Index

a
abatacept 49, 67, 97, 118, 220, 227, 228, 302
– clinical development 295–299
– construction 285–288
– design 285–288
– immunosuppressive properties 288–291
– rational design 291–294
adalimumab 273
adaptive strategy, for aggregates 169, 171
– illustration 171
ADCs. see antibody-drug conjugates (ADCs)
aflibercept 228, 311
– characterization 317, 318, 320
– clinical indications 311
– age-related macular degeneration 311–315
– macular edema with CRVO 315, 316
– metastatic colorectal cancer 316, 317
– clinical studies with 325
– AMD trial with 325–327
– cancer treatment 328–331
– combination phase 1 studies 332
– combination phase 2 and 3 studies 335, 336
– single-agent phase 1 studies 327, 331, 332
– single-agent phase 2 studies 332–335
– preclinical studies 320–325
age-related macular degeneration (AMD) 311, 312, 325, 327, 336
aggregation 130
– surfactants, mitigate silicone oil-induced
  aggregation 142
aglycosylated Fc 24
glycosylation 125
alefacept (LFA3-IgG1; lymphocyte function-
  associated antigen 3) 67, 98, 220, 223, 226, 227, 233
– carcinogenicity tests 239
– clinical pharmacology 248, 249
– clinical safety 249
– adverse events 249
– Amevive (R) discontinued 250, 251
– cancer rates 250
– infection 250
– laboratory tests 250
– efficacy 245
– CD4 monitoring 246
– PASI and PGA results 246
– patient population 245, 246
– quality of life 247
– remittance 247
– human clinical trials 241, 242
– phase 1 and 2 human clinical studies 240
– phase 3 studies 240, 242
– B-cell lymphomas 240
– mechanism of action 238
– multiple courses of treatment 247, 248
– preclinical primate studies 237–240
– lymphoma, related to 240
– structure 237
– study design 243
– dosing and blood work 244
– eligibility 243, 244
– endpoints 244
– intramuscular studies 712 and 717, 245
– intravenous studies 711 and 724, 244, 245
– statistical analysis 244
AMD. see age-related macular degeneration (AMD)
Amevive®. see Alefacept
AMG386 221. see Trebananib
amino acids 131
– lyoprotection mechanism 131
anakinra 273
analytical methods
– qualification and validation 211, 212
– for reference standard characterization 208
– used in product release 209

