathie |
| CAPA | Corrective Action Preventive Action |
| CBE30 | Changes Being Effected in 30 days |
| CDW | Cell Dry Weight |
| CFR | Code of Federal Regulations |
| CFU | Colony Forming Unit |
| cGMP | Current Good Manufacturing Practice |
| CI | Chemical Ionization |
| CIEX | Cation Exchanger |
| CIP | Cleaning in Place |
| CJD | Creutzfeldt–Jakob Disease |

| | |
|--------|--|
| CMC | Chemistry, Manufacturing, and Control |
| CMO | Contract Manufacturing Organization |
| CoA | Certificate of Analysis |
| CoC | Certificate of Compliance |
| COP | Cleaning out of Place |
| CRF | Case Report Form |
| CSV | Computerized system Validation |
| CTA | Clinical Trials Authorization |
| CTD | Common Technical Document, Clinical Trials Directive |
| CVMP | Committee for Medicinal Products for Veterinary Use |
| DIN | Deutsches Institut für Normung |
| DNA | Desoxyribonucleic Acid |
| DPPM | Digital plant maturity model |
| DQ | Design Qualification |
| DSC | Differential Scanning Calorimetry |
| EBR | Electronic Batch Record |
| ED | Effective Dose |
| EDQM | European Directorate for the Quality of Medicines |
| EIS | Electron Impact Spectroscopy |
| ELISA | Enzyme Linked Immunosorbent Assay |
| EMA | European Medicines Agency |
| EP | European Pharmacopoeia (PharmEur) |
| EPO | Erythropoietin |
| ERM | Enterprise recipe management |
| ERP | Enterprise resource planning |
| ETL | Extract–transform–load |
| FaaS | Function as a service |
| FAB | Fast Atom Bombardment |
| FBS | Fetal Bovine Serum |
| FCS | Fetal Calf Serum |
| FDA | Food and Drug Administration |
| FMEA | Failure Mode and Effect Analysis |
| FP | Final Product, Finished Product |
| HMI | Human machine interface |
| GAMP | Good Automated Manufacturing Practice |
| GCP | Good Clinical Practice |
| G-CSF | Granulocyte Colony Stimulating Factor |
| GEP | Good Engineering Practice |
| GFC | Gel Filtration Chromatography |
| GLP | Good Laboratory Practice |
| GM-CSF | Granulocyte Macrophage Colony Stimulating Factor |
| GMO | Genetically Modified Organism |
| GMP | Good Manufacturing Practice |
| GPC | Gel Permeation Chromatography |

| | |
|-------|--|
| GSP | Good Storage Practice |
| GSS | Gerstmann–Sträussler Syndrom |
| GTP | Good Tissue Practice |
| HCP | Host Cell Protein |
| HIC | Hydrophobic Interaction Chromatography |
| HIV | Human Immunodeficiency Virus |
| HPLC | High Pressure Liquid Chromatography (also High Performance LC) |
| HPMC | Hydroxypropylmethyl-cellulose |
| HSA | Human Serum-Albumin |
| HVAC | Heat Ventilation Air Conditioning |
| IaaS | Infrastructure as a service |
| ICH | International Conference on Harmonization |
| IEF | Isoelectric Focusing |
| JEC | Jon Exchange Chromatography |
| IEX | Ion Exchanger |
| IF | Interferon |
| IGG | Immunoglobulin G |
| IIoT | Industrial internet of things |
| IL | Interleukin |
| IMP | Investigational Medicinal Product |
| IMPD | Investigational Medicinal Product Dossier |
| IND | Investigational New Drug |
| IOM | Investigations Operations Manual |
| IPC | In-Process Control |
| IQ | Installation Qualification |
| IR | Infrared |
| ISO | International Organization of Standardization |
| ISPE | International Society for Pharmaceutical Engineering |
| JP | Japanese Pharmacopoeia |
| KPI | Key Performance Indicator |
| LADME | Liberation, Absorption, Distribution, Metabolism, Excretion |
| LAL | Limulus Amebocyte Lysate |
| LD | Lethal Dose |
| LES | Laboratory execution system |
| LFH | Laminar Flow Hood |
| LIMS | Laboratory Information Management System |
| LOD | Limit of Detection |
| LOQ | Limit of Quantification |
| MALDI | Matrix Assisted Laser Desorption Ionization |
| MBR | Master Batch Record |
| MCB | Master Cell Bank |
| MCO | Molecular Cut Off (MWCO) |
| MES | Manufacturing execution system |

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| MF | Microfiltration |
| MHLW | Ministry of Health, Labor, and Welfare |
| MSA | Manufacturing and Supply Agreement |
| MTD | Maximal Tolerated Dose |
| MWCO | Molecular Weight Cut Off |
| NDA | New Drug Application |
| NIST | National Institute of Standards and Technology |
| NPV | Net Present Value |
| OOS | Out of Specification (QC Context) or Out of Stock (Logistical Context) |
| OQ | Operational Qualification |
| PAB | Pharmaceutical Affairs Bureau |
| PAGE | Polyacrylamid Gel Elektrophoresis |
| PAS | Prior Approval Supplement |
| PAT | Process analytical technology |
| PCR | Polymerase Chain Reaction |
| PD | Pharmacodynamics |
| PD | Plasma Desorption |
| PDA | Parenteral Drug Association |
| PEG | Polyethylene glycol |
| PFBS | Pharmaceutical and Food Safety Bureau |
| PharmEur | European Pharmacopoeia |
| PIC/S | Pharmaceutical Inspection Convention/Scheme |
| PK | Pharmacokinetics |
| PLC | Programmable logic controller |
| PM | Posttranslational Modification |
| PMDA | Pharmaceutical and Medical Devices Agency (KIKO) |
| PoC | Proof of Concept (PoP) |
| PoP | Proof of Principle (PoC) |
| PQR | Product Quality Review |
| QA | Quality Assurance |
| QAA | Quality Assurance Agreement |
| QC | Quality Control |
| QM | Quality Management |
| rFVIII | Recombinant Factor VIII |
| RNA | Ribonucleic Acid |
| ROI | Return on Investment |
| RPC | Reversed Phase Chromatography |
| RP-HPLC | Reversed Phase HPLC |
| RPM | Regulatory Procedures Manual |
| SCADA | Supervisory control and data acquisition |
| SDS | Sodiumdodecylsulfate |
| SEC | Size Exclusion Chromatography |
| SIP | Sterilization in Place (also Steaming in Place) |
| SKU | Stock Keeping Unit |

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| SOP | Standard Operating Procedure |
| SPC | Statistical Process Control |
| SPC | Supplementary Protection Certificate |
| TEM | Transmission Electron Microscopy |
| TFF | Tangential Flow Filtration |
| TOC | Total Organic Carbon |
| TOF | Time of Flight |
| TSE | Transmissible Spongiform Encephalopathie |
| UF | Ultrafiltration |
| UML | Unified modeling language |
| URS | User Requirements Specification |
| USP | United States Pharmacopoeia |
| UV | Ultra Violet |
| WCB | Working Cell Bank |
| WFI | Water for Injection |
| WHO | World Health Organization |
| ZLG | Zentralstelle für Gesundheitsschutz bei Arzneimitteln und Medizinprodukten |

Part I

Introduction

