

Pharmaceutical Biotechnology

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Bernd Meibohm
Editors**

Pharmaceutical Biotechnology

Fundamentals and Applications

Fourth Edition

 **Springer**

Editors

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ISBN 978-1-4614-6485-3 ISBN 978-1-4614-6486-0 (eBook)
DOI 10.1007/978-1-4614-6486-0
Springer New York Heidelberg Dordrecht London

Library of Congress Control Number: 2013950613

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Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

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Preface

Over the past 25 years, biotechnologically derived drug products have become a major share of the therapeutically used pharmaceuticals. These drug products include proteins, including monoclonal antibodies and antibody fragments, as well as anti-sense oligonucleotides and DNA preparations for gene therapy. In 2001 already, biotech products accounted for more than 35 % of the New Active Substances that were launched in the USA. Twelve out of the twenty-nine approved marketing authorization applications at the European Medicines Agency (EMA) in 2009 were biotech products. Drug products such as epoetin- α (Epogen[®], Eprex[®], Procrit[®]), abciximab (ReoPro[®]), interferons- α (Intron[®]A, Roferon[®]A) and interferons- β (Avonex[®], Rebif[®], Betaseron[®]), anti-TNF- α agents (Enbrel[®], Remicade[®], Humira[®]), bevacizumab (Avastin[®]), and trastuzumab (Herceptin[®]) are all examples of highly successful biotech drugs that have revolutionized the pharmacotherapy of previously unmet medical needs. And last but not least, biotech drugs also have a major socioeconomic impact. In 2010, five of the ten top selling drugs in the world were biotechnologically derived drug products, with sales varying between five and eight billion US dollars.

The techniques of biotechnology are a driving force of modern drug discovery as well. Due to the rapid growth in the importance of biopharmaceuticals and the techniques of biotechnologies to modern medicine and the life sciences, the field of pharmaceutical biotechnology has become an increasingly important component in the education of today's and tomorrow's pharmacists and pharmaceutical scientists. We believe that there is a critical need for an introductory textbook on Pharmaceutical Biotechnology that provides well-integrated, detailed coverage of both the relevant science and clinical application of pharmaceuticals derived by biotechnology.

Previous editions of the textbook *Pharmaceutical Biotechnology: Fundamentals and Applications* have provided a well-balanced framework for education in various aspects of pharmaceutical biotechnology, including production, dosage forms, administration, economic and regulatory aspects, and therapeutic applications. Rapid growth and advances in the field of pharmaceutical biotechnology, however, made it necessary to revise this textbook in order to provide up-to-date information and introduce readers to the cutting-edge knowledge and technology of this field.

This fourth edition of the textbook *Pharmaceutical Biotechnology: Fundamentals and Applications* builds on the successful concept used in the preceding editions and further expands its availability as electronic versions of the full book as well as individual chapters are now readily available and downloadable through online platforms.

The textbook is structured into two sections. An initial basic science and general features section comprises chapters introducing the reader to key concepts at the foundation of the technology relevant for protein therapeutics including molecular biology, production and analytical procedures, formulation development, pharmacokinetics and pharmacodynamics, and immunogenicity and chapters dealing with regulatory, economic and pharmacy practice considerations, and with evolving new technologies and applications. The second section discusses the various therapeutic classes of protein biologics and nucleotide-based therapeutics.

All chapters of the previous edition were revised and regrouped according to therapeutic application. The section on Monoclonal Antibodies was differentiated into a section on general considerations for this important class of biologics as well as sections focused on their application in oncology, inflammation, and transplantation in order to allow for a comprehensive discussion of the substantial number of approved antibody drugs. A chapter on stem cell technologies was newly added to give greater depth to the area of cell-based technologies.

In accordance with previous editions, the new edition of *Pharmaceutical Biotechnology: Fundamentals and Applications* will have as a primary target students in undergraduate and professional pharmacy programs as well as graduate students in the pharmaceutical sciences. An additional important audience is pharmaceutical scientists in industry and academia, particularly those that have not received formal training in pharmaceutical biotechnology and are inexperienced in this field.