© 2014 Wiley-VCH Verlag GmbH & Co. KGaA. Published 2014 by Wiley-VCH Verlag GmbH & Co. KGaA.
annealing temperature 133
antibodies
  – antigen-binding fragments (Fab) 4
  – antigen-binding regions 4
  – proteolytic cleavage 4
  – antigen-binding sites 4
  – complementarity determining regions (CDRs) 4
  – domain sequence 4
  – generation 4
  – recycling 12
antibody–antigen interactions 16
antibody-based bispecific molecules 26
antibody-dependent cell-mediated cytotoxicity (ADCC) 4, 223
antibody derivatives by target 2, 3
antibody–drug conjugates (ADCs) 26, 118
antibody engineering, current trends in 25
  – bispecific 25, 26
  – drug conjugates 26–28
antibody fragment-based therapeutics 119–123
antibody recycling 12
anti-CD20 antibody 20, 21
anticytokines 223
antigen-binding fragments (Fab) 4
antigen-presenting cells (APCs) 234, 283, 284
  – T-cell activation signals required from 284
  – antigen recognition element 1
APCs. see antigen-presenting cells (APCs)
APG101, 221
apocept 221
Arcalyst® 67, 98, 220
atacicept 155
  – amino acid substitutions 157
  – criticality of quality attributes, assessment of 160
  – critical process parameters 160, 161
  – formation 155
  – intracellular signaling pathways
  – associated with BLYS and APRIL receptors 155, 156
  – molecular characteristics 155–157
  – extracellular domain 156
  – Fc domain 156
  – purification process (see Global Multistep Design Space)
  – quality by design concept 157–159
  – quality by design (QbD) development approach 158 (See also business case)
  – treatment 155
  – validity 159
auristatins 27
Autographa californica 60
autoimmunity 4, 284
autolysis 125
baculovirus 60–62
  – in eukaryotic post-translational modifications 62
  – expression vector system (BEVS) 60–62
  – transfer vectors 61
B-cells 1, 13, 25, 155, 240, 248, 289, 290
  – clones 4
B-cell maturation antigen (BCMA) 155
B-cell receptor (BCR) 1
BclXL gene 82
belatacept 49, 98
  – activity in primate renal transplant studies 294, 295
  – clinical development 299–302
BeneFIX 354, 359, 363
bevacizumab
  – clinical success 26
BEVS. see Baculovirus, expression vector system
bifunctionality 25
biotechnology 116, 183
biotherapeutics 1, 356, 357, 363
buffer crystallization-induced pH shifts 130
business case 183–186
  – compliance to new QbD standards 183
  – cost–benefit ratio analysis 185
  – average net product value (NPV) 184, 185
  – Monte Carlo-type simulations 185
  – “revenues,” 185, 186
  – evaluation of incremental costs
  – associated to implementation, QbD principles 184
  – risks associated with “poor quality development,” 183, 184
Ca²⁺ ions 354
calicheamicin 27
γ-carboxylation 68, 69, 353, 359
case studies 82
  – LTBr-Fc (baminercept) 82–85
  – quality by design applied to a Fc-fusion protein 155
  – rFVIIIFc 85–87
cationic lipids 57
catuximab 25
CDC. see complement-dependent cytotoxicity (CDC)
CD28–CD86 molecular interactions 302
CD86-mediated T-cell costimulation 302
CD28 receptor 302
CDRs. see complementarity-determining regions (CDRs)
cell–cell interactions 284
cell culture production systems 70
cell culture productivity 71
cell lysis 17
– ADC mediated 17
– CDC initiated 17
cell surface receptors BAFF-R (BAFF receptor) 155
Center for Drug Evaluation and Research (CDER) 49
central nervous system (CNS) 351
certolizumab pegol 273
cetuximab 3, 69, 120
C1q domain in Fc fusions 223
chemical degradation reactions 115
chemical modifications 115
citrate buffers 103
cleaning-in-place (CIP) procedures 109
CMV promoter 52
CNTo 530 221
codon optimization 52
cold denaturation 130
colloidal stability 126
commercial antibody-related products 118
commercial recombinant antibody 118
commercial vectors, for mammalian protein expression 53
complement 20
– C1q biology 20
– role of the complement system for 20
– therapeutic relevancy 20, 21
complementarity-determining regions (CDRs) 4, 115
complement-dependent cytotoxicity (CDC) 2, 4, 6, 17, 20, 21, 23, 24, 99, 203
complement regulatory proteins (CRPs) 20
conformational modifications 135
conformation changes 115
Consortium of Rheumatology Researchers of North America (CORRONA) registry 273
contaminants 159
contract research organizations (CROs) 51
control strategy 176, 177
– material control 179, 180
– process controls 177
– process monitoring 179
– testing controls 177–179
cooling rate 133
COS system 49
CovX-body 222
CQAs. see critical quality attributes (CQAs)
critical process parameters (CPP) 158, 160–162, 164
– failure mode and effects analysis, as tool to determine 161
– impact on anion-exchange chromatography step on 165
– measure process outputs 164
– modeling of load pH and load conductivity 164
– normal operating range (NOR) 163, 164
– process characterization 161–164
– risk assessment
–– define criticality of process parameters 162
–– potentially parameters after first risk assessment 163
critical quality attributes (CQAs) 158, 159, 161, 162, 164, 165, 169–171, 177, 178
– confirmed (CQAs) 159
– potential (pCQAs) 159
–– DoE software 164
–– identification 163, 164
–– parameters, after first risk assessment 163
– predictive statistical models 164
– prerequisites 163, 164
Crucell 51, 52
cryopyrin-associated periodic syndrome (CAPS) 98
crystallization 130
CTLA4 Ig (Orencia) homodimer 284, 288
CTLA4 Ig mutagenesis 302
current Good Manufacturing Practices (cGMPs) 157
CVX-060 221
cytokine 17, 23, 24, 97, 220, 221, 256, 286, 291, 294, 312
cytomegalovirus 52
cytotoxicity 2, 4, 17, 23, 57, 202, 203, 223, 264
d
device 141
– dual-chamber syringe 141
– prefilled syringe 141
diafiltration 107, 205
differential scanning calorimetry (DSC) 118, 125
dihydrofolate reductase (DHFR) 53
dimeric Fc region 357
dissulfide bond formation 62
dissulfide scrambling 115
DNA-interacting payloads 27
drug delivery 14, 116, 139–141, 143
drug product (DP) development 116
duocarmycins 27
e E2 glycoprotein 60
Ehrlich, Paul 1
electrostatic (AEX/CEX) 101
Enbrel® 67, 97, 220
endoplasmic reticulum (ER) 69, 352
endosomes 117, 223
endothelial cells 223
endotoxins 160
engineering design space 171
– principles 171–173
– shear stress as one element 173–176
enzyme-linked immunosorbent assays (ELISAs) 202, 203, 261, 363
eosinophils 17
epidermal growth factor (EGF) domains 353
EPO-Fc fusion 59, 223
erthropoietin 222, 356, 357
Escherichia coli
– aglycosylation in the C_H2 domain 125
– culture 68
– expression vectors 57, 59, 62, 107
– Fc-fusion proteins produced in 138
– markerDNA amplification 286
etanercept 100, 202, 227, 255, 273
– inhibition of TNF activity 265, 266
– key clinical trials 267
–– ankylosing spondylitis 270, 271
–– plaque psoriasis 271, 272
–– polyarticular juvenile idiopathic arthritis 269
–– potential indications 272
–– psoriatic arthritis 270
–– rheumatoid arthritis 267–269
– meta-analyses and combination therapy 273
– pharmacodynamics 266
– pharmacokinetics 266
– preclinical development 264, 265
– preclinical efficacy 266
– toxicology studies 267
– trials of TNF blockers and competitive landscape 273
– eukaryotic expression systems 50
– EU numbering system 4
– eutectic temperature 133
expanded change protocol
– and continual improvement 182, 183
extracellular domain (ECD) 47, 50, 191, 202, 220–222, 225, 228
– of a natural receptor 47
Eylea® 67, 220
factorial screening design 162
factor IX (FIX) 67, 228, 230, 353
– domain structure 353
– post-translational modifications (PTM) 353
– role in the coagulation cascade 352
factor V (FV) 352
factor VIII (FVIII) 67, 220, 228, 230, 353–355
– domain structure 353
– posttranslational modifications (PTM) 353
– role in the coagulation cascade 352
factor VII/tissue factor complex 354
failure mode and effects analysis (FMEA) 161
Fc binding peptides (FcBPs) 223
Fc–Clq complex 23
FccRIIa/FcRn ratios 22
Fc engineering 14, 15
– modify PK of an IgG or Fc fusion 15, 16
Fc/FcRn pathway 356
Fc-fusion AMG 819 48
Fc-fusion constructs, in vivo stability 222, 223
Fc-fusion molecules, specific process considerations 77
– dissolved oxygen (DO) 79, 80
– glycosylation 81, 82
– misfolding 78, 79
– osmolality 79
– pCO2 79, 80
– pH 79
– process parameters 78
– process strategies 78
– product quality challenges 77, 78
– sodium butyrate addition 79, 80
– temperature 78, 79
Fc-fusion proteins 47, 118
– biochemistry 99, 100
–– conformational flexibility 100
– design 226
–– factors, role in 226
– downstream processing 97
– expression systems used 50
–– codon optimization 52
–– host cells 51, 52
– mammalian cell lines 50, 51
–– stable vs. transient expression 53–55
–– transfection methods 55–57
fluorescence activated cell sorting (FACS) 202
formulated drug products
  – for commercial Fc-fusion protein
    therapeutics 124
  – for commercial monoclonal antibodies/
    antibody fragment-based therapeutics
    119–123
FTIR analysis 130

