

Index

a

absorption refrigeration plant 214
 compressor, technical data/cost estimation 213
 acetone–dry ice mixture 345
 active pharmaceutical ingredients (API) 150, 342
 additives
 crystallization temperature 24
 adonitol
 platelets untreated or pretreated 341
 agglomerate formation 371
 agglomeration 367
 air-conditioning technology 202
 air-cooled compressor 239
 alarm system 393
 albumin 299, 300
 alcohol bath 349
 alcohol retainintion, freezing speeds 147
 Al RNA viruses 330
 alumina powder 370
 aluminum blister packs 164
 aluminum oxide 218
 aluminum tubes 338
 ammonia vapor 213
 amorphous freeze-concentrated mixtures 79
 amorphous phase 27
 amorphous sucrose, acid-catalyzed inversion 163
 ampicillin 350

amplitude modulation 135
 anhydrolactase 101
 anhydrous lactose 25
 moisture sorption profiles 103
 annealing 359
 temperature 66
 time 78
 Annex 15-PIC/S PI 006-1 379
 anodized aluminum 82
 antibiotics 341
 freeze-drying of 341
 panipenem, two-stage freezing process 342
 antibodies
 antibody drug conjugate (ADC) 350
 anti-IgE monoclonal antibody (anti-IgE Mab) 325
 conjugates nanoparticles 351
 freeze-dried
 stability of monoclonal IgM 351
 monoclonal 350
 antimitotic drugs 190
 aqueous amorphous solution, freezing behavior 358
 atomizer–spray-drying system 148
 automated guided vehicle (AGV) 271
 automated thermodynamic lyophilization control, summary of prerequisites, limits, and suggestions 308

- automatic loading and unloading system (ALUS) 270
 built into isolator 233
 for two freeze-dryer installed in open RABS system 273, 278
 for vials fix installed in front of a freeze-dryer 273
 automatic loading system 269
 AzactamTM solution 76
- b**
Bacillus stearothermophilus 262
 D values 262
 backing pump 370
 bacterial challenge test (BDT) 222
 bacterial populations inactivation, during steam sterilization 256
 baker's yeast 336
 barium 372
 barometric temperature measurement (BTM) 86, 106, 115, 225, 340, 386
 disadvantage 120
 freeze-drying 122, 355
 measurements 126
 basic salt medium (BSM)
 Al DANN virus suspensions 330
 battery-free sensors 135
 betamipron 342
 BET surface area 371
 binding energy 295
 Bi-Pb-Sr-Ca-Cu-O powder
 precursors 367
 $\text{Bi}_{1.8}\text{Pb}_{0.2}\text{Sr}_2\text{Ca}_2\text{Cu}_3\text{O}_x$ (Bi)
 powder 371
 Bi powders 371
 Bi precursor 371
 blood plasma, desorption isotherm 151
 blood serum, freeze-drying of 341
 BOC Edwards Drystar GV pump 219
 bovine corona virus (BCV) 331
 bovine serum albumin (BSA) 60, 74
 and γ -globulin (BGG) 163
- water vapor partial pressure 127
 bovine somatotropin (BST) 102, 303
 Bragg law 77
 bromobutyl stoppers 161
 buffer 359
 bulking agents 359
 moisture contents 102
 butane-2,3-diol 28
- c**
 $\text{Ca}(\text{CH}_3\text{COO})_2\text{-}(\text{hydrolyzed})\text{PO}(\text{OCH}_3)_3$ system 369
 calcination 367, 372
 of instruments 392
 cancer therapy 190
 capacitance method 228
 advantages 122
 gauge 200
 manometer 235
 sensor, resolution of 226
 vacuum gauge 297
 capacity gauges 228
 carbohydrates, hypothetical substance 29
 carboxyfluorescein (CF) 345
 carboxymethylcellulose (CMC) 74
 catalase 313
 CD4-IgG, recrystallization 51
 ceramic powders, objectives 367
 CFC/ozone problem 204
 21 CFR Part 11 379
 chamber 118
 condenser configuration 143
 pressure 129
 pressure and nitrogen flow-rate as function of drying time 236
 volume 99, 122
 chemical shifts 69
 chicken meat
 size and number of pores 25
 cholesterol (CHOL) 345, 347
 claw principle 219
 cleaning agents 251
 clean in place (CIP) 180

