

Index

a

- N-acetylglucosaminyltransferase-III (GnTIII) 420
- active pharmaceutical ingredient (API) 25, 122, 248, 272, 466, 486, 497
- ADCs. *see* animal-derived components (ADCs)
- adeno-associated virus (AAV) 351, 357, 507, 519, 523–525, 528
- adenoviral vectors 520–522
 - large-scale productions 522
- adipose-derived somatic stem cells (ADSCs) 488, 489
- advanced therapeutic medicinal product (ATMP) regulation 497
- aglycosylated proteins 20, 23, 119
- Agrobacterium rhizogenes* 226
- airlift bioreactors 107, 239, 242, 300, 316, 317, 333, 428–430
- alcohol
 - concentration
 - in culture broth 112
 - monitoring principles 112
 - ethyl alcohol 2
 - fermentation 2
 - formation and biomass 99
 - oxidation 2
 - yield 99
- algae biomass 202
- alkaloids 288, 561, 562, 573, 580–583
- alpha-linolenic acid 30
- Ambystoma mexicanum* 465, 466
- amino acids 8, 43, 118, 263, 280, 309, 323, 325, 330, 360, 364, 578
 - catabolism 329
 - depletion 237
 - global market 30
 - isotope labeling 369
 - Japanese fermentation success story 8, 9
 - for nitrogen requirements 364
 - non-proteic 579
 - sequence, *in silico* analysis of 417
 - *in silico* analysis 417
- ammosamide A 559
- Amphiscolops breviviridis* 575
- Amphiscolops magniviridis* 575
- amylase 9, 27, 28, 31, 44, 135, 282
 - laundry and dish washer detergents 27
 - textile industry 27
- Anabaena cylindrica* 564
- anaerobic cultivations 107
- anaerobic fermentations 112
- anatoxins 560, 562
- anchorage dependent MDCK cells (CCL-34) 513
- animal-derived components (ADCs) 188, 265, 287
- animal vaccines market 24
- anthocyanins 225–227
- antibiotics 2, 4, 5, 7, 12, 22, 24, 25, 306
 - antibiotic-resistant bacterial infections 538
 - based selection systems 425
 - fermentation technology 5
 - laboratory scale, paromomycin cost 318
 - production 19, 133
 - resistance protein 424
- antibody dependent cell mediated cytotoxicity (ADCC) effect 397, 399, 421
- antibody-mimetic products 293
- antibody-producing GS-NS0 cell lines 417
- anticalins 293
- Anticarsia gemmatalis* cell line (saUFL-Ag-286) 536
- Anticarsia gemmatalis* multiple nucleopolyhedrovirus (AgMNPV) 534, 536
- AOX promoter 104
- Aplidium californicum* 572
- aplysiatoxins 562

- Aplysina aerophoba* 570
- Appelmans' method 540
- apratoxins 562
- arbutin 226, 227
- Archaea
 - DNA polymerases 558
 - global estimate of marine species 586
 - in relationship of microalgae to animal and plant kingdoms 166
 - substances of interest isolated from 557, 558
- artemisinic acid 96
- Arthrospira maxima* 560
- Arthrospira pacifica* 560
- Arthrospira platensis* 177, 209, 213, 560
- ascorbic acid 29, 96, 97
- Asia
 - fermentation plants 12
 - sterile suspension culture in 7
- Aspergillus awamori* 30
- Aspergillus flavus* 156
- Aspergillus fumigatus* 556
- Aspergillus nidulans* 137
- Aspergillus niger* 133, 135, 156
 - citric acid producer 134
- Aspergillus oryzae* 133, 135, 149, 156
- Aspergillus parasiticus* 156
- Aspergillus sojae* 133, 156
- Aspergillus terreus* 133
- astaxanthin 97, 187, 213, 567, 569, 580
- atorvastatin (Lipitor) 5
- Aujeszky's disease 507
- Australia
 - *Dunaliella* cultivation 202
 - microalgae production 209
- Austria 7
 - compliance with GMP regulations and recommendations 121
 - penicillin supply 6
- automated cell factory manipulator (ACFM) 484
- avian cell lines 393, 394
 - development of 397
 - AGE1.CR (Probiogen) 399, 400
 - EB66 (Vivalis) 398, 399
 - QOR2/2E11 (Baxter) 400–405
 - potential of
 - influenza vaccines 395–397
 - modified vaccinia virus Ankara (MVA) vaccines 393, 394
 - monoclonal antibodies 397
 - TBEV vaccines 395
 - yellow fever vaccines 394, 395
- Axolotl. *see* *Ambystoma mexicanum*
- b**
- Bacillariophyceae 167, 563
- Bacillus brevis* 46
- Bacillus megaterium* 46
- Bacillus subtilis* 46, 47
- bacteria
 - aerobic 205
 - bioprocess design 56–59
 - cultivation processes 51, 52
 - cyanobacteria (*see* cyanobacteria)
 - expression systems 114, 359, 360
 - commercial 46
 - industrial key aspects 45
 - filamentous 133
 - Gram negative 124, 538
 - heterotrophic 41
 - multi-drug-resistant 24, 538
 - non-photosynthetic 558
 - plant-cell transforming 282
 - probiotics 31
 - as production platform for various products 42–44
 - strains, selection for bacteriophage generation 538, 539
 - suspension cultures 41
- bacterial bioprocess design 56
 - media design 57, 58
 - product titer determined by 58
 - biomass concentration 59
 - productive time 59
 - specific productivity 58
 - technical and physiological constraints 56, 57
- bacterial cultivation processes 51
 - batch culture 51
 - continuous culture 52
 - fed-batch culture 51, 52
- bacterial expression systems 45, 114, 359, 360
 - commercial 46
 - company 46
 - trade name 46
 - industrial aspects 45
 - genetic stability 47–49
 - productivity 45
 - scalability 48, 50
 - solubility 45–47
 - speed/short development times, to identify production clone 50, 51
- bacteriophages 537
 - intact 24
 - isolation 539, 540
 - production 540

- bacteriorhodopsin 557, 558
- baculoviruses 350, 351, 356, 357, 372, 374, 525, 527, 528, 530, 533, 534, 536
- batch fermentation 49, 133, 146, 147, 279, 301, 377
- Baxter vaccines 514
- berberine 226
- betacyanins 226
- BHK-21 suspension cells 533
- biocatalysts 5, 14, 28, 120, 201, 205, 210
- biochemical products, serving industrial and chemical applications 28
- biodiesels 564
- bioengineering 2, 4, 64
- bioethanol 28, 96, 106
- biofuels 10, 11, 13, 17, 176, 565, 567
 - controversial issue 10, 11
 - first-generation 200
 - production 202
 - second-generation 106
- biomass 58, 77, 175, 201, 250, 556
 - acts as catalyst for product 75
 - and metabolite formation 75
 - algal 191
 - biomass growth rate 71
 - comparison of yeast biomass and alcohol yields 99
 - concentrations 58, 59, 75, 79, 106, 113, 140, 148, 150, 209, 212, 217, 219, 237, 241, 242
 - conversion rate 62
 - filamentous 275
 - growth and product formation 175
 - handling 275
 - microalgal 172, 202, 204
 - process characteristics of 268
 - production 206
 - specific activity 58
 - *Taxus chinensis* 251
 - yields 56, 60–62, 102, 177
- biooxidation 4
- biopharmaceuticals 13, 19, 33, 43, 79, 85, 96, 97, 416
 - approved proteins produced by yeasts 97
 - as fastest growing sector 43
 - glycoproteins 310
 - ICH guidelines 451
 - market 43
 - market potential for applications 312
 - plant-cell-suspension-culture-based 22
 - production of 13
 - IC/BEVS, using 357
 - products overview 20
 - relative market share of product groups 19
 - upstream processes 85
 - benefits of implementation 87
 - in infancy/questions need to resol 87
 - mechanistic process 86
 - quality by design 86
 - statistical process 86
 - bio-polishing 27
 - bioprocess(ing) 2, 39
 - accelerating bioprocess development
 - workflow 51
 - approaches towards design/optimization and manufacturing 55, 56
 - design aspects for recombinant products 51
 - bioreactor design aspects 7, 9, 24, 39, 42, 66, 107, 174, 272, 284, 302, 304, 316, 317, 331, 358, 405, 427
 - airlift bioreactors 429–430
 - anaerobic bioreactors 66
 - avian suspension culture cell lines
 - for production of vaccines and other biologicals 405, 406
 - cardinal rules for design and construction 68
 - cleaning in place 72, 73
 - configurations 39
 - for cultivation of bacteria 70
 - dimensioning 67
 - materials of construction 67, 69
 - nozzles and ports 70
 - surface quality and welding 69
 - factors, concerning design/construction 67
 - function of bioreactor 66
 - large scale suspension culture of mammalian cells 427–431
 - mass transfer 70–72
 - for microalgal cultivation 174
 - monitoring and control of bioprocesses 73
 - challenges with bioreactor standard sensors 74
 - real-time monitoring of process variables 74–76
 - standard instrumentation 73, 74
 - non-stirred bioreactors 66
 - for paclitaxel plant cell fermentation process 250
 - scale up considerations 430–431
 - mass transfer 432
 - mixing 431–432
 - pressure 432–433
 - shear 432
 - strategy 433
 - single use bioreactors (SUBs) 42, 435–436
 - standard measurement and control in 74
 - steaming in place 73