We are convinced that this fourth edition of *Pharmaceutical Biotechnology: Fundamentals and Applications* makes an important contribution to the education of pharmaceutical scientists, pharmacists, and other healthcare professionals as well as serving as a ready resource on biotechnology. By increasing the knowledge and expertise in the development, application, and therapeutic use of “biotech” drugs, we hope to help facilitate a widespread, rational, and safe application of this important and rapidly evolving class of therapeutics.

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Abbreviations

5-FU	Fluorouracil
6-MP	6-mercaptopurine
A	Adenine
AA	Amino acid
AAV	Adeno-associated virus
Ab	Antibody
ABVD	Cytostatic protocol
ACE	Angiotensin converting enzyme
ACER	Average cost-effectiveness ratio
ACR	American College of Rheumatology
ADA	Adenosine deaminase
ADA	Anti-drug antibody(ies)
ADCC	Antibody dependent cellular cytotoxicity
ADME	Absorption, distribution, metabolism, and elimination
ADR	Adverse drug reaction
ADR	Antibody-drug conjugate
AE(s)	Adverse event(s) or Adverse effect(s)
Ag	Antigen
AGT	Angiotensinogen
AHFS	American Hospital Formulary Service
AIDS	Acquired immunodeficiency syndrome
ALCL	Anaplastic large-cell lymphoma
ALL	Acute lymphoblastic leukemia
AMD	Age-related macular degeneration
AMI	Acute myocardial infarction
AML	Acute myeloid leukemia cells
AMR	Antibody-mediated rejection
ANC	Absolute neutrophil count
AP	Alkaline phosphatase
APC	Antigen-presenting cell
ART	Assisted reproductive technologies
AS	Ankylosing spondylitis
ASCT	Autologous stem cell transplant
ASHP	American Society of Health-System Pharmacists
ASSENT	Assessment of the safety and efficacy of a new thrombolytic
ATAs	Anti-therapeutic antibodies
ATF	Alternating tangential flow
ATMP	Advanced therapy medicinal products
AUC	Area under the concentration-time curve
AZA	Azathioprine

BCG	Bacille Calmette-Guérin
BCGF	B cell growth factor
BFU	Burst-forming unit erythroid
BHK	Baby hamster kidney cells
BILAG	British Isles Lupus Assessment Group
BLA	Biologics license application
BLys	B lymphocyte stimulator
BMD	Becker's muscular dystrophy
BMP	Bone morphogenetic protein
Bp	Base pair
B _p	Peripheral blood band cell population
BPCI	Biologics Price Competition and Innovation Act
BSE/TSE	Bovine or transmissible spongiform encephalopathy
BSI	British Standards Institute
C	Cytosine
C	Drug concentration in plasma
CAPS	Cryopyrin-associated periodic syndrome
CAR	Coxsackievirus and adenovirus receptor.
CAT	Committee for Advanced Therapies
CBA	Cost benefit analysis
CBER	Centre for Biologics Evaluation and Research
CCK	Cholecystokinin
CD	Circular dichroism
CD	Cluster designation/cluster of differentiation (term to label surface molecules of lymphocytes)
CD	Crohn's disease
CDAI	Crohn's disease activity index
CDC	Centers for Disease Control and Prevention
CDC	Complement-dependent cytotoxicity
CDI	Chronic kidney insufficiency
cDNA	Copy DNA
CDR	Complementarity-determining region
CEA	Cost effectiveness analysis
CF	Cystic fibrosis
CFR	Code of Federal Regulations.
CFTR	Cystic fibrosis transmembrane conductance regulator
CFU	Colony-forming unit
CFU _e	Colony-forming unit erythroid
CG	Chorionic gonadotropin
CGM	Continuous glucose monitoring
cGMP	Good manufacturing practice
C _H	Constant heavy chain region in MAB
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese hamster ovary
CIP	Clean in place
CK	Chemokines
CKD	Chronic kidney disease
CL	Clearance
C _L	Constant light chain region in MAB
CLL	Chronic lymphocytic leukemia
C _{max}	Peak plasma/serum concentration
CMC	Chemistry, manufacturing, and controls
CMI	Cell-mediated immunity