- cleaning process
 - phases 251
 - reproducible 251
- goals of 248
- parameters documented 251
- principle 250
- processes types 252
- processes validation 253
 - FDA notes 253
- Skid installation 252
- spray rod, in drying chamber for
 - cleaning of shelves and chamber walls 257
- system hardware 252
- systems require documentation 253
- with two tanks for cleaning with
 - detergent and WFI 259
- CO_2 clogs 149
- CO_2 emissions 202
- coffee extract, freezing and thawing plot 72
- coils in condenser, covered by ice 193
- cold denaturation 313
- collagen 189, 351
 - sponge
 - magnification of 358
 - porous structure 357
 - suspension 357
- collapse temperature (T_c) 387
- colony-forming unit (CFU) 336
- complete pumping system, for freeze-drying plant 218
- compressors 201, 211
 - capacity 202, 207
 - cooling system 203, 205
 - consists of 205
 - conventional 208
 - evaporator 205
 - throttling valve (expansion valve) 205
 - two-stage compressor 205
 - using R404A 211
 - ratio 206
- condensation 195, 200
- condenser 118, 194, 198
 - automatically measured and recorded pressure rise 133
- coils 200, 201
- cooling 387
- design 143, 144, 199, 201
- drop 200
- efficiency 376
- fulfill essential requirements 196
- geometric layouts of 139
- performance, within
 - specifications 393
- qualities, judged in general terms 199
- temperatures 200, 202, 375
 - with evaporator plates 268
- configurational entropy 315
- CONRAD® freeze-drying plant 285
- contact heat transfer coefficient 94
- continuous-wave (CW) 135
- control pressure 129
- ControLyō™ 184
- conventional adsorption isotherm
 - measurements 324
- conventional freeze-drying 149
- cooling 54
 - capacity 195, 202, 207
 - comparison 206
- circuit application, with recirculated flow 211
- efficiency 208
 - calculation 207
- freeze-dryers with LN_2 , over conventional cooling systems 208
- heating rate 35
- liquids
 - physical data 12
- method 11, 192, 203
- rate 3, 35
 - comparable vials 11
 - human blood derivative 43
 - surfaces 178
- copper 372
- CQC freeze-drying plant 284
- CRUSToFREEZE®, exit lock 181
- CRUSToFREEZE™ plants 179
- Cryobreak™ process 182
- Cryogen Rapid Pelletizer 182, 183

- cryomicroscope 44, 53
 drying 80
 during freezing 51
 research system 56
 scheme of 51
 studies 53
 cryomicroscopy 51
 photographs 65
 Cryopel™ 182
 cryoprotection agents (CPA) 19, 26,
 316, 358
 freeze- and air-drying 32
 molecules 71
 schematic model 71
 crystalline hydrate 25
 crystalline structure former 358
 crystallinity (CI) 77
 crystallization 17, 27
 energy 63
 flows 5
 exotherm overlapping 65
 crystals growth 16
 Curie temperature 372
 cyclophosphamide in liposomes
 (CPL) 346
 cytostatica 190
 cytostatics 341
- d**
- DANN-proteins 317
 data management 232
 data records, process parameters
 384
 deacetylvinblastin hydrazide
 conjugate 323
 deflector/protective shield 227
 degree of supercooling 184
 dehydration by successive pressure drops
 (DDS) 336
 dehydration–rehydration vesicles
 347
 dehydroemetine (DHE) 350
 demineralized water (DE) 251
 density 371, 372
 deoxyribonuclease (rhDNase) 325
 design qualification (DQ) 380
- desorbable water (dW) 110, 111
 calculation 308
 data from DR measurement 303
 DR data 356
 desorption drying
 shelf temperatures 339
 desorption isotherm 150
 desorption rate (DR) 105, 106, 107,
 109, 113, 130, 303, 353
 data 297, 299, 304
 drying time 111
 function of drying time 111, 112, 301
 measurements 125, 130, 304
 plots of pressure 356
 values 129, 299
 product temperature 327
 devitrification 19
 dextran 28, 102, 317, 321, 342,
 345, 358
 additions 346
 concentration
 acid retention 147
 moisture sorption profiles 104
 solution
 pore diameter 25
 dicetyl phosphate (DCP) 342
 dielectric analysis (DEA) 76
 dielectric constant 372
 dielectric relaxation spectroscopy
 (DRS) 77
 differential scanning calorimetry
 (DSC) 27, 60, 145, 359
 DSC 3+ instrument, schematic
 drawing 61
 DSC 3+ replaces 62
 for tBA 79
 heat flow 344
 measurements, commercial
 apparatus 62
 thermogram, heat flow 75
 differential thermal analysis (DTA)
 26, 45
 measurements 46, 47
 diffusion flow test 223
 diffusion pump 370
 dimethyl sulfoxide (DMSO) 26

- dimyristoylphosphatidyl-DL-glycerol (DMPG) 347
- dipalmitoylphosphatidylcholine (DPPC) liposomes 346, 348
- disk dryer 286
- dispersions structure of 14
- distiller, for WFI (Water for injection) T/TC-MWS 259, 450
- doxorubicin (DXR) 348, 349
- droplet freezing 11, 181
- droplet size 183
- dry basis (db) 336
- drying 79 chamber 115, 186, 218 geometric layouts of 139 critical process steps 313 cycle 196 main 82 material 94 methods 177, 352, 371 without vacuum 148 protocol of T_{ice} 118 secondary 102, 108, 111, 123, 144 time 85, 88, 121, 131, 196, 286, 334 activity loss during freeze-drying 319 DR function 132 four DR plots 132 product temperature 114 shelf temperature 352 water distribution 104 weight loss 95
- dry substances changes 162 qualities 162
- dry vacuum pump combination with dry roots pump for fast evacuation 220 during freezing 113
- e**
- EC-GMP Guidelines 379, 380
- egg albumin solution 38, 150 enthalpy 6
- egg lecithin (EPC) 345
- egg phosphatidylcholine (DPPC) 345 freeze-dried 346
- liposomes dextran as CPA 345
- EH 500 roots pump 221
- electrical cabinet door 232
- electrical energy 224, 226
- electrical power consumption 207
- electrical resistance (ER) 34, 135, 145, 322, 323
- human blood derivative 43
- human protein solution 44 measurement 34, 35, 41, 47, 48, 120 of 10% egg-albumin solution 42 schematic drawing 34 suspension cooled at 0.8 °C/min 42
- electrodes 227 arrangement 228
- electronic bridge circuit 225
- electronic records 379
- electronic signature 379
- electron scanning microscopy (ESM) 33, 148
- endothermic shift 63
- endpoint determination 144
- end product color 180
- energy consumption 82
- energy transmission by radiation 82
- enthalpy 208 meat/fish/egg 6
- enzymes molecules 31
- enzymic activity 31
- equilibrium vapor pressure 86, 150 pressure rise 117
- equipment performance tests 392 leak test 392 shelves roughness 392 water vapor flow 393
- equipment to operate processes, quality of installation to document ability 395
- equivalent microbial lethality, time to achieve at exposure temperatures 254
- erythropoietin 317
- Escherichia coli* 333 freeze-drying 334