- sterilization/cleaning 73, 433–435
- stirred and aerated bioreactors 66
- for submerged cultivation 142
- for suspension culture of phototrophic plant cells 272–279
- for *Tetrahymena suspension* culture 316, 317
- vessel design, and construction 67
- wave-based bioreactor 430–431
- for yeast cultivation 107
- biosilica 575
- biotechnologically relevant species 168
 - and genetic improvement 168–172
- biotechnology products 11, 17, 19, 377
- biotherapeutics
 - microalgae-based upstream process for 189
 - protein production
 - cell line for 413
 - milestones in mammalian culture 414
 - recombinant biotherapeutic protein 414
 - biotransformation 5, 25, 120
 - benzaldehyde 5
 - steroids 5
- blue-green algae 167, 200, 563
- Bombyx mori* 350
- Botryococcus* 564
- botulinum neurotoxin 23
- bovine spongiform encephalopathy (BSE) 481
- Brachiopoda 584
- brackish toxins, from marine 562
- brevetoxin A 571
- Brevibacillus choshinensis* 46
- BRIC countries
 - industrial suspension culture 12
- brown algae 166, 563, 568, 581
- bryostatins 572
- BryoTechnology™ 262
 - basic process design aspects 265
 - cell banking 267
 - downstream 271, 272
 - expression vectors 266
 - harvest 269, 270
 - strain development (see *Physcomitrella patens*)
 - timelines of process development 272
 - transformation 265, 266
 - upstream process 267–269
 - bioreactors
 - basic design aspects 272–275
 - biomass handling 275, 276
 - current GMP-compliant upscale cascade 277
 - current limitations 277–279
 - illumination 275
 - in-process controls 276
 - process scale-up 276, 277
 - used for pharmaceutical production with 274
 - developmental timelines 273
 - homologous recombination 263–265
- butanediol 96
- butanol 3, 28
- C**
- calcitonin 23
- calibration models 113
- Candida famata* 97
- Candida lipolytica* 98
- Candida rugosa* 98
- Candida utilis* 97
- capacitance spectroscopy 112
- CAP-T cells 507
- carbon dioxide
 - emission, anthropogenic 200
 - evolution rate (CER) 111, 113
 - waste 205
- carbon source 9, 10, 29, 60, 74, 101, 102, 170, 174, 216
- γ -carboxylation 311
- β -carotene 187, 564
- carthamin 226
- case studies
 - Flublok® regulatory history 376, 377
 - paclitaxel 248–252
 - PhytoCellTec™ *Malus domestica* 243–248
 - typical DSP strategy of an IC/BEVS-derived VLP 373, 374
- Catharanthus roseus* 241
- cDNA(s) (complementary DNAs) 233
- cell banks 47, 48, 122, 124, 169, 249, 267, 392, 401, 452
 - characterization of 452, 453
- cell culture techniques 412
- cell density effect 521
- cell factory (CF) 483
- cell lines and expression technologies 417–419
 - for biotherapeutic protein production 413
 - expression vector architecture 421–424
 - chromatin opening sequences 423–424
 - insulator sequences 423–424
 - expression vectors based upon use of either DHFR/GS 417
 - expression of GOI 418
 - human (FiH) studies 420
 - manufacturing therapeutic proteins, host cell lines for 419–421

- CHO cell line, productivity 419
- current status/future developments 420–421
- development timeline 420
- product characteristics 420
- regulatory acceptance 419
- molecule compatible with cGMP 417
- NS0 cell lines, proteomic study 418
- productivity characteristics 417
- antibody-producing GS-NS0 cell lines 417
- selection criteria 421, 423
- selection markers 424–425
- targeted integration 425–427
- cell stack (CS) 483
- cell therapy product (CTP) 477, 488, 491, 493, 497
- cellulase 27, 28, 135
 - textile industry 27
- cellulose 31, 132, 135
- cephalosporin 7
- CER. *see* carbon dioxide, evolution rate (CER)
- cGMP (current good manufacturing practice)
 - compliant process 251
- Chaetoceros* 564
- chemical reactor design 39
- chemicals
 - (liquid- and solid-phase) synthesis 23
 - production volume, and bacterial host 44
- “chemostat” cultivation 147, 206
- chick embryo fibroblasts (CEF) 517
- Chikungunya 506
- China
 - *Chlorella* and *Spirulina* species, as “health food” and cosmetics 202
 - “classic fermentations,” leading in 12
 - global forces in fermentation 12, 13
 - insulin products 23
- Chinese hamster ovary (CHO) cell line 23, 32, 271, 272, 311, 397, 399, 412, 413, 414, 419, 421, 439, 442, 542
- Chlamidiales 572
- Chlamydomonas reinhardtii* 163, 169, 188, 189, 191
 - chloroplastic transformation 188
- Chlorella protothecoides* 170, 177, 191
- Chlorella pyrenoidosa* 170
- Chlorella regularis* 170
- Chlorella vulgaris* 164, 202, 204, 209
 - maintenance requirements 171
- Chlorella zofingiensis* 164, 173
- chlorophylls *a*, *b*, *c*1, *c*2, and *c*3 564, 566
- chlorophyte 188
- chloroplasts 163, 172, 188, 190, 201, 293
- cholesterol-lowering agent 25
- chrysophyceae 564
- ciliates 296
 - *Colpidium campylum* 299, 302
 - cytocortex of ciliates and a cilium 298
 - endogenous intracellular/extracellular enzymes from 312
 - established expression vectors 305–307
 - fermentation usability 304, 305
 - high-efficiency transformation protocols 305
 - mass cultivation in suspension culture 304
 - model bioreactor system
 - for simultaneous cell culture and foodstuff treatment 304
 - nuclear dimorphism 298
 - perfusion bioreactor used for high-cell-density cultures of 302
 - post-translational modification 309
 - *N*-glycosylation of proteins 309, 310
 - recombinant protein production 305
 - challenges for using *Tetrahymena* in 310, 311
 - scalability 304, 305
 - serum-free complex- and chemically-defined media 307–309
 - specific features 296
 - strengths of 304
 - suspension culture of 299–304
 - *Tetrahymena thermophila* (*see Tetrahymena thermophila*)
- ciliophora 296
- Cinachyrella* 573
- Cistanche deserticola* 238
- citric acid 3, 4, 6
 - annual production 133
 - *Candida lipolytica* 122
 - *Candida quilliermondii* 122
 - fermentation 8
 - *Yarrowia lipolytica* 96
- Clark-type electrodes 111
- cleaning in place (CIP) 72, 113, 435
- closed-loop control strategies 113
- Clostridium perfringens* 541
- coagulase-negative staphylococci (CoNS) 538
- Colpidium campylum* 299, 302
- commercial recombinant protein (insulin) 4
- common technical document (CTD) 81
- CONCO project, for venomous marine snails 15
- continuous cultivation 103, 105, 106, 147, 213, 313, 325
- continuous ethanol production 112
- continuous stirred-tank reactor (CSTR) 106, 107
- convective mass transfer 205