CMV	Cytomegalovirus
CNS	Central nervous system
COBALT	Continuous infusion versus double-bolus administration of alteplase
COS	Controlled ovarian stimulation
CPP	Cell-penetrating peptide
cQT	Corrected QT
CR	Complete response rate
CRC	Colorectal cancer
CsA	Ciclosporin A
CSII	Continuous subcutaneous insulin infusion
cSNPs	SNPs occurring in gene coding regions
CT	Cholera toxin
CT	Computerized tomography
CTA	Clinical trial application
CTL	Cytotoxic T lymphocytes
CTLA	Cytotoxic T lymphocyte antigen
CTP	Carboxy terminal peptide
CUA	Cost utility analysis
CyNA	Cyclohexene nucleic acid
CYP	Cytochrome P450
CZE	Capillary zone electrophoresis
dATP	Deoxyadenosine 5'-triphosphate
DC	Dendritic cell
dCTP	Deoxycytidine 5'-triphosphate
DDA	Diocadecyldimethylammonium bromide
DDBJ	DNA Data Bank of Japan
ddNTPs	Dideoxynucleotidetriphosphates
DF	Diafiltration
dGTP	Deoxyguanosine 5'-triphosphate
DHHS	Department of Health and Human Services.
DLS	Dynamic light scattering
DMARDs	Disease-modifying anti-rheumatic drugs
DMD	Duchenne muscular dystrophy
DNA	Deoxyribonucleic acid
DNaqse I	Human deoxyribonuclease I
dNTPs	Deoxynucleotide triphosphates
DOE	US Department of Education
DS	Degree of cross-linking
DSC	Differential scanning calorimetry
DSP	Downstream process(ing)
dsRNA	Double-stranded RNA
dTTP	Deoxythymidine-5'-triphosphate
E	Effect measure
EBV	Epstein-Barr virus
EC ₅₀	Concentration of the drug that produces half of the maximum effect
EDF	Eosinophil differentiation factor
EDSS	Expanded disability status scale
EDTA	Ethylenediaminetetraacetic acid
EGF	Epidermal growth factor
EGFR	Endothelial growth factor receptor
EGS	External guide sequences

EHR	Electronic health records
EI	Electrospray ionization
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
E_{\max}	Maximum achievable effect
EMBL	European Molecular Biology Laboratory
eNOS	Endothelial nitric oxide synthase
EPAR	European Public Assessment Report
EPO	Erythropoietin (alfa)
EPOR	Erythropoietin receptor
EPR	Enhanced permeability and retention
ER	Endoplasmic reticulum
ES	Embryonic stem cell
ESA	Erythropoietin stimulating agents
ESCF	Epidemiologic study of cystic fibrosis
EUCOMM	European conditional mouse mutagenesis program
Eur. Pharm.	European Pharmacopeia
F	Systemic bioavailability compared to IV administration
FANA	2-phosphoarabino nucleic acid
Fc	Constant region of MAB
FcRn	Neonatal Fc-receptor
FDA	US Food and Drug Administration
FDC	(US) Food, Drug, and Cosmetic Act
FEV ₁	Mean forced expiratory volume in 1 second
FGF	Fibroblast growth factor
FSGS	Focal segmental glomerulosclerosis
FSH	Follicle stimulating hormone
FTET	Frozen-thawed embryo transfer
FTIR	Fourier transform infrared spectroscopy
FVC	Forced vital capacity
G	Guanine
GAD	Glutamic acid decarboxylase
GBM	Glioblastoma multiforme
GCP	Good clinical practice
G-CSF	Granulocyte colony stimulating factor
GF	Growth factors
GFP	Green fluorescent protein
GFR	Glomerular filtration rate
GHBP	Growth hormone binding protein
GHD	Growth hormone deficient
GHR	hGH receptor
GHRH	Growth hormone releasing hormone
GI	Gastrointestinal
GLA	γ -carboxyglutamic acid
GlcNAc	N-acetylglucosamine
GLP	Good laboratory practice
GLP-1	Glucagon-1-like peptide
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GMO	Genetically modified organism
GMP	Good manufacturing practice
GnRH	Gonadotropin-releasing hormone
GO	Gemtuzumab ozogamicin