- ethanol 370
 ethylene glycol (EG) 26
 phase diagram 50
 ethylene oxide 264
 European Union, the Directive 91/356
 EEC 379
 eutectic point/temperature 359
 evaporating temperatures 208
 evaporator coils, inside of ice
 condenser 258
 evaporators 194
 cooling capacity 203
 excipients 359
 T_g' and UFW 321
- f**
- FDA-PAT initiative 385
 2008 Compliance Policy Guide 385
 2002 Guideline 385
 2004 Guidance for industry 385
 FDA Regulations 379
 21 CFR Part 211, §211.68 (a, b)
 379
 FDGS freeze-drying stage 60
 F-gas Regulation 202
 filter membrane 222
 fish, enthalpy 6
 FK 906 solution 29
 fluidized-bed
 drying 148
 freezers 179
 process 150
 fluorinate-containing cooling
 agents 202
 fluorinated greenhouse gases 202
 fluororesin 370
 FM257/2
 moisture analysis 162
 foaming 179
 formaldehyde 264
 Fourier transformation 64
 IR spectroscopy 325
 four runs data 120
 four-stage dry vacuum pump 220
 four test runs
 product thickness 93
 freezable water 63, 64
- freeze-dryer 288
 chamber with shelves 265
 loading system, turning table of
 270
 freeze-drying 34, 91, 95, 187, 358, 367
 advantages 1
 chambers, basic types 186
 components of 185
 control system programming 234
 drying chambers and forms of
 trays 186
 for flasks or bottles 185
 installations for flasks and
 manifolds 185
 measuring capabilities 234
 conditions 138
 conventional 149
 cycle 82
 disadvantages 1
 glycine 79
 installations 44
 maltodextrin 23
 microscopy 60, 76
 of coffee and tea extracts 180
 of maltose solution
 loss of 1-butanol 146
 of pharmaceuticals 82
 performances 94
 position 137
 powder 367, 372
 precipitates 367
 problems during operation 235
 deviations to be documented 237
 trouble before the evacuation
 starts 236
 trouble requiring immediate
 action 236
 trouble to be corrected
 automatically/manually in
 minutes 237
 process 81, 101, 145, 204
 microscopy 59
 production plant 267
 temperature 341
 transfer from pilot to production
 plant 304
 type of tray 189

- product 162, 372
 equilibrium water content 160
 photographs 58
 pure water, in vials 96
 water vapor transport 136
 freezer details 182
 freeze–thaw cycles 34
 freezing 2, 54, 95
 frozen products
 changes of structure 78
 heat conductivity/heat transfer/
 cooling rate 3
 of cells and bacteria 32
 of extracts and pulps 179
 point 367
 processes 19, 54, 178
 product 372
 temperature 327
 rates 370
 speed 178
 temperatures 9, 10
 thermodynamic data during 291
 time 6, 7, 8, 113
 TT at beginning of drying 54
 frequency distribution
 of T_{ice} 119
 frozen
 into glassy state 314
 products 340
 temperature percentage 6
 water 9
- g**
 β -galactosidase (GS) 313, 317
 gas desorption
 from stoppers 164
 gases, purity of 164
 gas moisture 387
 gas velocity 387
 glass-fiber material 38
 glass formation
 anhydrous carbohydrates
 T_g values 315
 excipients 163
 property 76
 sugar solutions
 non-Arrhenius behavior 76
 theoretical diagram of low-
 temperature behavior 32
 viscosity of 315
 glass transition 46, 359
 temperature 24, 60, 326
 global warming potential (GWP) 69,
 202, 204
 γ -globulin 19, 74
 solution frozen 21
 glucose-6-phosphate dehydrogenase
 (G6PDH) freeze-dried 24
 glucose solution, DTA plot 50
 glycerin
 DTA measurement 49
 equilibrium 22
 phase diagram 27
 glycerol (GL) 26
 devitrification 19
 glycine 102
 immersed in LN_2 23
 phase transitions 23
 Good Automation Manufacturing
 Practice (GAMP) 232, 379
 Good Manufacturing Practice
 (GMP) 379
 Good Practices for Computerized
 Systems in Regulated GXP
 Environments 379
 Gordon–Taylor equation 29, 60
 grain size 180
 distribution 370
 granulated coffee extract 88
 granulated end product 180
 gravimetric measurements 303
 gravimetric sorption analysis (gsa)
 324
 GT50/95/2, test protocol, for loading
 and unloading installation
 394
 Günther–Jaeckel–Oetjen equation 139
 GV80 dry vacuum pump (BOC
 Edwards) 221
- h**
 hardware architecture 232
 hatched columns 191
 H bonds 73

