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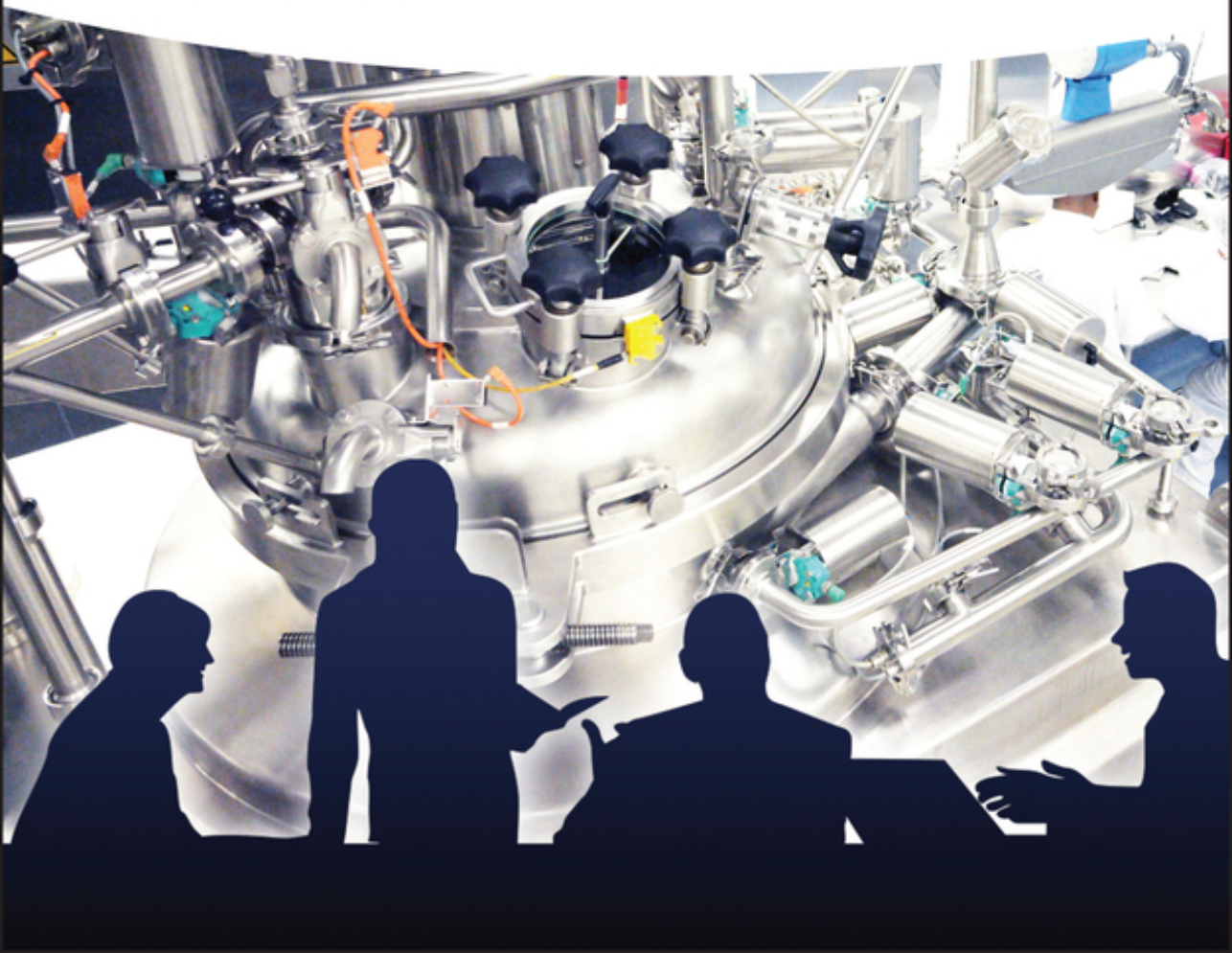
Stefan Behme

Manufacturing of Pharmaceutical Proteins

From Technology to Economy

Third Edition



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Contents

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

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

SOP	Standard Operating Procedure
SPC	Statistical Process Control
SPC	Supplementary Protection Certificate
TEM	Transmission Electron Microskopy
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 fur Gesundheitsschutz bei Arzneimitteln und Medizinprodukten

Part I
Introduction

Manufacturing of Pharmaceutical Proteins: From Technology to Economy, Third Edition. Stefan Behme.