Index

3D printing see three-dimensional (3D) printing

abnormal events, PAT detects 469, 470 see also disturbances; impurities Abo Akadmi University 541 Accendo Conjure 131 accuracy of dosing of oral drugs 511, 512 acetaminophen, printing of 533-4 acetylsalicylic acid 202, 204 activation energy in nucleation 177-8 active pharmaceutical ingredients see APIs actuators 436, 437 in control frameworks 438, 439, 440 pairing with control variables 87-8 selecting 434 additive manufacturing (AM) 541-6 adipic acid 192 adsorptive and desorptive techniques (catch-release) 142, 143 Advancement of Emerging Technology Applications to Modernize the Pharmaceutical Manufacturing Base Guidance for Industry 518

Advion NanoTek 131 Aesica 382 agglomeration 179 agility, CM increases 9 agitators see impellers and impeller blades alarm management 469, 470 Alexanderwerk Inc (roller manufacturer) 314, 326 alglucosidase alpha 242 aliskiren hemifumarate 151, 152, 169, 197-8 continuous manufacture 448-52 Allergan 365 alternating tangential flow see ATF AM Technology 3 American Chemical Society (ACS) 127 American Society for Testing Materials standards 109, 357, 383 p-aminobenzoic acid 196-7 analytical techniques/tools 375-6, 411 and flow technology 144-50 and innovative manufacturing 516, 518 off line, summary of 213-15 see also PAT (process analytical technology)

Continuous Manufacturing of Pharmaceuticals, First Edition.

Edited by Peter Kleinebudde, Johannes Khinast, and Jukka Rantanen.

© 2017 John Wiley & Sons Ltd. Published 2017 by John Wiley & Sons Ltd.

anti-biofilm properties 546 anti-inflammatory drugs 155, 158-9 anti-solvent 171, 174, 175, 176 antibodies 248-9, 255-7, 263 analysis of 274, 275 filtration used 259 formulation 266 printing of 538 antihemophilic factor VIII 242 APIs (active pharmaceutical ingredients) 2, 4, 5, 6.38 crystallization 471-2 flow technology 127-62 multi-step synthesis 150-6 high-potency 570-3 in hot melt extrusion 337 liquid dispensing technology (LDT) for 562-3 adding to carrier tablet 556, 560-3 pad printing 565-7 for liquid dosage 169 low aqueous solubility 472-4 and low potency 552 printing of 508, 533, 537 compared to LDT 554 onto porous substrates 533-4 app-based personal monitoring 521 aqueous solubility, poor 472-4, 535 Arburg GmbH 545 artemisinin 151, 152-3 arthritis drugs 161 ascorbic acid 192-3 ASPEN Plus 78 Aspen Technology Inc 425 aspirin see acetylsalicylic acid ASTM standards 109, 357, 383 AstraZeneca 3, 155, 161, 365 at-line monitoring 233, 270 see also in-line measurement/monitoring ATF (alternating tangential flow) 252-3, 256, 268, 274-5, 374 atomic force microscopy 214 ATR (attenuated total reflectance) spectroscopy 207 automated control loops 455-6 and disturbances 460, 461-3, 465 soft sensors for 469-70 see also control loops automation and flow technology 142-50 auxostat operation 231

averaging level control 466-8 axial mixing 291-3, 418, 419 baby hamster kidney cells (BHK) 251 back mixing 416, 419, 431 balance equations 15-19 Balda Medical 513 ballroom design 380-1 Banzel 155 basiliximab 242 batch, definition of 110, 111, 123-4, 249-50, 372 for individualized products 520 batch manufacturing/processes 1, 2, 28, 485-6 of biopharmaceuticals 247, 248, 249 comparison with continuous 250-1 downstream 257, 258 and categorizing unit operations 14 fermentation 229-30, 232, 242, 243 modeling process chains 489-90 problems with 33-4 for solid drug manufacture 38, 452 space comparisons 390 batch release 115-16, 568, 571 Bayer 3, 161 Beecham 155 bend-mode inkjet technology 531 benzoic acid 187, 195-6, 200 Bepex (roller manufacturer) 313 BET analysis 214 beta-glucocerebrosidease 242 BHK (baby hamster kidney cells) 251 binders and fillers 328, 330 bioactive substances, printing for 526 see also drugs biobased polymers 239 bioequivalence considerations 123 bioethanol 238 see also ethanol biological applications of flexographic printing 538 biomanufacturing, continuous 250-1 biomedical area, 3D printing in 545-6 Biopharm services 270, 274 biopharmaceutical industry 371 biopharmaceuticals 5-6, 228 continuous fermentation 227-43 continuous manufacture 6, 247-76 current status of manufacturing 247-9 innovative 519