- coral bleaching 573
corrosion resistant material 88
Corynebacterium glutamicum 30, 46
Coscinodiscophyceae 167
CPPs. *see* critical process parameters (CPPs)
CQAs. *see* critical quality attributes (CQAs)
Crabtree effect 113
critical process parameters (CPPs) 82, 83, 113
critical quality attributes (CQAs) 82, 83, 85, 86, 113, 426, 453, 482, 488, 490
Crohn's disease 469
cryopreservation 168, 169, 233, 249, 251, 282, 470, 473, 497
Cryostor5 and 10 (Biolife Solutions) 473
Cryptocodium cohnii 177
CTP. *see* cell therapy product (CTP)
culture media 202
cumulative population doublings (CPD) 487
current good manufacturing practice (cGMP) 157
cyanobacteria 15, 165–168, 200, 557, 560, 564, 567, 570, 572
– characteristic metabolites from 561
– haracteristic metabolites 561
– substances of interest isolated from 560
– toxins from 562
Cydia pomonella granulovirus (CpGV) 534
cylindrospermopsin 562
cytokines 472, 474, 482, 492, 493
cytotoxic fermentation conditions 106
- d**
DARPs (designed ankyrin repeat proteins) 293
deamidation 118
dendritic cell culture 469, 473–474
dengue 506, 518
development master cell bank (DMCB) 400
D-glucose. *see* glucose
diabetes 96, 478
diatoms 15, 167, 168, 192, 564, 565, 568
Dictyostelium discoideum 296
dielectric (capacitance) spectroscopy 112
dietary supplements 27
dinoflagellates 568
– atypical substances isolated from 571
– cnidaria and platyhelminths symbiosis, molecules isolated from 576
– human intoxications 570
– main human intoxications caused by 570
DNA polymerases 558
docosahexaenoic acid (DHA) 30, 187, 567, 569
donor-donor variability 472
DOT sensor 147
downstream processing (DSP) 106
– complexity 54
dry cell weight (DCW) 106
Duchenne's muscular disease 523
duckweed. *see* *Lemna minor*
Dunaliella salina 188, 209, 564
Dunaliella tertiolecta 564
- e**
ecologic efficiency 204
eicosapentaenoic acid (EPA) 168, 187, 569
electronic tongues 114
electroporation 233
Elelyso™, recombinant enzyme 226
embryonic duck stem cells (EB66) 507
end-of-production cell banks (EOP) 399
endoplasmic reticulum 189
endotoxins 124, 125
enthalpy 102
enzyme-linked immuno-sorbent assay (ELISA) 266, 276, 287, 402, 403, 474, 492, 509, 578
enzyme replacement therapy (ERT) 265
enzymes 9, 30
– amylase 9, 27, 28, 31, 44, 135, 282
– bacterial proteases 9
– global sales figure 9
– glucoamylase 9
– glucoisomerase 9
– industrial, produced in yeast organisms 98
– rennin 9
– sales for food and beverages 30
– tanning industry 9
ephedra plant 5
ephedrine 5
erythropoietin 189
Escherichia coli 30, 44, 46, 52, 96, 132, 146, 413, 557
ethanol 2, 3, 28, 51, 96, 101, 117, 135, 169, 170, 434
– production 106
eukaryotes, phylogeny 563
eukaryotic expression technology 23
Europe
– companies, as leading enzyme producers 9
– companies transferred fermentation production to 12
– complementary “qualified presumption of safety” (QPS) approach 177
– EMA (European Medicine Agency) 121, 193, 450, 476
– insect cell-recombinant baculovirus platform 24

- European Recovery Program (ERP) 7
 - large scale fermentation technology in 9
 - microalgal-derived nutritional products 176
 - sterile suspension culture 7
 - vitamin manufacturers 4
 - eustigmatophyceae 564
 - exopolysaccharides (EPSs) 557
 - expression systems type of cells 40
- f**
- Fabs (fragment antibodies) 293
 - ω -3 fatty acid eicosapentaenoic acid 565
 - fed-batch cultivation 47, 50, 105, 147
 - feed products 18, 27, 31, 124
 - fermentation
 - alcoholic 2
 - amino acids 8, 9
 - antibiotics 5
 - cell density 329, 332
 - China and India, global forces 12
 - continuous fermentation coupled with tangential microfiltration 303
 - cost of
 - goods for 318
 - *Leishmania* fermentation 333
 - Europe, and European companies 9
 - fermentation of *T. thermophila* 305
 - of filamentous organisms 140–157
 - genetic stability of host and plasmid to support 47
 - heterotrophic 273
 - industrial 2, 3, 8, 133, 156, 157
 - key factors related to process economics 116
 - manufacturing of APIs by cell culture 124
 - moss fermentation processes 276
 - paclitaxel-rich fermentation 251
 - parallel 279
 - parameters defined precisely 540
 - penicillin in the USA 12
 - photoautotrophic fermentation 268
 - plant cell fermentation 248
 - products 16–32
 - sterile 2
 - technology 2, 5–8, 9, 12, 99, 126, 332
 - turning point 5–8
 - *Tetrahymena pyriformis* 300
 - batch fermentation 313
 - vitamins 4
 - yeast fermentation processes 99–105
 - fetal bovine serum (FBS) 481
 - filamentous fungi, as a production platform 39, 131, 132, 135
 - economic aspects 157
 - evolutionary advantages for 132
 - expression systems 135, 136
 - fermentation 140
 - agitation and aeration 141–143
 - bubble column reactor (BCR) 140
 - correlation between viscosity and $k_{i,a}$ 151, 152
 - dissolved oxygen tension (DOT) 140
 - mass transfer 143–146
 - mixing time and cavern formation 151
 - platforms 140, 141
 - reactor control 146, 147
 - reactor design 141
 - rheology 147–151
 - stirred-tank reactor (STR) 140, 141
 - genomic tools 137, 138
 - morphology 136, 137
 - organic acids produced at industrial scale by 134
 - process scaling 152, 153
 - dimensionless numbers 153
 - modeling oxygen mass transfer 155, 156
 - power draw 154, 155
 - validation 152
 - regulatory aspects 156, 157
 - sequencing and genome annotation 139, 140
 - available sequences of *Aspergilla* 139
 - fine chemicals 32, 96
 - flagellates 319
 - basic bioreactor design aspects for suspension culture 331, 332
 - basic process design aspects for 328–330
 - biotechnological applications, non-human pathogenic species 322
 - hemoflagellates
 - challenges for application 326, 327
 - recombinant proteins expressed in LEXSY 327
 - strengths 324, 325
 - suspension culture of 322–324
 - process economics, key factors for 332, 333
 - specific features 319
 - trypanosomatids
 - morphological types of 319–322
 - transcription in 320
 - flashing-light effect 205
 - flavoring agents 4
 - flavors 32, 165
 - flow cytometers 75
 - Flublok[®] 350, 376
 - flu cell culture (FCC) based influenza vaccines 515
 - fluoroquinolones 25
 - food and feed market 29
 - foot-and-mouth disease (FMD) vaccine 532