- heat conductivity 3, 87, 88, 196, 224
 gauge 224
 vacuum gauge 123
 during SD 127
 heat convection 387
 heat exchanger 149
 heat fluid, in shelves 387
 heating plates 189
 heat transfer 3, 186, 189, 190, 192, 196,
 212, 292, 354
 advantage of pressure control 100
 by radiation 83
 coefficient 8, 83, 84, 119, 189
 fluid 192, 202
 from shelf with temperature 84
 mechanisms 94
 rates 149
 resistance 84
 helium leak detector 231
 helium spray pistol 231
 hemoglobin, in liposomes (LEH) 347
 hepatitis B surface antigen
 (HBsAg) 347
 dried liposomes 347
 HEPC liposomes 345
 heterogeneous nucleation rate 26
 hexane
 kinetic parameters for
 transesterification 320
 HIMA bacterial challenge test 223
 homogeneous nucleation 15
 horizontal vibration dryer 287
 hormones 313
 human calcitonin (hCT) fibrils 74
 human serum albumin (HSA) 60, 102
 humicola lanuginosa lipase (HLL)
 328
 hydrated egg lecithin (HEPC) 345
 hydrates (mannitolhydrate) 77
 hydraulic cylinder 249
 hydraulic system 186
 hydraulic valve drive 194
 hydrofluoroclorocarbon (HCFC) 202
 hydrophobic inlet filters 222
 hydrophobic protein 324
 hydrous lipid
 trehalose molecules 346
 hydroxyethyl starch (HES) 79, 101,
 325, 338
 2-hydroxypropyl-cyclodextrin
 (HPCD) 325, 342
 hygrometer 128
 during MD 92
 hygroscopic product 150
 hypothetical product
 maximum moisture content 162
 hysteresis 71, 226
- i*
- ibuprofen 341, 342
 ice
 annealing (thermal treatment) 64
 crystals 25, 33
 disadvantages 78
 in water 15
 dendrites 80
 equilibrium water vapor
 pressure 116
 forms 82
 installations up to 10 kg ice
 capacity 238
 cleaning installations,
 sterilization 248, 254
 manipulators and stoppering
 systems for vials 244
 pilot plants 240
 universal laboratory plants 238
 planar front 55
 structure 14, 359
 sublimation rate 191
 temperature 107, 138
 IgM antibodies 351
 incipient melting 50
 industrial microwaves applications 149
 influenza virus
 strain PR 8 in physiological
 saline 330
 injection molding 367
 inlet venting filters 221
 installation qualification (IQ) 380
 integrity testing 222, 224
 interrogation unit (IRU) 135
 interval uniformity 94
 investment costs 213

- IQF-freezing process
 CRUSToFREEZE® 180
- IR spectroscopy 325, 346
- ISO 100 11 Guidelines for Auditing Quality Systems 379
- isohexyl cyanoacrylate (IHCA) 349
- IsoK baseline data 67
- isolator system 274
 advantages 276
 air handling system 275
 ALUS and Isolator design considerations 277
 biodecontamination system 275
 decontamination, validation procedure 282
 disadvantages 276
 isolator design considerations 278
 isolator documentation considerations 280
 lyophilizer and ALUS design considerations 277
 module with air handling 275
 validation decontamination processes 280
- isothermal annealing 65
- ISPE Commissioning and Qualification 379
- j**
- jet flow, water vapor flow
 density of 140
 rate of 141
- k**
- Karl Fischer method 97, 161, 303, 333
 colorimetric titration 351
 solution 151
 titration 156, 353
 data 156
 RM data 156
- keratocyte growth factor (KGF) 163
- KS1/4 hydrazide conjugate 323
- l**
- laboratory freeze-drying plant 239, 333
 laboratory lyophilizer 386
 first stage 386
- lactate dehydrogenase (LDH) 30, 31, 313, 317, 325
 activity recovery 319
 vs. concentration 318
- by maltodextrins 26
 vs. residual moisture content, activity recovery of 320
- Lactobacillus bulgaricus* 33
- Lactobacillus plantarum* 333
- lactose 160, 349, 358
 adsorbed 25
 photographs 59
 solutions 78
 water content 160
- large unilamellar vesicles (LUV)
 347
- lead lanthanum zirconium titanate 372
- leak detection, by helium leak detector 231
- leak hunting with the part stream method 231
- leak rate (LR) 307, 392
 detection 229
- lean beef meat
 enthalpy 5
- liposomes 342
 CPA and Tris buffer 344
 drug formulation 347
 encapsulated hemoglobin 347
 freeze-dried 345, 348
 inclusion of drugs 346
 structures, morphology 343
- liquefier capacity 203
- liquefying pressure 203
- liquid nitrogen (LN₂) 8, 182, 205, 208, 369
 condenser 210
 in freeze-drying plant 212
 evaporator plate 210
 freeze-drying course 326
 freezing device 178
 frozen product 340
 frozen RBCs, survival rate 340
- maximum theoretical cooling rate 14