GON	Guanidinium-containing oligonucleotide
GRF	Growth hormone releasing factor
GSD II	Glycogen storage disease II
GSK	Glycogen synthase kinase
GST	Glutathione-S-transferase
GUSTO	Global utilization of streptokinase and tissue plasminogen activator for occluded coronary arteries
GVHD	Graft-versus-host disease
GWAS	Genome-wide Association Studies
HACA	Human anti-chimeric antibodies
HAHA	Human anti-human antibody
HAMA	Human antibodies to murine antibodies
HSA	Human serum albumin
Hb	Hemoglobin
HbA1c	Glycated hemoglobin
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCT/Ps	Human cell, tissue, and cellular and tissue-based products
HDAC	Histone deacetylase
HEMA	Hydroxyethyl methacrylate
HEPA	High-efficiency particulate air
Her or HER	Human epidermal growth factor receptor
HGF	Hematopoietic growth factors (Chap. 18)
HGF	Hepatocyte growth factor (Chap. 24)
hGH	Human chorionic gonadotropin (Chap. 13)
hGH	Human growth hormone (Chap. 14)
HGI	Human Genome Initiative
HGNC	Human Genome Nomenclature Committee
HGP	Human Genome Project
HGPRT	Hypoxanthine-guanine-phosphoribosyl transferase
HGVbase	Human genome variation database
Hib	<i>Haemophilus influenzae</i> type b
HIC	Hydrophobic interaction chromatography
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HMWP	High molecular weight protein
HO-1	Heme oxygenase-1
HPLC	High-performance liquid chromatography
HPV	Human papilloma virus
HRP	Horseradish peroxidase
HSA	Human serum albumin
HSC	Hematopoietic stem cell
HSV	Herpes simplex virus
HTS	High-throughput screening
HUPO	Human Proteome Organization
HV	Hypervariable sequences in MAB
IBC	Institutional Biosafety Committees
IBD	Inflammatory bowel disease
ICAM-1	Intercellular cell adhesion molecule
ICER	Incremental cost effectiveness ratio
ICH	International conference on harmonization
ICSI	Intracytoplasmic sperm injection
IEF	Isoelectric focusing

IFN	Interferon
IGF	Insulin-like growth factor
IL	Interleukin
ILPS	Insulin lispro protamine suspension
IM	Intramuscular
IND	Investigational new drug application
INJECT	International joint efficacy comparison of thrombolytics
INN	International Non-proprietary Names
INR	International normalized ratio
InTIME	Intravenous nPA for treatment of infarcting myocardium early
IP	Intraperitoneal
IPN	Intravenous parenteral nutrition
iPS(C)	Induced pluripotent stem
IR	Infra red
IRB	Institutional review board
ISCOM	Immune stimulating complex
ISS	Idiopathic short stature
ITP	Immune thrombocytopenia purpura
ITR	Inverted terminal repeats
IU	International units
IV	Intravenous
IVF	In vitro fertilization
IVT	Intravitreal
JAK-STAT	Janus Kinase/Signal Transducers and Activators of Transcription
JIA	Juvenile idiopathic arthritis
K _a	First-order absorption rate constant
k _{app}	Apparent absorption rate constant
KOMP	Knockout mouse project (NIH)
LABA	Long-acting β -adrenoceptor agonist
LAtpA	Long acting tissue plasminogen activator
LC/MS/MS	Liquid chromatography-tandem mass spectrometry
LDL	Low-density lipoprotein
LFA	Leukocyte function antigen
LH	Luteinizing hormone
LHRH	Luteinizing hormone-releasing hormone
LIF	Leukemia inhibitory factor
LNA	Locked nucleic acids
LRP	(low density) Lipoprotein receptor-related protein
LTR	Long terminal repeats
LVEF	Left ventricular ejection fraction
M	Microfold
MAA	Marketing authorization application
MAB	Monoclonal antibodies
MAC	Membrane attack complex
MALDI	Matrix-assisted laser desorption
MBP	Maltose-binding protein
MCS	Multiple cloning site
M-CSF	Macrophage-colony stimulating factor
MDR	Multidrug resistance
MDS	Myelodysplastic syndrome
MEO	Methoxy ethyl