- Foraminifera 556, 584
 Fragilariophyceae 167
Fragilariopsis cylindrus 169
 fragment antibodies 23, 293
 fragment antigen-bindings (Fabs) 43
 fucoxanthin 564–567, 581
 fungal cultures 2
- g**
- gambierol 571
 GAP promoter 104
 gene of interest (GOI) 418
 generally recognized as safe (GRAS) 121, 156, 176, 334
 gene therapy 24, 351, 357, 377, 504, 519, 532
 genetically modified organisms (GMOs) 107, 136, 157, 163
 genetic transformation
 – to cell banking 189
 – of plant cells, methods 234
 Germany 9
 – companies joined amino acid party 9
 – fermentation technology 6
 – mass cultivation of microalgae 203
 – photobioreactor 214, 216
 – producing *Chlorella* as food additive 213
 – selling extracted enzymes for tanning industry 9
 ginseng saponins 226
Glarea lozoyensis 137
 global chemical market 27
 global stem cell market 23
 global vaccine sales 24
 glucanase 26, 29, 31
 glucoamylase 31
 β -glucocerebrosidase 265
 glucoisomerase 9, 31
 gluconic acid 4, 134
 glucose 4, 30, 46, 60, 102, 104, 133, 169, 171, 192, 309, 329, 333, 358, 366, 404, 437
 glucose isomerase 3, 29
 glucose-transporter 170
 – for trophic conversion 172
 glucuronoxylomannan 32
 glutamate 29, 30, 170, 364
 glutamic acid 3, 8, 9, 44, 311
 glutamine synthetase (GS) 417
 glycerol 47, 48, 96, 101, 102, 104, 170, 233, 564
 glycoamylase 136
 glycopeptides 23
 glycoproteins 136, 189, 191, 312, 351, 354, 373
 glycosylation 118, 125
 glycotransferases 264
- GMOs. *see* genetically modified organisms (GMOs)
 GMP. *see* good manufacturing practice (GMP)
 good manufacturing practice (GMP) 77, 192, 226, 231, 273, 370, 399, 472, 474, 524, 528
Gorgonia flabellum 573
Gorgonia ventalina 573
 gram negative cell factory 52, 53
 – chaperones 53
 – compartments 52
 – disulfide bond formation system 53
 – periplasmic space 52, 53
 – pH homeostasis 52
 – targeting proteins 53
 – translocation 53
 – twin-arginine translocation 53
 granulocyte monocyte colony stimulating factor (GM-CSF) 475
 granulocytes 469
Grateloupia turuturu 578
 griffithsin (GRTF), anti-HIV protein 578
 gross national product (GNP) 8
 growth factors 20, 23, 26, 355, 399, 472, 474, 478, 482, 491
- h**
- HA-1179 cells growth 535
Haematococcus pluvialis 176, 188, 209
Haloarcula japonica 557
Halobacterium halobium 557
Halobacterium salinarum 557, 558
Haloferax mediterranei 557
Hansenula polymorpha 97, 98
Haslea ostrearia 564
 HaSNPV, *in vitro* production 536
 heat of combustion 103
 heat transfer 77, 79
 heavy chain (HC) mRNA 418
 HEK293 cells 517, 520–523, 525, 526, 528, 529, 530
 hematopoietic stem cells (HSCs) 469, 475
 hemicelluloses 31
 hemocyanin 575, 579
 Henrietta Lacks cell line (HeLa) 412
 Henry Ford 11
 hepatitis C virus (HCV) 518
 – non-structural antigens 518
 – therapeutic vaccine (TG4040) 518
 heterologous proteins 172
 heteromeric proteins 23
 heterotrophic bacteria 41, 42
 heterotrophic plant suspension cells 235
 – categorization approach based on 239
 – critical dissolved oxygen (DO) levels 236

- cultivation temperature 236
 - culture characteristics 235
 - DDCs and CMCs 235, 236
 - culture media 236, 237
 - primary cell metabolism 236, 237
 - process design 235
 - process mode 237, 238
 - specific oxygen uptake rate 236
 - suitable bioreactors 238
 - categorization approach 238–240
 - disposable bioreactor 241, 242
 - OrbShake Bioreactor 241, 242
 - plastic-lined bioreactor 241, 424
 - re-usable vs, disposable bioreactors 240
 - Saltus™ 242
 - single-use bioreactors 239
 - types 240–243
 - typical cultivation parameters 235
 - heterotrophy 203, 204
 - H5N1 wild-type virus 514
 - history 2–15, 39, 98, 124, 132, 156, 202, 215, 349, 376, 412, 514
 - homogenizer 88
 - Horseshoe crab 575
 - host cell proteins 55, 100, 104, 125, 283, 285, 287, 374, 376, 445
 - secreted 271
 - human mesenchymal stem cells (hMSCs) 467
 - human serum albumin (HSA) 495
 - Hydrocoleum lynghyaceum* 560
 - hydrolase 30
 - 3-hydroxypropionic acid 27
 - hygienization 206
 - Hymenostomatia 297
 - Hyoscyamus muticus* 242
 - hyperstack (HS) 483
- i**
- inactivated polio virus vaccine (IPV) 505, 508, 509, 511
 - India 13
 - *Dunaliella* cultivation 202
 - global forces in fermentation 12, 13
 - insulin products 23
 - microalgae production 209, 217
 - indoleamine 2,3-dioxygenase (IDO) 492
 - indolic alkaloids 561
 - industrial fermentation 2, 133, 157
 - application of fungi 133
 - commodity-oriented 13
 - large-scale sterile 2
 - industrial production strategy
 - batch phase for accumulation of biomass 60
 - concept of time-space yield 65, 66
 - fed-batch phase process
 - design from scratch 61–63
 - fed-batch process parameters
 - with impact on induction phase productivities 65
 - induction phase 63, 64
 - process parameters impacting recombinant product formation 64
 - structured approach towards batch design 60, 61
 - by two-step cultivation 59
 - industrial scale suspension culture 2
 - of living cells, history 3
 - industrial strategies 53
 - active protein conformation demand protein refolding 54, 55
 - downstream process complexity 54
 - implementing chromatographic steps 55
 - measures to reduce extent of inclusion body formation
 - and formation of soluble target protein 54
 - recombinant products
 - soluble extracellular production of 53
 - soluble intracellular production of 53
 - recombinant proteins
 - production as insoluble aggregates 53
 - influenza virus/vaccines 395, 506
 - anchorage dependent cell lines, use of 512–514
 - cell lines adapted to suspension growth 514–517
 - conventional methods 512
 - drawbacks associated with egg-based production 396
 - influenza A virus 517
 - scale-up production 512
 - trypsin at an optimal activity, to allow cleavage of HA precursor 512
 - Vero and MDCK technologies 397
 - virus replication 511
 - virus strains 512
 - in-process control (IPC) strategies 113, 119, 125, 251, 275, 276, 467
 - insect cell/baculovirus expression vector system (IC/BEVS) 350, 373, 374
 - insect cell culture 351–358
 - bioreactors 358–364
 - design requirements 358–364
 - DO values 362
 - modes of operation 362
 - variable, to consider/control 361

- characteristics and comparison with other expression systems 359, 360
- IC/BEVS gained acceptance as a universal manufacturing platform
- approval of vaccines, Glybera 377
- history 349
- industrial insect cell based cultures 365
- bottom-up approach 366, 367
- downstream process development strategies 370–374
- upstream process development strategies 367–370
- maintaining insect cells in culture 358
- production cycle and yields, improvements in 377
- cell culture media 377
- fed-batch fermentation 377
- viral and host modifications 377
- regulatory hurdles, for insect derived human products 374–376
- additional testing 376
- Flublok[®] regulatory history 376
- Q-PERT assay data 375
- insect cell metabolism 364–366
- insect cell–recombinant baculovirus platform 24
- insulin products 23
- interleukin 189
- internal ribosome entry site (IRES) 422
- inverted terminal repeats (ITRs) 523
- IPTG-induced promoters 46
- IPV. *see* inactivated polio virus vaccine (IPV)
- isobutanol 96
- Isochrysis galbana* 565

j

- Japan 11
- amino acid fermentation 8
- *Chlorella* and *Spirulina* species, as “health food” and cosmetics 202
- companies to produce penicillin 7
- culture-based secondary metabolites 226
- fermentation industry, annual turnover 8
- mass cultivation of microalgae 203
- production of flavor enhancer 9
- UNRRA provided support to 7
- Japanese Encephalitis 506, 518

k

- Kahalalides 579
- kainic acid 578
- Keyhole limpet hemocyanin (KLH) 579
- kinetoplastida 296

- Kluyveromyces lactis* 30, 98
- Kolmogorov’s eddy length model 505
- kSepTM, elutriation technology 495

l

- lactic acid 2, 4, 29, 96, 134, 140, 404, 441
- Lactobacillus plantarum* 31
- Lactococcus lactis* 46
- Lamelloglycydium herbacea* 570
- L-arabinose 46
- Lauderia borealis* 565
- Leishmania tarentolae* 322, 324, 334, 335
- bioreactor design 331, 332
- cell densities 324, 329, 330
- challenges for application 326, 327
- classes of products and main markets 327
- constitutive protein production in recombinant strain 332
- EGFP expression 322, 323
- market value 327
- LEXSY 327, 328
- RAPSODI 328
- media costs for fed batch culturing 333
- resistant to shear stress 331
- strengths 324
- suspension culture, basic process design aspects 328–331
- Lemna minor* 260, 262, 280
- α -amylase signal peptide 282
- morphology 281
- lentinan 29, 32
- lentiviral (LV) vectors 519
- Lepidoptera 349–351, 536
- Leuconostoc mesenteroides* 31
- leukocytes 468
- LEX-System (LEX[®]-technology) 280
- basic bioreactor design aspects 284, 285
- basic process design aspects 281
- downstream 283
- expression vectors 281, 282
- master-plant banking 282
- strain development 282
- upstream process 282, 283
- biotechnological aspects of Duckweed 280, 281
- developmental timelines in 281
- Duckweed taxonomy 280
- key factors related to process economics 285, 286
- *Lemna*- and *Physcomitrella*-based production 285
- advantages 285
- economic considerations 285