- liquid nitrogen (*continued*)
 relative cooling rate 13
 storage 44
- liquefaction 202
- $\log(\text{TOF})$ vs. $1/K$
 collapse plot 77
- long-term refrigerant alternatives 204
- Lyoguard™ freeze-drying trays 191
- lyophilization 1, 358
 on salt-induced activation of enzymes 320
- rhuMAb
 second-derivative spectra 158
- TEMPRIS Wireless temperature system 136
- lyophilizers 184, 388
 DANN-viruses 331
- lyoprotectants (LP) 78, 324, 348
- lyoprotection 324
- LYOVAC™ FCM 600-D
 production system, comprising of three production freeze-dryer 271
- LYOVAC® GT6, manipulator connected to 247
- lysozyme D₂O solution 316
 freeze-drying 316
- m**
- magnesium sulfate solution 369
- magnetic noise 69
- main drying (MD) 79, 184
 freeze-drying 82
- maintenance costs 213
- maltose 349
- maltrotoxin (MD) 336
 effect of trehalose 338
 parameters 87
 pressure control 89
 pressure drop 128
- manipulator including vacuum lock 246
- mannitol 23, 24, 358
 crystallization 71
 crystallizes 71
- D-mannitol solution, freezing -and thawing plot 72
 in resin vials 94
 solution 19, 294
 solution frozen 21
- mannitol hydrate 23
- mass flow controller (FMC) 235
- mass spectrometer (MS) 154
 signals 127
- mass transfer, external 84
- Mayekawa Mycom two-stage screw compressor, cut model of 207
- mean water content (RF) 104, 303
- meat
 enthalpy 6
- media fill test (MFT) 394
 proposal for MFT program 394
 purpose of 394
 requirement 394
- melting point 78
- melting temperatures 26
- Messzelle DL 36 coulometer
 residual moisture content (RM) measurement 152
- metal oxides 367
- met-oxyhemoglobin (met-HBO) 148
- Mettler-Toledo AG 135, 153
- Mettler-Toledo DL 38 Karl Fischer apparatus 153
- mice oocytes
 cumulated abundance of intercellular ice forming 57
- microregion entrapment 147
- microstructure 372
- microwaves 149
 freeze-drying 149
 power 149
- milk frozen 20
- MilliQ water 155
- minimum cell volume 33
- miso sauce
 UFW content 73
- MKS Instruments, encapsulate the sensor 228
- Mn²⁺, Co²⁺, and Ni²⁺ sulfate 370

Mn₃CO₂Ni(SO₄)₆·15-16H₂O
transformed into 370

modulated-temperature DSC (MTDSC) 65
amorphous lactose 66
in lyoprotected liposomes 67

molecular weight (MW) 23

monitor AW 2 44

Montreal Protocol 1986 204

mouse cell volume change 56

mouse oocytes intracellular ice 57

multistage systems 192
screw compressors 212

Mycom screw compressors 206

n

Na-cefazolin 63
crystallization energy 63

Na-cephalotin (Na-CET) 341

NaCl crystallization 47

NaCl influence 299

NaCl solution 38
DTA measurement 46, 47
electrical resistance 36, 37, 39

nanoparticles 342

near-infrared (NIR)
penetration depth 156
spectroscopy 154, 301

needle-shaped ice crystals 79

Nei's opinion 33

n-hexane 183

nitrogen 208
consumption 182

nonequilibrium conditions 200

non-hygroscopic 24

nozzle 182

nuclear magnetic resonance (NMR)
68
analyzer 68
measurements 68, 353
spectroscopy 73
spectrum 69

nucleation 184
heterogeneous and homogeneous temperatures 26
of ice 57

nucleation-on-demand technology 184, 185
nucleation rate J* 16
nucleation temperature 101, 184

o

one-stage roots pump, working principle 217
operating pressure 299
operational qualification (OQ) 380
organic binders 367
organic solvents 367
ozone depletion 204

p

packed red cells 338
packing
product, critical qualities of 305
Parenteral Society Specification and Validation of Freeze-Dryers No. 9 379
partial gas pressures 228
Pb(Zr_xTi_{1-x})O₂ (PZT) production 372
P_{ch} data, TM measurements/mass spectrometer signals 127
Pedvax HIB TM 159
PEG 8000 26
Peltier modules 51
performance qualification (PQ) 380
Perkin-Elmer NMR spectrometer 353
Petri dish 338
pharmaceutical product 192
cryomicroscope photograph 55
electrical resistance 41
freeze-drying 141
freezing of 179
frozen, cryomicroscope photograph 53
phase diagrams 49
phase transition, second-order 315
phosphate–citrate buffer 326
phosphofructokinase (PFK) 30
during freeze-drying and subsequent storage 31
NaCl solution 314