galactose-α,1,3-galactose (α-Gal) antigens 69
galactosylation 82
gamma immunoglobulin 1
gemtuzumab ozogamicin 2, 27, 28
genetic fusion of scFv 25
genotype–phenotype linkage strategy 4
GLA domain (GLA) 353
glass transition temperature 130, 131, 133
Global Multistep Design Space
  – as adaptive strategy, for purification
    process 169, 171
  – defined 164, 165, 167
  – flexibility at AEX step 168
  – restrictive CQA 165, 167
  – level of aggregates as 165
  – statistical models 165
  – step Design Space boundaries, restricted
    by 165
  – verification, validity of 168
  –– robustness studies 168, 169
  –– results 169, 170
glomerular filtration rate (GFR) 299
glucose flux 80
glutamic acid 132, 292, 353, 354
 glutamine synthetase (GS) 53
  – as amplifiable and selectable marker 52
  – expression system 364
γ-glutamyl carboxylase 353
glycans 8
  – modulation of 82
  – negatively charged sialylated 195
  – N-linked 77, 78, 84, 107
  – nonfucosylated 23
  – O-linked 68, 78
glycine 103, 120, 124, 127, 133
glycoengineering 22, 23
glycoproteins 50, 60, 61, 69, 82, 155, 265, 353, 354
glycosylation 8, 22, 50, 58, 61, 62, 67, 68, 81, 82,
  87, 100, 125, 125, 160, 193, 353, 355, 364
  – of Fc-fusion proteins 192
Gly–Ser linkers 359
index