- *Lemma* USP-design 284
- physiology and morphology 280
- regulatory aspects 286–288
- timelines of process development 281
- L-glutamic acid 8, 44
- Limulus* amoebocyte lysate (LAL) test 575
- Limulus polyphemus* 575
- linoleic acid 30, 134
- linolenic acid 29, 30, 560
- lipases 27, 30
 - laundry and dish washer detergents 27
 - leather industry 27
- lipopeptides 561
- lipoprotein lipase 24
- Lissodendoryx isodictyalis* 572
- Lithospermum erythrorhizon* 225, 241
- live biotherapeutic products (LBP) 32
- L-lysine 30, 44
- lovastatin 133
- L-rhamnose 46
- L-threonine 30
- L-tryptophan 30
- lyngbyatoxins 562
- lysosomal storage diseases (LSDs) 265

- m**
- macroalgae 15, 165, 564, 575
- macrocyclic lactones 568
- macroorganisms culture, substances isolated
 - by 575, 575
 - green algae 579
 - marine spermatophyta 578
 - molluscs 579
 - red algae 578
- malyngamides 561
- mammalian-cell-based expression system 293
- mammalian cell culture 416
 - batch and fed-batch culture 436–438
 - bioreactor design 427, 428
 - airlift bioreactor 429, 430
 - stirred-tank bioreactor 428, 429
 - wave-based bioreactor 430, 431
 - commercial importance 414–415
 - milestones in production of biotherapeutic proteins 414
 - control parameters 440
 - carbon dioxide concentration 442
 - dissolved oxygen concentration 442
 - osmolarity 443
 - pH value 441–442
 - temperature 440–441
 - culture media/feeds 439
 - development, significant milestones 413
 - history 412–413
 - industry 415–417
 - to maintain sterile operation 433–435
 - cleaning in place (CIP) system 435
 - sterilization process 435
 - non-nutrient additions 439–440
 - perfusion culture 438
 - process economics 443–450
 - antibody process economics case studies 447–450
 - challenges 443–444
 - fed-batch vs. perfusion decisions 448–449
 - legacy purification facilities, robustness 450
 - stainless steel vs. single use decisions 447–448
 - for protein production 413–414
 - regulatory aspects 450
 - cell banks 452
 - cell substrate stability 452
 - characterization of cell banks 452, 453
 - expression vector 452
 - ICH guidelines relating to biopharmaceutical production 451
 - quality by design (QbD) 453
 - source, history, and generation of 451–452
 - scale up considerations 431
 - mass transfer 432
 - mixing 431, 432
 - pressure 432, 433
 - scale up strategy 433
 - shear 432
 - single use bioreactor systems 435, 436
 - suspension 296
- manufacturing flexibility 79
- marine cyanobacteria. *see* cyanobacteria
- marine-derived compounds, estimate 567
- marine organisms, cultivable
 - archaea, culture 557–558
 - cyanobacteria 560
 - non-photosynthetic bacteria 558–560
- marine species, global estimate 556
- marketed products, of marine origin 580–583
- markets 16–32, 42, 177, 312, 417
- Marshall Plan 6
- mass flow controllers (MFCs) 112
- mass transfer 70
 - rates 77
- master-cell bank (MCB) 267, 399, 452, 453
- maximum oxygen transfer rates 62, 77, 78
- MCB. *see* master-cell bank (MCB)
- MDCK cell line 506, 514, 516

- adapted to suspension growth (MDCK. SUS2) 516
- in serum-free medium 513
- mechanism of action (MoA) 490
- MedImmune Vaccines 513
- Megathura crenulata* 579
- mesenchymal stem cells (MSCs) 467, 476, 477
- metabolite monitoring 113
- metabolomics 235
- methanol 10, 101–104, 108–110, 117
 - concentration in culture broth 112
 - concerns regarding usage 108
 - flash point and NFPA guideline 108
 - ignition energy 108
 - lower explosion limit 108
 - equipment design 108, 109
 - process monitoring and control solutions 111
 - classical four parameters 111, 112
 - regulations 110
 - authorities and standards 110
 - Logos for safety standards 110
 - risk assessment 109, 110
 - parameters defined, during fermentation 109
 - safety measures 108
 - storage tanks 110
- methanol/sorbitol ratio 103
- methylotrophic *Pichia* strains 10
- methylotrophic yeasts 101
- microalgae 165, 166, 201
 - access to axenic cultures 167, 168
 - basic process design aspects 203–206
 - biomass as source of high quality
 - and standardized plant-like ingredients 173
 - bioreactor design 174
 - in biotechnology 201, 202
 - cells cultivation, for recombinant therapeutic proteins 189–192
 - cryopreservation 190
 - extensive screening to isolate best clones 190
 - GMP requirements 192
 - guideline Q5A/Q5B 193, 194
 - ICH provide useful basis for upstream process development 193
 - regulatory aspects 192, 193
 - transformation of microalgal cells 190
 - commercialization of microalgae-derived products 176–178
 - cultivation for biomanufacturing applications 193
 - cultivation under different trophic conditions 171
 - culture media, and process control strategies 174–176
 - evolution and taxonomy 201
 - industrial microalgae biotechnology 202, 203
 - large-scale cultivation systems 206, 207
 - maintenance requirements of *Chlorella vulgaris* 171
 - mass cultivation systems
 - cultures collections 203
 - general assets and drawback 208
 - historical perspective 202
 - open ponds technology 207–211
 - production sites using 209
 - process design 174
 - process economics 176
 - production site 217
 - propagation 173
 - regulatory aspects 176–178
 - relationship to animal and plant kingdoms 166
 - screening for bioactivities 167, 168
 - species with ability, to grow on organic carbon sources 170
 - strategies for productivity enhancement 175
 - taxonomy 166, 167
- microalgal lipids 172
- microalgal technologies, commercialization 176
- microbial production, of acids 4
- microbial transformations
 - of steroids 5
- microcarrier based cell cultures 485, 505
 - development of 506
 - HEK293/Per.C6 cells 522
- Micromonospora marina* L-13-ACM2-092 559
- microorganisms 31
 - for food processing 31
 - photosynthetic 200
 - phototrophic (*see* cyanobacteria; microalgae)
 - suspension cultures 508
 - yeast for human requirements 95
- modified vaccinia Ankara (MVA) 517
 - ACAM3000 517
 - biosafety 517
 - cell lines, derived from 517
 - immunogenicity testing for recombinant vaccines 518
 - investigated as a vaccine vector, against infectious disease targets 518
 - production in suspension cell lines 517–519