met-hGH	Methionine recombinant human growth hormone
MF	Morpholino phosphoramidate
MHC	Major histocompatibility complex
miRNA	MicroRNA
MMAD	Mass median aerodynamic diameter
MMAE	Monomethyl auristatin E
MOA	Mechanism of action
MPS	Mononuclear phagocyte system
MRM	Measles-rubella-mumps
mRNA	Messenger ribonucleic acid/messenger RNA
MRT	Mean residence time
MS	Multiple sclerosis
MSC	Mesenchymal stem cell.
MTD	Maximum tolerated dose
MTX	Methotrexate
mVar	Murine variable
NBCI	National Center for Biotechnology Information
NBP	Nonionic block copolymers
ncRNA	Noncoding RNA
NDA	New drug application
NDV	Newcastle disease virus
Neo ^r	Neomycin resistance gene
NF- κ B	Nuclear factor kappa B
NGS	Next-generation genome sequencing
NHGRI	National Human Genome Research Institute
NHL	Non-Hodgkin lymphoma
NICE	National Institute for Health and Clinical Excellence
NIH	National Institutes of Health.
NK	Natural killer
NMR	Nuclear magnetic resonance
NOAEL	No observable adverse effect level
NorCOMM	North American conditional mouse mutagenesis project
NPH	Neutral protamine Hagedorn
NPL	Neutral protamine lispro
NSAIDs	Nonsteroidal anti-inflammatory drugs
NSCLC	Non-small cell lung cancer
OAS	2',5'-oligoadenylate synthetase
OATP	Organic anion transporting polypeptide
OBA	Office of Biotechnology Activities
OHRP	Office for Human Research Protections
OMe	2'-O Methyl
ON	Oligonucleotide
ONJ	Osteonecrosis of the jaw
OR	Overall response rate
ORF	Open reading frames.
Ori	Origin of replication
PAGE	Polyacrylamide gel electrophoresis
PAMP	Pathogen associated molecular patterns
PASI	Psoriasis activity and severity index
PBMC	Peripheral blood mononuclear cell
PBM _s	Pharmacy benefits management companies
PBPC	Peripheral blood progenitor cells
PBPK	Physiologically based pharmacokinetics

PCR	Polymerase chain reaction
PEG	Polyethylene glycol
Peg-MGDF	Pegylated megakaryocyte growth and development factor
PEI	Polyethyleneimine
PEPT1, PEPT2	Proton driven peptide transporters
PGA	Physician's global assessment
PHS	Public Health Service
PI3K	Phosphatidylinositol 3-kinase
PIC	Polyion complex
pit-hGH	Pituitary-derived growth hormone
PJIA	Polyarticular juvenile idiopathic arthritis
PK/PD	Pharmacokinetics/pharmacodynamics (modeling)
PLGA	Poly(lactic-co-glycolic acid)
PLL	Poly (L-lysine) (Chap. 24)
PLL	Prolymphocytic leukemia (Chap. 17)
PML	Progressive multifocal leukoencephalopathy
PNA	Peptide nucleic acids
PRCA	Pure red cell aplasia
PRR	Pattern recognition receptors
PS nucleotides	Phosphothioate nucleotides
PsA	Psoriatic arthritis
PsO	Plaque psoriasis
PT	Prothrombin time
PTLD	Post-transplant lymphoproliferative disorder
PTM	Posttranslational modification
PVC	Pneumococcal conjugate vaccine (Chap. 22)
PVC	Polyvinyl chloride (Chap. 9)
PVDF	Polyvinylidene difluoride
PWS	Prader-Willi syndrome
Q2W	Every two weeks
Q3W	Every three weeks
QALY	Quality-adjusted life-year
QCM	Quartz crystal microbalance
QW	Weekly
RA	Rheumatoid arthritis
rAAT	Recombinant α_1 -antitrypsin
RAC	Recombinant DNA advisory committee
rAHF-PFM	Recombinant antihemophilic factor-plasma/albumin free method
RANK(L)	Receptor activator of nuclear factor <i>kappa</i> B (ligand)
RAPID	Retepase angiographic phase II international dose-finding study/retelase versus alteplase patency investigation during myocardial infarction
RBC	Red blood cell
RCA	Replication competent adenovirus
RCL	Replication competent lentivirus
rDNA	Recombinant DNA
RES	Reticuloendothelial system
rFVII or rFVIII or IX	Recombinant factor VII or VIII or IX
RGD	Arginine-glycine-aspartic acid
rhAT	Recombinant human anti-trypsin
rhGH	Recombinant human growth hormone
rhIFN α -2a	Recombinant human interferon α -2a