Golgi apparatus 82
golimumab 3, 121, 262–264, 273
good laboratory practices (GLP) 360
granulocyte macrophage colony-stimulating factor (GM-CSF) 20
green fluorescent protein (GFP) 58, 61

h
hamster antibody production (HAP) test 206
HDAC inhibitors 80
hemophilia 351
– factor IX (FIX) in hemophilia B 351
– factor VIII (FVIII) in hemophilia A 351
– monomeric Fc technology 356–358
– treatments 351, 352
-- FVIII and FIX plasma-derived concentrates 351
-- recombinant FIX (rFIX) 352
-- recombinant FVIII (rFVIII) 351
heparin 117, 312
hepatitis C (HCV) 351
heterodimeric Fc:Fc-FD molecule 68
hIgG4 residues 24
higher-protein-concentration products 143
high-molecular-weight (HMW) aggregates 101
hinge and interchain disulfide bonds 8
histone deacetylase (HDAC) 80
HMW aggregates 101, 103, 104, 106, 109, 111
homodimeric Fc:Fc molecule 68
homodimeric Fc-FD:Fc-FD molecule 68
host cell proteins (HCPs) 101, 159, 205
human growth hormone (rhGH) 131
human immunodeficiency virus (HIV) 351
humoral immunity 1
hybridoma technology 1, 4
hydrogen bond 130
hydrolysis 136
hydrophobic interaction chromatography (HIC) 101
hydroxypatite chromatography 101, 106
hypersensitivity reactions 69
hypoxia 80, 312, 313, 316, 324