- MVA (MVA-CR19), selection novel genotype 519
 - programs in clinical development using
 - TG4040 518
 - TroVax 518
 - monensin 44
 - monoclonal antibodies (mAbs) 23, 33, 43, 293
 - sales volume 23
 - technology 414
 - ADCC effect, CHO cell line engineering 421
 - therapeutic antibodies 415
 - monocytes culture 473
 - monophage 538
 - monosodium glutamate (MSG) 30
 - Moss. *see Physcomitrella patens*
 - mouse hind-limb ischemia model 478
 - MRC-5 cells 505
 - MSCs. *see* mesenchymal stem cells (MSCs)
 - multi-drug-resistant bacteria 24
 - multiple-drug-resistant organisms (MDROs) 25
 - multiplicity of infection (MOI) 540
 - murine-cells-based expression platform technologies 23
 - MVA. *see* modified vaccinia Ankara (MVA)
- n**
- Nannochloropsis oculata* 170, 213, 565
 - natural killer (NK) cells 397, 469, 474–475
 - natural products 43
 - near-infrared (NIR) probe 112
 - neosaxitoxin 571
 - Nereis succinea* 573
 - Nicotiana benthamiana* 578
 - Nicotiana tabacum* 229, 241
 - DDC-based suspension culture 236
 - nisin 29, 31
 - nitrogen 205
 - sources 74
 - Nitzschia alba* 168, 170, 564
 - Nitzschia laevis* 168, 170
 - non-acidophilic organisms 132
 - non-GMO microalgal strains 172
 - optimization 172
 - non-MAb glycoproteins 20, 23
 - non-photosynthetic bacteria 206, 557
 - substances of interest isolated from 558–560
 - non-transformed suspended plant cells 233
 - genetically modified 233, 235
 - NS0 cell lines 418
 - nutraceuticals 27
 - nutraceuticals, dietary supplements 27
 - nutrition companies 31
 - nutrition market 27
- o**
- obligate photoautotrophs 172
 - off-gas analysis 74
 - okadaic acid 571
 - omega-3 and omega-6 fatty acids 30
 - open ponds technology 207, 208
 - energy consumption 210, 211
 - performance 209, 210
 - production sites 208, 209
 - Opika-1™ 578
 - optical density (OD) 112, 540
 - optical sensors 114
 - oral polio vaccine (OPV) 508
 - organic acids 2, 4, 134
 - producing by global pharmaceutical companies 4
 - organic carbon source 206
 - Oscillatoria spongelliae* 570
 - oscillatoxin A 562
 - osmotic strength 174, 233, 266, 362
 - OTR. *see* oxygen, transfer rate (OTR)
 - OUR. *see* oxygen, uptake rate (OUR)
 - oxygen
 - control of dissolved oxygen 73
 - heterotrophic metabolism decreases levels 206
 - imposes additional cost to the process 72
 - limitation 78, 79
 - modeling oxygen mass transfer 155, 156
 - transfer rate (OTR) 66, 71, 77, 78, 107, 361
 - uptake rate (OUR) 58, 61, 63, 71, 99, 111, 113, 236, 361
- p**
- paclitaxel 96, 226
 - bioreactor for paclitaxel plant cell fermentation process 250
 - case study 248–252
 - cultivation systems and bioreactor sizes 251
 - PCF™ process 252
 - Palmaria palmata* 578
 - Paramecium aurelia* 299
 - Paramecium caudatum* 299
 - Paramecium tetraurelia* 299
 - partial least-squares (PLS) analysis 113
 - Pasteur, Louis 2
 - PAT system 84, 111, 113
 - Pavlova lutheri* 565
 - pBAD promoter 46

- PBRs. *see* photobioreactors (PBRs)
- PCCT (plant cell culture technology) 225, 227
 - commercially manufactured by 227
- pectin 31
- pectin methyl esterase 31
- penicillin
 - manufacture 6
 - plant 6
 - production in China 7
- Penicillium camemberti* 133
- Penicillium chrysogenum* 133
- Penicillium notatum* 133
- Penicillium roqueforti* 133
- peptide hormones (cytokines) 23
- Per.C6 cell line 509, 515
- peridinin 571
- personal care products 25–27
- Phaeodactylum tricoratum* 169, 188, 191, 192, 194, 214, 564, 565
 - cultivation expressing a monoclonal antibody using
 - single-use wave-system bioreactor 192
 - cultivation under heterotrophic condition by metabolic engineering 192
- pharmaceutical companies
 - producing vitamins/organic acids 4
- pharmaceutical QbD framework 80
- phosphorous 205
- photoautotrophy 188, 195, 265
- photobioreactors (PBRs) 177, 203, 211, 212, 215, 272, 278
 - design 211
 - requirement 212
 - flat-panel airlift (FPAs) photobioreactors 216
 - light source 212
 - setup for indoor and outdoor cultivations 212
 - tubular (*see* tubular photobioreactors)
- photoinhibition 204, 205, 207, 213
- photolimitation 204, 207, 213
- photolithoautotrophy 203–205
- photosynthetic microorganisms 200
- pH sensors probe 70, 74, 112, 213, 239
- phycobiliprotein 578
- phycocyanine 173, 560
- (*R*)-phycoerythrin 578
- Physcomitrella patens* 259, 262–265, 263, 273
 - cake 270
 - glycodesign and tailored production platforms 264
 - homologous recombination 263–265
 - industrial scale development 265
 - life cycle and physiology 262, 263
 - HCP background 271
 - production process, with cGMP bulk API 272
 - recombinant protein production in 265
- phytase 31
- PhytoCellTech™-derived bioactive compounds 226
- Pichia angusta* 98
- Pichia pastoris* 47, 97, 104, 118
 - key characteristics on glycerol, methanol, and sorbitol 104
 - specific parameter for design of fed batch process 102
 - typical fed batch production strategy
 - for methanol induced recombinant protein production (RPP) by 101
- pigments 170, 172, 173, 204, 564, 567
 - unicellular eukaryotes 567
 - unicellular photosynthetic microorganisms 566
- Planctomycetales 572
- plant cell-derived cosmetics 243
- plant cells, methods for genetic transformation 234
 - *Agrobacterium*-mediated transformation 235
- plant cell suspension cultures 229
 - plant stem cells 231–233
 - *in vitro* initiation and maintenance 229
- plant genome 226
- plant-made pharmaceuticals (PMPs) 226, 286
- plant stem cells 231–233
- plasmid DNA (pDNA) 24
- platyhelminths symbiosis, molecules isolation from 576
- pleuromutilin 7
- Plexaura flexuosa* 573
- pluricellular organisms, substances isolated from
 - bacteria 570–572
 - bryozoans 572
 - cnidaria 573–574
 - didemnidae 572–573
 - dinoflagellates 573–575
 - platyhelminthes 575
 - prochlorophyta 572–573
 - sponges 570–572
- pO₂ and pH sensors 74
- polio virus/vaccines
 - Global Polio Eradication Initiative 508
 - IPV production, future perspective 511–512

- using Per.C6 cell line 509–511
 - oral polio vaccine (OPV) 508
 - production of different polio virus strains and D-antigen
 - using Vero and Per.C6 based culture processes 510
 - stirred-tank reactors using Vero cells 508, 509
 - poly- β -hydroxyalkanoate 560
 - poly- β -1,4-*N*-acetylglucosamine 188
 - poly(ethylene glycol) (PEG) 233
 - polygalacturonase (pectinase) 31
 - polyhedral inclusion bodies (PIBs) 536
 - poly(hydroxyalkanoate)s (PHAs) 557, 559
 - poly β -hydroxybutyrate (PHB) 559, 560
 - polymethoxyalkene 560
 - polysaccharides 32, 173, 187
 - polyunsaturated fatty acids (PUFAs) 30
 - polyvalent phage preparations 538
 - poribacteria 572
 - post production cell bank (PPCB) 401
 - post-translational modifications 39, 52, 97
 - eukaryotic 265
 - prebiotics 29, 31
 - pre-master cell bank (PMCB) 401
 - preservatives 4
 - principal component regression (PCR) 113
 - prion 172
 - probiotics 24, 29, 31
 - process analytical technology (PAT)
 - initiative 111
 - process design flexibility 79
 - process economics 87
 - comparison of product yields, intracellular vs. extracellular 88–90
 - economic effects by intracellular product location 88
 - optimization of overall productivity
 - and capital expenses of production facility 87, 88
 - Prochloron didemni* 573
 - Prochlorophyta 572
 - ecological characteristics of genera 572
 - Prochlorothrix* 572
 - products by fermentation 16–32
 - product candidates, for autologous cell therapies 470, 475
 - proinsulin 188
 - proteases 27, 30, 31
 - inhibitors 117
 - laundry and dish washer detergents 27
 - leather industry 27
 - textile industry 27
 - protein based virus-like particles (VLPs) 23
 - protein deamidation 118
 - protein expression processes 511
 - protein-free suspension growth 514
 - protein production, in yeasts 98
 - proteins 96, 134, 135
 - anti-freeze 14
 - biopharmaceutical 303, 336
 - biotherapeutic 414, 417
 - glycoproteins 238, 578
 - heterologous 134, 136, 358
 - lentiviral 529
 - pharmaceutical 44, 264
 - recombinant 10, 45, 52, 53, 57, 76, 114, 126, 189, 190, 194, 269, 310, 313, 314, 327, 335, 355, 358, 368, 412, 536
 - single cell proteins (SCP) 9
 - protozoa
 - defined as 295
 - ICH guidance for industry S6 334
 - production organism, regulatory aspects of 334, 335
 - Pruteen 10
 - prymnesins 565, 566
 - Prymnesium* 565
 - Pseudomonas fluorescens* 46
 - Pseudo-nitzschia multiseries* 169, 564
- ## q
- QOR2/2E11 (Baxter) 400
 - characterization and GMP qualification 401
 - chicken embryo cell line PBS-12SF 405
 - establishment of QOR2/2E11 400, 401
 - MVA virus replication on cells at different MOIs and temperature 403, 404
 - virus growth in QOR2/2E11 cells 401–403
 - “qualified presumption of safety” (QPS) 177, 178
 - quality by design (QbD) 79–87, 111, 453
 - challenges for putting QbD into practice 84
 - industrial doubt and vague regulatory guidance 84, 85
 - industrial hesitation to share information 85
 - validation of design space 85
 - validity of risk assessment 85
 - entry points to QbD for manufacturers 84
 - process development along QbD principles 82–84
 - regulatory drive towards implementation 80–82
 - quality management system 251
 - quality risk management tools 81
 - quality target product profile (QTPP) 82