Biopharmaceutics Risk Assessment Roadmap (BioRAM) 508 biopolymer hydrogel matrices 538 bioprocessing, continuous manufacturing in 371-81 bioreactors 372-3 disposable 268, 269 ethanol production 238-9 fermentation in 228, 229-32 lactic acid production 239 in single cell protein production 240-1 see also perfusion reactors Biosolve software package 274 blend uniformity metrics 57-8 blenders (mixers) 415-21 modeling 56-63, 78, 79, 80, 81 scaling-up problems with 26 blood coagulation factors 247 blood plasma 263 blood plasma proteins 248 body-feed filtration 259 Bohle 3 Bosch 3 Bristol-Myers-Squibb 156, 159 brivamib alaninate, synthesis of 156 buffering 45-8 see also holding vessels bullwhip effect, supply chain 393-4 business case for CM 387-91 business environment 382, 387, 388 business excellence 370, 387-95 C-SOPS 3, 85, 86 caffeine, printing of 533-4 calcium lactate 187 calibration 208-9, 320, 411

Camo, Unscrambler X by 438 campaign basis manufacturing 2 cancer 509 *see also* tumors capacity flexibility 399 capsules 38–9, 43, 313 *see also* solid drug products carrier tablets in LDT 555–6, 564, 567 printing or coating of 565–6 cascade (series) of ideally mixed systems 22–3 cascading control loops 434 cash flow 388, 391–2 Catalent 382 cell culture 254–7, 372–3, 377, 378–9 cell harvest 373-4, 376 cell line stability 250, 251-2 cell retention devices 252-4 cell separation 373-4 Celligen packed bed reactor 254 Center for Drug Evaluation and Research (CDER) 371, 396 Centre for Continuous Manufacturing 381 centrifugation 265, 272 centrifuges, continuous 257 Cerezyme 242 CFD model 19,75 CFR see Code of Federal Regulations cGMP (current Good Manufacturing Practice) 53 and batch release 115-16 FDA publication 372, 553-4 see also GMP ChemCAD 78 chemical imaging for HME 361 chemical intensification 131, 132 chemical potential 174 chemostat operation 231, 254 Chemtrix 3, 131, 161 Chinese hamster ovarian cells (CHO) 251-2 chromatography 374-5, 377 continuous 260, 262, 268, 272-3, 275 inverse gas phase 214 liquid (LC), higher throughput 468-9 semi-continuous, economics of 275 classical nucleation theory (CNT) 177-8 cleaning 121-2, 173 and liquid dispensing technology 572-3 in vertical CM lines 386-7 cleanrooms 379-81 PODs as 397, 398 clinical trials 33, 464 LDT in 553, 556, 557, 560, 563 rapid scale-up after 520 closed-loop systems 270, 405, 442 characterization and verification 440-2 definition 432 evaluation 90-1 integrated model of 436-8 and open-loop compared 432, 433 closures in balance equations 15-16 CM see continuous manufacturing CMAC Future Manufacturing Research Hub 2 CMAs (critical material attributes) 409, 429 in closed loop systems 432, 442 in open loop performance 428, 429 co-current mode 14 co-extrusion 354-6 co-rotating twin-screw extruders 347, 348 Code of Federal Regulations 123-4, 249, 372, 568 coil/tubular reactor 131 comil 40, 78, 79, 80, 81 see also milling/co-milling commercial comparisons 377-9 commercial scale LDT machine 557, 558 cleaning 573 commercial line operation 559-60 inspection systems 563-5 compared to pilot scale 567 compaction, models of 64 compartmental structures 514, 515, 516, 518 competitive advantages 369-71 computational fluid dynamics (CFD) model 19, 75 conceptual flow modeling 298-300 conductive heating 134 conservation equations 180 ConsiGma 3, 284-7, 396, 398-9 contact transfer printing 535 see also flexographic printing contacting method, categorizing unit operations by 12-14 contamination risk 232 continuous biomanufacturing, rationale for 250-1 continuous bioprocessing (CBP) 371-2 continuous blenders 415-21 continuous centrifuges 257 continuous chromatography 260, 262, 268, 272 - 3.275semi-continuous, economics of 275 continuous crystallization 169-217 crystallization principles 173-80 crystallizers and applications 185-207 key stages 170 particle characteristics 213-15 process development 180-5 process monitoring, analysis and control 207-13 continuous downstream processing 257-66 see also continuous manufacturing (CM)