- phospholipid egg phosphatidylcholine (EPC) 348
- phospholipids 342
- pH-sensitive DANN viruses 331
- physiological NaCl solution 163
- pilot freeze-dryer LYOVAC™ FCM
- 10-P 261
 - pilot lyophilizer 386
 - second stage 387
 - pilot plant (PP) 243, 306
 - performance data 305
 - piston compressor 208
 - Planck's constant 68
 - Plexiglas™ 186
 - polyethylene oxide 33
 - poly(isohexyl cyanocrylate)
 - nanoparticles 350 - polymerization 24
 - polytetrafluoroethylene (PTFE) 222
 - filter membrane 223
 - polyvinylidene fluoride (PVDF) 222
 - polyvinylpyrrolidone (PVP) 23, 26, 336
 - phase diagram 28
 - pore-size 368
 - porosity 369, 370, 371
 - porous ceramic, microstructures 370
 - Power-Down method 357, 358
 - practical analytical technology (PAT) 385
 - precipitation 368
 - precooled shelves
 - freeze-drying 126 - pressure, in chamber/condenser as function of time 229
 - pressure rise measurement (PRM) 230, 386
 - pressure sensors 226, 228
 - primary drying, principles for 386
 - process analytical technologies (PAT) 60, 136, 380
 - used during cycle development 388
 - process automation 287
 - prerequisites for process and related plant automation 287
 - thermodynamic lyophilization control (TLC) 289
 - control of process without temperature sensors in product 289
 - measurement of ice temperature at sublimation front/desorption rate 292
 - process control systems 232, 384
 - process time
 - temperature and pressure 114
 - product, in flow of cold air 179
 - production freeze-dryer AFD
 - 10-C/S 247 - production installations, and handling 391
 - production lyophilizer 386
 - production plants 264
 - acceptable standard 271
 - push/push system 271
 - data of machines supervised 234
 - design criteria 264, 272
 - for food 283
 - continuous plants with product transport by wipers/vibration 285
 - continuous plants with tray transport 283, 284
 - loading and unloading systems 269
 - preconditions for aseptic production 269
 - product manufacturing
 - process developed for 389
 - additional test run 390
 - filling of vials 389
 - process adopted based on product quality 390
 - product temperature 388, 389
 - Programmable Logic Controller (PLC) 232
 - 2-propanol 367
 - protein (destabilizing) 31, 313
 - comparison of 324
 - molecule 71
 - stability of 314
 - T_g' and T_c for 318
 - protons tetramethylsilane (TMS) 69

- providone (PVP K24) 101
Pseudomonas diminuta 222
Pseudomonas syringae 26
 pumping capacity 216, 218
 pumping speed 216, 217, 219
 Pure Steam Generator T/TC-PSG 450
 (Brand Finn-Aqua/Austar) with a
 capacity of 255
 Pure Water Generator PWG2-0550,
 with FDA cGMP
 compliance 255
 PVC–poly(vinylidene chloride) 164
 aluminum blister packs 164
- q**
 qualification model, following GAMP
 guidelines 382
 quality by design 385
 quality of product 388
 manufactured, documentation
 of 396
 Quality Systems Manual 388
 quartz-coated vials 95
 quick-freezing processes 21
- r**
 radiant efficiency 82
 radiation 387
 energy 190
 heating 190, 192, 371
 shield 97
 Raman spectroscopy 78
 rats, percentage of hepatocytes 33
 R&D freeze-drying plant, for cycle
 development 187
 recombinant α -antitrypsin (rAAT)
 326
 recombinant bovine somatotropin
 (rbSt) 324
 recombinant DNA protein 318
 recombinant human albumin
 (rHSA) 351
 recombinant human factor XIII
 (rFXIII) 328
 recombinant human interleukin-2
 (rhIL-2) 325
- recombinant human interleukin-1
 receptor antagonist (rhIL-1ra) 84
 recombinant humanized monoclonal
 antibody (rhuMAb) 155, 157
 HER2 163
 RhuMAbVEGF 78
 recrystallization 78, 85, 145
 rectangular chamber (CIP/SIP)
 steam-sterilized with 188
 with small loading door and main
 service door 188
 red blood cell (RBC) 340
 storage time 340
 refrigerants 194, 201, 204
 coils 177
 capacity 209
 plant, total annual cost of 214
 systems 201, 202
 regulatory authorities 222
 regulatory issues 379
 qualification and validation of
 processes and installations
 379
 European and US guidelines 379
 relative humidity (RH) 102, 103
 relaxation
 for acetone proton transverse
 magnetization 26
 enthalpy 65
 times 66, 67, 70
 reproducibility 228
 residual moisture (RM) 154, 297, 356,
 359, 378
 content 98, 109, 158, 317, 352, 389
 desorption isotherms 134
 measured by KF 159
 data 155, 328
 rehumidified samples 337
 residual moisture content (dW)
 as function of time 302
 distribution 99
 measurement 151, 302
 gravimetric method 151
 infrared spectroscopy 154
 Karl Fischer (KF) method 151
 thermogravimetry (TG) 153

- residual moisture content
 - influence of vial stoppers 156
- residual tBA 79
- resistance measurements
 - frequency distribution 40
- resolution 228
- respiratory syncytial virus (RSV) 331
- rhesus monkeys, oocytes
 - volume changes 57
- ribonuclease (Ri) 324
- Ri-LP products 324
- RMEZ98 (Novartis) 350
- RNA virus group 331
- RNIR
 - calibration 156
 - RF, relationship 157
- Rolfsgaard states 190
- rotating spray head, in condenser 257
- roughness 192
- rubber stoppers
 - moisture distribution 161
- rubredoxin (CEB) crystals 323
- R6 vials 95