i
ice-surface interfacial effects 130
idiopathic thrombocytopenic purpura (ITP) 59, 98, 229
IgG antibodies
-- general domain 6
-- Fab domain 6
-- Fc domain 6
-- variable domain (VL) and constant domain (CL) 6
-- isotype 1
-- structure and features, interactions 5, 6
-- T-cell-dependent response 48, 49
IL-6 antibody 273
IL-1 receptors 98
IL-6 trap 221
Immune thrombocytopenic purpura (ITP) 59
immunogenicity 15, 23, 24, 48, 159, 193, 205, 226, 360
immunoglobulin-mediated effector function 223–225
immunomodulators 49, 155
impurity tests 208
industrial cell culture, basic aspects 69
— develop/optimize a culture production process 74–77
— production cell line, central role of 69, 70
— CHO cells 69, 70
— Murine cell lines 69
— production mode 71
— fed-batch/perfusion 71–73
— benefits and challenges 72
— production systems 70, 71
— raw materials, and process control 74
— scale-up 73, 74
— energy dissipation rates 73
— mitigate GEV-related problems 73
infliximab 121, 251, 263, 265, 273, 297
inotuzumab ozogamicin 27
in situ Raman spectroscopy 134
interferon α 318, 357
interferon-β 356
interferon-γ 17, 222, 294
interferons 223
interleukin-2 (IL-2) 283
interleukin-10 (IL-10) 222
intracellular degradation 223
ionic strength 116, 129, 197
isoelectric point (pI) 100
isopropyl-β-D-thiogalactoside (IPTG) 60

k
Karl Fischer titration 136
Kozak sequence 53

l
labile proteins 116
L-arginine 131, 132
leukocyte infiltration 321
L-histidine 132
Index

licensed vector system 51
ligand binding affinity assays 202
lipofectamine 57
liquid/lyophilized formulations 118
liquid vs. lyophilized formulations, factors in selecting 126
Lonza 51, 53, 54, 364
low-protein concentration drug products 143
low-protein-concentration lyophilized products 138, 139
luminescence 202
lymphocytes 4, 67, 223, 239, 248, 255, 256, 283, 296
lymphokine-activated killer (LAK) cells 234
lyophilization 117, 126–128, 130, 132, 133, 136, 138
formulation strategy 118, 127, 128
cryoprotectant 129–132
lyoprotectant 129–132
pH and buffer 128, 129
stabilizing agents 129–132
lyophilized drug product 126, 127
lyoprotectant 131
lysosomes 223

m
macrophages 18, 223, 283
Maillard reaction 130
major histocompatibility complex (MHC) 11, 19, 283, 284, 289, 295, 301
mammalian cell lines 50, 51
mannitol 130, 133
amorphous 133
hemihydrate 133–136
transformation in Fc-conjugate protein formulation 135
metastable 133
marketed antibodies 2, 3
mast cells 223
maytansine derivatives (DM1, DM2, DM3) 27
membrane attack complex (MAC) 17
membrane chromatography 109
metal chelate chromatography 106
methionine sulfoximine (MSX) 365
MHC peptide 23
mixed-mode chromatography 106
mixed-mode resins 101
modified Gordon–Taylor equation 130
modifying effector functions 21
engineering 22
FcR-dependent effector function 21, 22
glycoengineering 22, 23
reducing and silencing effector function 23–25
molecule design 115
challenges 115
monoclonal antibodies (mAbs) 1, 20, 57, 71, 109, 118, 132, 191, 264, 291, 363
commercial, formulated drug product for 119–123
monocytes 13, 17, 18, 283
monomeric Fc-fusions 356, 357, 359
molecules 68
monomeric rFIXFc-fusion protein 360
monomethyl auristatin E (MMAE) 27
monomethyl auristatin F (MMAF) 27
MS-275 inhibitor 80
multidose formulation 142
specificity 25
murine equivalent 50
muromonab-CD3 2, 23
mutations 9, 10, 15, 21, 22, 24, 117
A29Y mutation 293
belatacept, characterized by 285
complementary mutations on Fc chains 360
in CTLA-4 extracellular domain 302
cysteine-to-serine 288
enhanced ADCC as 225
Fc mutations that silence effector function 24
Fc mutations with increased effector function 21
leucine to glutamic acid 292
refinement of abatacept 284
sites in LEA29Y, avidity-enhancing 293
YTE mutation 223

n
nanofiltration 161
natural killer (NK) cells 17–20, 22, 234, 256, 264
neonatal Fc receptor (FcRn) 4, 9, 97, 356
nerve growth factor (NGF) 48
net product value (NPV) 185, 186
average 186
calculation 186
neutralization activity 202
neutrophils 17–20, 223
N-Glycan 62
N297 glycan 125
N-glycolyneuraminic acid (NGNA) 69, 81, 85, 359
N-linked glycans 67
N-linked glycosylation
– in insect cells 62
NPlate® 67, 68, 98, 220
NPV. see net product value (NPV)
nuclear factor kB (NF-kB) 202
Nulojix® 49, 67, 98, 220