r

- rabies virus 504, 532
- Raman spectroscopy 74, 113
- Raphidium* 564
- Raphidophyceae 564
- real-time monitoring 113
- recombinant *Autographa californica* nuclear polyhedrosis virus (AcNPV) 350
- recombinant chymosin 30
- recombinant DNA technologies 11, 42, 96
- recombinant glucocerebrosidase 23
- recombinant protein production 265
 - cost effectiveness 114
 - estimation of cost of goods with model simulations 119, 120
 - expression system and its impact on the cost of 118
 - influence of expression system on analytical scope in production 119
 - additional costs 119
 - final release analysis 119
 - in-process controls (IPCs) 119
 - key factors influencing manufacturing costs
 - downstream processing 115
 - equipment requirements 114, 115
 - by yeast suspension culture 114
 - key factors related to process economics 114
 - cycle time 117
 - formation of by-products 118
 - raw materials 116, 117
 - with microalgae (*see* microalgae)
- recombinant proteins 10, 11, 42, 44, 45, 52, 53, 54, 57, 76, 114, 126, 189, 194, 269, 310, 313, 314, 327, 335, 355, 358, 368, 412, 536
- recombinant therapeutic proteins 42, 189, 190, 193, 419
 - cultivation of microalgal cells for production of 190–192
 - regulatory aspects 192–194
- red biotechnology 42
- Redoxon 4
- redox potential measurement 112
- regenerative medicine 465
 - allogeneic therapies 476
 - activity 477–478
 - animal models 478–479
 - definitions, current 477
 - historical backgrounds 476, 477
 - immunity/manufacturing 480
 - lack of rejection 479–480
 - manufacturing/technology transitions 480
 - safety 479
 - aquatic salamander 465, 466
 - autologous therapies 468–470
 - dendritic cell culture 473–474
 - hematopoietic stem cells (HSCs) 475
 - natural killer (NK) cells 474–475
 - T-cells 470–473
 - challenges, to manufacturing 480
 - adult somatic stem cells 488
 - biological limitations, to culture expansion yields 482
 - bioproduction *vs.* MSC biology, lessons from 484–485
 - cell testing 493–494
 - critical quality attributes (CQAs), for therapeutic cells 488–490
 - current solutions 483, 484
 - dosing expectations 481
 - industrial cell lines, adaptation/directed evolution of 486
 - markers *vs.* process 483
 - potency testing 490–493
 - practical challenges 493
 - regulatory expectations 482
 - stirred-tank bioreactors, providing scalable adhesion surfaces 487–488
 - therapeutic cells, adaptation 486–487
 - downstream processing 494–496
 - economic success 496–497
 - regulatory aspects 497
 - therapeutically valuable cells 466–468
- regulatory standards 120
 - comparability of biotechnological products after process changes 125, 126
 - compliance with GMP regulations and recommendations 121
 - construction and quality of cell banks 122, 124
 - food ingredients 121
 - GMP regulatory aspects 121
 - HACCP principles 121
 - ICH guidelines 121
 - International Organization for Standardization 121
 - ISO certification and control authorities 121
 - manufacturing of APIs by cell culture/microbial fermentation 124
 - pharmaceuticals 121, 122
 - phases of clinical drug development: 123
 - product applications and corresponding regulatory levels 120, 121
 - regulatory aspects to consider/guidelines 122
 - ICH-quality (ICHQ) guidelines 122

- test procedures and acceptance criteria for biotechnological products 125
- Reichstein, Tadeusz 4
- rePAX[®] 350
- replication competent adenoviruses (RCA) 520
- replication competent lentiviruses (RCLs) 527, 531
- retroviral transduction 471
- Rhizopus oryzae* 156
- Rhodobacter* 564
- risk management 81
- RNA processing signals 418
- Ross River 506
- rotavirus 506
- Russia 7
 - cultivation, microalgae using artificial media 202
 - fermentation plants for production of enzymes 12
 - penicillin production 7
 - production of phages as medical preparations 537
- S**
- Saccharomyces boulardii* 31
- Saccharomyces cerevisiae* 96, 97, 132
- Salinispora tropica* 559
- salinosporamide A 559
- Samia cecropia* 349
- Santalum album* L. 241
- saxitoxin 571
- Scenedesmus actus* 170, 203, 564
- scFv (single chain antibodies) 293
- Schizosaccharomyces pombe* 98
- secondary-metabolites 25, 96
 - heterogenic nature 25
 - with industrial relevance produced by yeasts 97
 - lovastatin 133
- sensor accuracy 73
- serum-containing culture medium 470
- serum-free suspension cultures 507
- shikonin 225
- single cell protein (SCP) 9, 10, 205
- single use bioreactors (SUBRs)
 - advantages 76
 - for insect cells 365
 - for mammalian cells 431
 - for microbial cultivation 76–79
 - applications 79
 - microbial bioprocess development using single use bioreactors 77–79
 - multi-use/single use 76, 77
 - for plant cells 239
- SIN-LV vector 528
- sitagliptin (Januvia) 5
- smallpox virus vaccines 506
- software sensors 75
- solvents 2, 28, 42, 43, 88, 89, 109, 172
- sorbitol 28, 102, 103, 233
- specific growth rate 77, 113
- spiruline 560
- Spodoptera exigua* multiple
 - nucleopolyhedrovirus (SeMNPV) 534
- Spodoptera frugiperda* 350
 - cell lines IPLB-Sf21 536
 - Sf-9 and Sf-21 348, 351, 356
- sponge cell culture, substances isolated from 575, 577
- squalene 569
- stabilizers (gelatin) 31
- stainless steel bioreactors 77
- stainless-steel reactors 174
- standard stirred tank bioreactor 70
 - time–space yield 67
 - typical dimensions, for microbes cultivation 67
- Staphylococcus aureus* 195, 538
- starch 30
- steaming in place (SIP) 73
- stem cell factor (SCF) 475
- stem cell therapy 480
- sterilization 73
 - as crucial factor 206
 - empty 73
- steroids 5
- stirred-tank bioreactors 69, 485
 - design 429
- streptomycin 6
- submersed cell culture 2
- substances isolated from
 - cyanobacteria 560
 - dinoflagellates 571
 - macroorganisms culture 575–579
 - microorganisms/bryozoans and microorganisms/ascidians associations, 574
 - unicellular eukaryotes 560–567
- succinate 27
- SUCIAC, pilot plant for the fermentation process 6
- sulfated cinnamic acid 578
- sulfonamides 25
- suspension culture (fermentation). *see specific suspension cultures*