- s**
- saccharin molecules 73
 - cross-link 73
- Saccharomyces cerevisiae* (SC) 335
 - thermal stability 336
- saccharose 358
 - solution 297
- safety hazards 222
- saline stability 338, 339
- scanning electron microscopy (SEM) 58
- S. cerevisiae*
 - drying time 336
 - S. cerevisiae* CBS 1171 (SC 1171)
 - additives on survival 337
 - screw compressors 208, 212
 - secondary drying (SD) 80, 101, 144
 - principles for 387
 - product temperature 124
 - semilogarithmic scale, DR values 109
 - sensors 226, 227
 - influence on temperature 289
 - serum albumin (SN) frozen 330
- shelf heat transfer system 205
- shelf package 195
- shelf temperature 185, 200, 375, 377, 378, 387
 - influence of 335
- shell-freezing 177, 178
- shielding, in temperature range 97
- sieving system 180, 183
- sintering 367, 372
 - MgO compact, relative density 368
 - rate 371
- sodium carboxymethylcellulose (CMC)
 - dimension change 74
- soft agglomerates 367
- solidification processes 23
- solid lipid nanoparticles (SLN) 350
- solid–liquid state diagram
 - isoplethal section 30
- solid nitrogen 12
- solid-state reaction 372
- solutions
 - isotherms 23
 - structure of 14
- soya bean–phosphatidylcholine (soy PC) 347
- spherical $\text{YBa}_2\text{Cu}_3\text{O}_{7-\delta}$ material 372
- spin-freezing 177, 178
- spin-lattice relaxation time 163
- spin orientation 69
- spin–spin relaxation time 69
- spray drying 367
- spray freeze-drying 150, 325
- spray-lyophilized formulations 150
- stabilizer 359
 - destabilizing effect 31
- stainless steel bellow 249
- stainless steel shelves 192
- standard deviation (SA) 35
- steam sterilization 160, 222
 - closing mechanism for vials 248
- production plant with two LYOVAC®
 - GT 500-D 266
 - stainless steel bellows 265
 - stoppers 158
- StepScan® DSC 67
- sterile conditions 183

- sterilization in place (SIP) 192, 222, 228, 260
 could cause leaks 261
 design criteria 256
 D values 262
 efficiency 222
 factors critical to ensure 254
 phases 263
 standard procedure 261
 technical prerequisites 263
 VHP require conditions 262
- Steris Corp 264
- stoppers
 on water vapor transport 137
 stoppering with bellows 249
- storage, of freeze-dried product 150
- subcooling 95, 388
- sublimation 192, 200, 201, 292
 energy 82, 87
 front
 plot of temperature 327
 performance 192
 of food lyophilizer 193
- pressures 196
- rate 190, 192
- sucrose
 crystallization of 23
 solution
 collapse temperature 321
 dimension change 75
 NaCl behavior 46, 48
- superconductivity 372
 $\text{YBa}_2\text{Cu}_3\text{O}_{7-\delta}$ and $\text{YBa}_2\text{Cu}_3\text{O}_{7-x}$
 ceramic plates 372
- supercooling 184
- Supervision, Control, and Data Acquisition (SCADA) 232, 233
- surface heat transfer coefficient
 total vs. thermal conductivity 7
- t**
- take-off frequency (TOF) 76
- temperature
 at sublimation front of ice 293
 coefficients 228
- controlled shields 340
 depended electrical resistance (RTD)
 systems 113
 temperature measurement
 (TM) 127
 as function of drying time 291
- modulated DSC (TMDSC) 65
- ranges in freeze-drying units 205
- remote interrogation system
 (TEMPRIS) 135
- wireless temperature system 136
- sensor 9, 113, 340
- temperature modulated DSC
 (TMDSC) 30
- tert-butanol (t-BA) 358, 372
- tert-butyl alcohol (TBA) 317
- T_g onset 65
- theoretical density 372
- thermal conductivity 190, 370
 gauges 378
 of ice 7
- thermal decomposition 367, 372
 product 367
- thermal elements (Th) 113
- thermal transpiration 228
- thermal treatment (TT) 53, 78, 177.
see also annealing
- thermodynamic freezing point 184
- thermodynamic lyophilization control
 (TLC) process 290, 386
- thermogravimetric analysis 67, 153
 derivative of weight over time 154
- thermomechanical analysis (TMA) 74
- thermostatic expansion valves 204
- thermovac 122
- three freeze-drying, process data 304
- T_{ice}
 function of p_c 293
 indicator of frozen structure of a 10% mannitol solution 294
- 10% saccharose solution as function of MD time with different number of vials 296
- synopsis 108