O
O-linked glycosylation
O-linked glycans 67
Opsonin–CR interaction 20
Orencia®. see abatacept
orthogonal assays, for purity 208
Orthoclone(R) OKT-3. see muromonab CD3
overages 142, 143

P
PAT strategy 106
PEGylation 223
peptibodies 59, 68, 69, 107
peptide–Fc fusions 59
phagocytosis mediation 17
– ADCP mediated 17
– CDCC mediated 17
pharmacokinetic (PK) life span 4
pharmacokinetics 115, 159
pH-engineered antibodies 16
pH optimization 115
Phosphorylation 62
Pichia pastoris 100
PK engineering method 16
placental growth factor (PlGF) 311
plasmids 53, 59, 286, 361
polyelectrolytes 109
polyethyleneimine (PEI) 57
polyhedron gene 61
posttranslational modifications (PTMs)
  50, 69, 79, 191, 199, 228, 353, 355, 361, 362
potency assay 208
process analytical technology (PAT) 136
process characterization 161
process-related impurities 159
process verification, continuous 180–182
product characterization 193, 195
– characterization of Fc-fusion proteins in 194
– physiochemical analysis 195
– determination of identity
– and evaluation of charge variants 195–198
– mass analysis and confirmation, of primary
structure 198, 199
– measurement of strength by absorbance at
  280nm 195
– oligosaccharide analysis 199, 200
– potency, measurement of 201–204
– process-related impurities and
  contaminants 204
– host cell protein 204, 205
– residual DNA 205, 206
– residual protein A 206
– tests for contaminants 206
– purity (product-related variants) 200, 201
– purity and integrity, measurement of
  198
product collapse temperature 136
product life cycle 143, 159
product release, typical
– analytical methods used in 209, 210
prokaryotic vectors 59
propeptide (PRO) 353
proprotein convertase 359
prostate surface antigen (PSA) 60
protein A 68, 103, 105, 165, 193, 206, 292, 362
protein A chromatography 68, 100, 103–105, 108, 109, 208
protein aggregation 125
protein formulation, challenges of 115
protein mobility 126
protein–protein interactions 284, 355, 360
proteins stabilization 130
protein stability 117
proteoglycans 312, 317
proteolysis 115, 126, 320, 355
proteolytic degradation 117
prothrombin 352, 354
psoriasis
– plaque psoriasis, chronic 233, 234
– treatments for 234, 235
PTMs. see posttranslational modifications (PTMs)
purification 100
– downstream purification
– future innovations 109–110
– peptibody 108
– platform approaches for 100–102
– Fc-fusion proteins
– from mammalian cells 100
– from microbial systems 107–109
– vs. mAbs during processing 104
– Global Multistep Design Space
  boundaries 169, 171
– based on statistical models 169
– polishing steps 103, 105–107
– protein A chromatography 103, 105–107
strategies to reduce aggregation 105–107
viral inactivation 103, 105–107
pyrrolobenzodiazepines (PBDs) 27
Quadroma antibodies 25
Quality by design (QbD) 157–159, 183–186
implementation (see business case)
Raman images, lyophilized samples 133, 134
recombinant FIX (rFIX) 352, 354
recombinant FVIII (rFVIII) 351
recombinant technologies 1
recombinant variants, for Fc-fusion protein 48
reference standard 207
analytical methods 208
characterization 207
regulatory guidance documents 207
relative luminescence units (RLUs) 203
release assays 207
residual moisture, impact on lyophilization 135–137
rFIXFc 228, 358–363
clinical development 367, 368
dimeric 361
factor IX for hemophilia B 67, 69
license 368
monomeric 361
process for making 362
monomeric rFIXFc in preclinical models
pharmacokinetics 366
pooled IgG competition 361
preclinical development 365, 366
and rFVIIIFc-fusion proteins 356
rFIX protein 354
rFVIIIFc 228, 363–365
clinical development 367, 368
factor VIII for hemophilia A 67, 69
license 368
preclinical development 366
rilonacept 3, 98, 220, 226, 229
risk assessment 158, 159, 162. See also critical process parameters (CPP); critical quality attributes (CQAs)
defining criticality of process parameters 162
rituximab 2, 19, 22, 48, 123, 227, 273
romiplostim 3, 59, 98, 100, 124, 220, 222, 226, 229
serine protease catalytic domain (CATALYTIC) 353
shelf life, of drug product 116
Shine–Dalgarno sequence 59
sialic acid 82
sialidase 82
sialylation 62, 104, 106, 110, 191
signal peptide (SIG) 353
single-use bioreactors 110
site-based mutagenesis 116
sorbitol 127
Spodoptera frugiperda 61
stability assays 207
methods for 210
stabilizing agents 130
steric hindrance 117
structural heterogeneity 191
characterization 191
multiple sources, result in 191
structural integrity tests 207
subtype properties 2
sugar-to-protein molar ratio 131
sulfation 68, 353, 355, 359
surface plasmon resonance (SPR)–based assays 202
surfactants
nonionic 134
reducing protein unfolding and aggregation, during lyophilization 135
synapse 26
systemic lupus erythematosus (SLE) 155
T-cell-mediated autoimmune disease 233, 234
preclinical development 234
CD2/LFA-3 234, 236
fusion protein alefacept (LFA3TIP) 236
T-cell receptor complex (TCR) 23
cells 26, 98, 234, 236, 238, 249, 283, 285, 294, 302, 332
temperature 57, 58, 83, 116, 172
ambient 137
eutectic 133
glass transition 129
and misfolding 78, 79
therapeutic agents 116
therapeutic antibodies 1
therapeutic Fc-fusion proteins 219
thermal stability 118, 125
thermogravimetric analysis (TGA) 136
thrombin 352, 354, 355
Index