- sVero cells suspension 511
- sweeteners 31
- Symbiodinium* 569, 573, 576
- t**
- Taiwan
 - *Chlorella* and *Spirulina* species, as “health food” and cosmetics 202
 - microalgae production sites using open ponds 209
- tangential flow filtration (TFF) 494, 495
- Taxus chinensis* 241, 248
- T-cell receptor (TCR) 474
- T-cells 470–473, 472
- temperature 57, 60, 66, 100, 111, 112, 137, 219, 240, 317, 356, 404
 - cultivation 55, 558
 - fermentation 109, 540
 - reduced conditions 441
- Tetrahymena pyriformis* 300, 334
- Tetrahymena rostrata* 300
- Tetrahymena thermophila* 297, 300, 301, 303, 304, 335
 - acceptor vectors pAX and pKOIX 308
 - basic process design aspects for suspension culture 313
 - aeration 315, 316
 - agitation rate 315
 - antifoam reagents 315, 316
 - cell counting 314, 315
 - dissolved oxygen concentration 315, 316
 - dry mass 314, 315
 - inoculation titer 314, 315
 - mucocyst material 316
 - principal bioreactor set up for 313
 - shear stress 315
 - bioreactor design aspects for suspension culture 316, 317
 - technical data of bioreactors 317
 - Cre-recombinase dependent vector system for 307
 - key factors in process economics 317
 - cost of goods for fermentation 318
 - investment costs 317, 318
 - as new production platform technology 311–313
 - recombinant proteins expressed in 314
- Tetraselmis* 564
- Thalassiosira pseudonana* 169
- thallophytes 200
- therapeutic cell therapy 480
- therapeutic proteins 17, 120, 188, 242, 419, 420, 431
 - therapeutic stem cells, commercial scale production 488
- thiamin 4
- thiocoraline 559
- thraustochytrids
 - docosahexaenoic acid (DHA) production 568
 - EPA/DHA production 567
 - substances of interest 569
- thraustochytriosides 569
- thrombopoietin (TPO) 475
- time–space yield 65, 67
- tissue plasminogen activator (TPA) 414
- Tistrella bauzanensis* 573
- Tistrella mobilis* 573
- total fatty acids (TFA) 565
- transglutaminase 31
- transmissible spongiform encephalopathy (TSE) 309
- T-regulatory cells (TREGS) 470
 - CD4/CD8 cell 471
- Trichoderma reesei* 135, 156
- Trichoplusia ni* 350
- Tridacna gigas* 560, 569
- trophic conversion 172
- TroVax 518
- truncation 125
- trypsin 512
- trypsin-like microbial enzyme (TrypLE) 494
- tubular photobioreactors 212–218
 - alkalinity 213
 - disadvantage/limitation 212, 213
 - energy consumption 214, 215
 - flat-plate 215–218
 - performance 213
 - production sites 213
 - suitable for 212
- tumor infiltrating lymphocytes (TILs) 471, 472
- tumor necrosis factor (TNF) 473
- tungsten arc welding 69
- turbidostat 206
- u**
- UK
 - acquisitions 416
 - AMBR system 487
 - commercial production of SCP 10
 - human commercial protein-based product 357
 - ICI production site 10
 - single-cell production 3
 - strain development 262

- unicellular eukaryotes, substances isolated
 - from 560
 - chrysophyceae 564–565
 - diatoms 564–565
 - dinoflagellates 567–570
 - eustigmatophyceae 564–565
 - fungi 565–567
 - haptophyceae (= prymnesiophyceae) 565
 - raphidophyceae 564–565
 - rhodophyta 563–564
 - thraustochytrids 565–567
 - unicellular chlorophyta 563–564
- unicellular photosynthetic microorganisms
 - pigments of interest and ichthyotoxins 566
- UNRRA program 6
- USA 12
 - *Dunaliella* cultivation 202
 - fermentation technology 6
 - mass cultivation of microalgae 203
 - microalgae production 209
- v**
- vaccines 23, 189, 354
 - CCL-derived human 393
 - CEF-derived 394
 - Circumvent[®] PVC 357
 - culture-derived 392
 - GMP vaccine 401
 - influenza 395–397, 512, 514, 516
 - polio 392, 505, 508
 - recombinant hemagglutinin influenza vaccine (*see* Flublok)
 - recombinant MVA vaccines 518
 - second-generation smallpox vaccine 517
 - TBEV 395
 - tools for biologics 350
 - veterinary viral vaccines 506, 507, 532
 - yellow fever 394, 395
- vaccines and biologicals production
 - basic bioreactor design aspects 405
 - basic process design aspects 405
 - cell culture development for 391
 - continuous cell lines 392, 393
 - diploid cells 392
 - primary cells 392
 - cell lines (*see* avian cell lines)
 - overview of available avian suspension cell lines for 398
 - process economics, key factors related to 405, 406
 - regulatory aspects 406
 - viral vaccines for human use
 - produced with microcarrier based manufacturing processes 506
 - VRBPAC guidelines 376
- vascular endothelial growth factor (VEGF) 188
- Vero cells line 505, 511
 - derived polio virus 506, 509
 - development for production of vaccines 506, 512, 514
 - and Per.C6 based culture processes 510–511
- Verrucomicrobiales 572
- veterinary viral vaccines
 - using BHK-21 suspension cells 507
- vinegar 2
- violaxanthin 564
- viral recombinant proteins. *see* recombinant proteins
- virus like particles (VLPs) 350, 507
- virus production, under suspension conditions 503
 - adherent vs. suspension culture 504–506
 - bacterial contaminations/infections, treatment of 532
 - for gene therapy purpose 519
 - large scale AAV production 523–527
 - large scale adenovirus production using 520–523
 - LV vector production 527–532
 - influenza virus/vaccines (*see* influenza virus/vaccines)
 - insect cell/baculovirus system, for biopesticides 533–537
 - microcarrier based manufacturing processes 506
 - viral vaccines for human 506
 - polio virus/vaccines (*see* polio virus/vaccines)
 - production of bacteriophages, for phage-therapy 537–538
 - bacterial strains, selection 538, 539
 - bacteriophages, isolation 539, 540
 - bacteriophages, production 540
 - large scale production of phages 540–542
 - production yields of rAAV using production systems 524, 526
 - based on use of stable HeLa- or A549-cell clones 524
 - scalable production system based on use of Sf9 cells – suspension growth 525
 - scalable system based on use of HSV-1 524, 525

- suspension based transfection process, using HEK293 524
- single cell suspension processes 506–508
- AGE1.CR 507
- CAP and CAP-T 507
- EB66 507
- Per.C6 507
- QOR2/2E11 507
- for veterinary vaccines 532–533
- rabies virus vaccine process protocol for BHK-21 suspension cells 533
- viscosity 136, 137, 156
- vitamins 96
 - applications 4
 - discovery 4
 - global pharmaceutical companies, production 4
 - vitamin B₁₂ 4
 - vitamin C 4, 44
- volumetric productivity 100

W

- Wacker ESETEC[®] technology 53
- water-soluble vitamins 4
- Wave reactors 273, 278, 279, 518, 524–526
 - light racks for 276
- West Nile Encephalitis 506
- wet cell weight (WCW) 106
- WI-38 cells 505
- working cell banks (WCBs) 452, 533
- World Health Organization (WHO) program 24
- World War I 2, 3
 - fermentation industry, and 3
- World War II 4, 6, 8, 12
 - fermentation technology 12
 - substantial industrial-scale fermenters installed 6
 - synthesis of vitamins 4

X

- xanthan gum 32
- Xanthomonas campestris* 32
- Xanthophyllomyces dendrorhous* 97
- xylanase 31

Y

- Yarrowia lipolytica* 96
- yeast biomass and alcohol yields, of different production processes 99
- yeast fermentation processes 99–105
 - suitable strategy 99
- yeast species, used in biotechnology 96
 - approved biopharmaceutical proteins produced by 97
 - basic process design aspects 98
 - process history 98, 99
 - expression systems 98
 - feeding strategies for yeast fed batch cultures 100
 - high cell density fermentations 106, 107
 - industrial enzymes produced in 98
 - process design for ethanol production 106
 - process history 98
 - products
 - categories 96
 - primary metabolism with industrial relevance 96
 - secondary metabolism with industrial relevance 97
- yellow fever virus 504

Z

- Zoanthus* 573, 576
- zooxanthellactone 571
- zooxanthellae 569, 573
- Zostera marina* 578
- zosteric acid 578
- Zygosaccharomyces bailii* 97