- times linearly enlarged
derivative of 37
- tissue-type plasminogen activator (tPA) 111
- TNKase 157
- α -tocopherol 347
- tolerances 396
given in braces 388
maximum 393
- transfer cart (open RABS) for automatic loading/unloading
using one track and guide rail system 272
- transition energy 68
- transplants 351
freeze-dried 352
- trays forms 186
for special applications 190
- trehalose 25, 342, 345, 349, 358
as glass-forming agents 24
lipid concentration 346
NaCl–water system 29
- solution
freeze-dried DPPC liposomes 348
freeze-dried, in vial
photographs 59
- stabilize alkaline phosphatase 24
- trehalose plus sodium tetraborate (TST) 325
- trouble shooting
different structures of dried product in center and border of a shelf 378
prolonged evacuation time 375
slow pressure increase in the chamber during main drying 376
stoppers pop out or slide into the vials 377
- sublimation front temperature irregular 376
- sublimation front temperature too high 376
- traces of highly volatile solvents (acetone, ethanol) 377
- T_{sh} cooled controlled 11
- TUEV/ASME rating 184
- tumor necrosis factor (TNF) 329
- MAb monomers 330
- tunable diode laser absorption spectroscopy (TDLAS) 144
- tunnel freeze-drying systems 284
- turkey meat 88
- two-stage piston compressor 205
- two-stage screw compressors 206
- two-stage semihermetic compound screw compressor 206
- U**
- ultrasonic spray freeze-drying (USFD) 368
apparatus 369
- unequally freezing 185
- unfreezable water (UFW) 4, 6, 69, 70, 146, 320, 337, 359
- concentration 22
data 5
in an amorphous state 21
- unilamellar vesicles schematic construction 343
- User Requirements DIN 69905 379
- US Standard Pertussis Vaccine Lot 9
freeze-dried 155
- V**
- vaccines 330
- vacuum chamber 121
- vacuum-drying process 184
- vacuum gauges 122, 144, 225
- vacuum installations 148
- vacuum measuring systems 224
- vacuum pump 217
freeze-drying plant 90
multistage pump sets, working range 215
pressure as function of evacuation time 216
pumping system 215
set 218
- validation
concept, following GAMP
V-diagram 381
- HIMA bacterial challenge test 224

- master plan (*see validation master plan (VMP)*)
- validation master plan (VMP) 380
- change control 384
 - cleaning validation 383
 - documentation 381
 - planning for validation 381
 - process validation 383
 - qualification 383
 - design qualification 383
 - installation qualification 383
 - operational qualification 383
 - performance qualification 383
- revalidation 384
- risk analysis 384
- sterilization validation 384
- validation principles 380
- worst-case scenario 385
- valve
- automatically measured and recorded
 - pressure 133
 - inside condenser 268
 - size 192
 - valve D 195
- vancomycin 160
- vaporized hydrogen peroxide (VHP) 273, 281
- degraded into nontoxic by-products
- during aeration process 281
- VHP-process®, pressure during sterilization 264
- vapor pressure 228, 377
- of solvents as a function of temperature 377
- vapor pressure moisture methodology (VPM) 154
- for α -interferon 155
- vapor transport 138, 144
- varicella zoster viruses (VZV) 331
- venting filter for *in situ* integrity tests, basic principle 224
- vials
- cooling curve 8
 - cooling time/freezing rate 10
- freeze-drying plant 96
- runs with different numbers 119
- stoppers 156
- installed antenna, placed on ALUS conveyor belt 278
- vibration dryer 288
- viruses 330
- freeze-dried 330
 - suspension 52
- viscosity 184
- visualization
- at PC level designed 235
- W**
- warming 53
- water
- ammonia mixture 213
 - binding residues 324
 - cluster 359
 - condenser 149
 - content, sublimation rate 335
 - cooled condenser 218
 - cooled semihermetic motor 207
 - crystallizes 73
 - desorption 105, 155
 - evaporation
 - energy of 14
 - rate 190
 - frozen, temperatures for foods 4
 - glycerin mixture 20
 - glycerin phase diagram 18
 - glycerol 20, 26
 - glycine–sucrose 27
 - ice crystals phase boundary 26
 - ice phase transformation 16
 - molecule, electrical charges 15
 - phase diagram 2, 17
 - tBA mixtures, crystallization behavior 79
 - vapor 18, 105, 199
 - vapor condensers 192
 - for freeze-drying plant 194
 - vapor desorption 128
 - vapor equilibrium pressure 134
 - vapor flows 143, 197
 - from drying chamber 266

- water (*continued*)
vapor partial pressure, logarithm
of 128
vapor permeability 137
vapor pressure 2, 138
vapor transport 87, 139, 201
in freeze-drying plant 136
rate 198
stoppers, influences 137
water for injection (WFI) 251
water intrusion method (WIT) 223,
224
preconditions for 223
water penetration point (WPP) 223
water ring pump (WRP) 224
welded diaphragm 227
white columns 191
whole freeze-drying process 184
Williams–Landel–Ferry equation 323
glass transition theory 323
wireless temperature
measurement 135
- battery-free temperature
measurement system 135
- x**
X-ray diffraction 27, 102, 323
X-ray diffractometry
on lyophilized products 77
X-ray powder diffractometer (XRPD) 77
diffractometer–Raman
spectroscopy 77
- y**
Y–Ba–Cu oxides 367
yeasts 330
Yersinia pestis EV 76, 333
ytterbium 372
- z**
zero mobility temperature 315
ZnO powders 371
ZrOCl₂–YCl₃ system 369
ZTM 334