thrombolytics 49

time-resolved fluorescence resonance energy transfer (TR-FRET) immunoassays 202

TNFα-Fc-fusion protein 79, 262
– characterization 262
– construction 262
– design 262
– rationale for a receptor-Fc-fusion protein 262, 264
– state of therapeutic antibodies 262, 264
tocilizumab 3, 123, 273

TPO receptor-activating peptides 67

trade-offs 115

transcytosis 11, 12, 14

transfection 50–52, 54, 55, 57, 292, 361, 362
– transient 57, 286

transmission electron microscopy (TEM) 206, 209

trastuzumab 3, 26, 28, 123, 335
– afibercept plus 324, 325
– clinical success 26
trebananib 59, 221, 222, 226, 229
trehalose 123, 130, 131
trichostatin A 80
tubulin inhibitors 27

tumor necrosis factor (TNF) 67, 255
– drugs targeting TNF for treating chronic inflammatory 262
– FDA-approved indications 262
– receptor 2, 97, 264
– receptor signaling 256–259
– role in chronic inflammatory disease 259
– ankylosing spondylitis 260, 261
– Crohn’s disease 261
– juvenile idiopathic arthritis 260

– psoriasis 261, 262
– psoriatic arthritis 260
– rheumatoid arthritis 259, 260
– ulcerative colitis 261
– signaling 256–259
– structure and function 255, 256
– therapeutic TNF blockers, structures 263
– types 256

typical product release 207

ultrafiltration 107, 351
– membrane 73

valproic acid 80

vascular endothelial growth factor (VEGF) 3, 67, 98, 311, 312, 315, 321, 322
– expression 316
– intracellular signaling pathways and downstream effects 314

viral filtration 107, 110

viscosity 115, 116, 132, 139, 140, 143, 173

vitamin K 354

Xase complex 352
– activation of factor X 352

YTE mutation 223

Zaltrap® 220