rHuEPO	Recombinant human erythropoietin
rhVEGF	Recombinant human vascular endothelial growth factor
RIA	Radioimmunoassay
rIL-2	Recombinant interleukin-2
RISC	RNA-induced silencing complex
RIT	Radioimmunotherapeutic
RME	Receptor-mediated endocytosis
RNA	Ribonucleic acid
RNAi	RNA interference
RP	Reverse primer
RP-HPLC	Reversed-phase high performance liquid chromatography
RSV	Respiratory syncytial virus
RT	Reverse transcriptase
RT-PCR	Reverse-transcriptase polymerase chain reaction
SABA	Short-acting β -adrenoceptor agonist
SARS	Severe acute respiratory syndrome
SBGN	Systems biology graphical notation
SBS	Short bowel syndrome
SC	Subcutaneous
SCCHN	Squamous cell cancers of the head and neck
SCF	Stem cell factor
scFv	Single chain Fv
SCID	Severe combined immune-deficiency
SCNT	Somatic cell nuclear transfer
SCPF	Stem cell proliferation factor
SCT	Stem cell transplant
SDR	Specificity determining residues
SDS	Sodium dodecyl sulfate
SDS-PAGE	Sodium dodecyl sulfate polyacrylamide gel electrophoresis
SEC	Size-exclusion chromatography
SGA	Small for gestational age
SHOX	Short stature homeobox containing gene deficiency on the X chromosome
SIP	Steam in place
siRNA	Small interfering RNA
SIV	Simian immunodeficiency virus
SLE	Systemic lupus erythematosus
SNP	Single nucleotide polymorphism
SOCS	Suppressors of cytokine signaling
SOS	Sinusoidal obstructive syndrome
S _p	Segmented neutrophil population
SPR	Surface plasmon resonance
SREs	Skeletal reverse events
SRI	SLE Responder Index
SRIF	Somatotropin release-inhibitory factor
SRP	Signal recognition particle
SUPAC	Scale-up and post approval changes
T	Thymine
T1 (or 2) DM	Type 1 (or 2) diabetes mellitus
t _{1/2}	Half-life
tcDNA	Tricyclo-DNA
TF	Tissue factor

TFF	Tangential flow filtration
TFPI	Tissue factor pathway inhibitor
T_g	Glass transition temperature
TGF	Tissue growth factor (Chap. 5)
TGF	Transforming growth factor (Chap. 21)
TGF- β	Tissue growth factor-beta
TIMI	Thrombolysis in myocardial infarction
TIW	Three-times in a week
TK	Thymidine kinase
TLR	Toll-like receptor
TLS	Tumor lysis syndrome
TNF	Tissue necrosis factor
TNF- α	Tumor necrosis factor alpha
TO	Total relative uptake
t-PA	Tissue plasminogen activator
TPMT	Thiopurine methyltransferase
TPO	Thrombopoietin
TRE	Tet response element (see context Chap. 24)
TRE	Transcription regulatory element (see context Chap. 24)
TRF	T-cell replacement factor
tRNA	Transfer ribonucleic acid/transfer RNA
TS	Turner syndrome
TSC	The SNP Consortium
TSH	Thyroid-stimulating hormone
TSP	Thrombospondin
UC	Ulcerative colitis
UF	Ultrafiltration
UFH	Unfractionated heparin
USP	United States Pharmacopeia
UTR	Untranslated region
Vd	Volume of distribution
Ve	Exclusion volume
V_H	Variable region of the heavy chain of a MAB
V_L	Variable region of the light chain of a MAB
VLDL	Very low-density lipoprotein
VLP	Virus-like particles
V_{max}	Maximum catabolic/enzymatic capacity
V_{ss}	Volume of distribution at steady-state
VSV	Vesicular stomatitis virus
WBC	White blood cell
WCB	Working cell bank
WHO	World Health Organization
ΔG_U	Difference in free energy



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