continuous fermentation for biopharmaceuticals 227-43 examples 238-41 operation of fermentation systems 229-37 prospects and challenges 241-3 reactor operation 231-2, 238 continuous filtration 258-60 continuous formulation 266 continuous inkjet systems 527-9, 531 continuous line roller compaction 313-34 continuous manufacturing (CM) advantages of 8-11, 28 authors' views 3-7 of biopharmaceuticals 247-76 challenges to developing 249-50 current status 247-9 in bioprocessing 371-81 examples of 376-7 compared to batch 390, 485-6 crystallization see continuous crystallization definitions 1-2 design of systems 405-43 development considerations, and regulations 111-12 downstream processing 257-66 early stage decision-making 485-503 economics of 274-5 engineering principles of 11-28 fermentation see continuous fermentation for biopharmaceuticals flow technology 127-62 hot melt extrusion (HME) in 356-60 importance of closed-loop control in 442 improved technology 477 industry investment in 161 for innovative flexible products 518, 520 integration of unit operations 447-80 liquid dispensing technology (LDT) as 552 for oral solid dosage forms 381-95 printing technologies 525-46 process simulation and control, solid drug products 33-94 processes for aliskiren hemifumarate 448-52 of proteins, problems with 247-8 quality considerations 115-23 regulatory environment 108-15 roller compaction 313, 330-2 process control of 332-3 of solid drug products 33-94, 381-95 equipment for 39-44

process control 81-93 as ultimate application of ObD 447 unit operation 14-15 roller compaction as 313, 330-2 see also continuous processing Continuous Manufacturing and Crystallization 161 continuous membrane filtration 260, 261 continuous oscillatory flow reactors 199 Continuous Pharmaceuticals 3 continuous phase contact 12-13 continuous phases 12 continuous precipitation 263-6 continuous process verification (CPV) 110, 117 - 18continuous processing 108 industry drivers for 369-71 lack of flexibility in 406 status and perspective 369-401 see also continuous manufacturing (CM) continuous quality verification (CQV) 109 continuous tubular blenders 418-20 continuous upstream processing 251-7 continuous wet granulation 284-7 continuously stirred-tank reactors see CSTRs continuum models 44, 49 control averaging level control 466-8 of continuous fermentation processes 234-7 and disturbances and nonlinearities 460-4 manufacturing of biopharmaceuticals 270-3 model-based 447, 452 plant-wide 455-6 state of control see state of control see also process control; process monitoring control algorithms 24 control architecture design of 431, 432-6 implementation 436-8 control framework, implementation and verification of 438-40 control loops 434-5 implementation and verification 438-40 integration of 436-7 running entire process 440-2 see also automated control loops control objectives, classification between 455-6 control strategies in continuous manufacture 469 fermentation 242-3

hot melt extrusion (HME) 338, 356-7 in crystallization 210-13 and design of systems 409 for liquid drug dispensing technology 569-70, 574 and regulations 112-14 control structures 471 in continuous fermentation processes 236-7 control systems 451, 469 running entire process 440-2 supervisory 364-5, 432 see also process control control variables critical 86-7 and modeling fermentation 235-6 pairing with actuators 87-8 controllers 436 in continuous tablet manufacture 88-9, 92-3 level controllers 466-8 MPC see MPC controllers parameters and constraints 437 PID see PID controllers selecting at design stage 435-6 convective heating 132-4 convective mixers 40 conveying system in feeders 48, 53 cooling 174-6, 177 cooling calender 354 Corning glass microreactor 161 corrective action and preventative action (CAPA) system 119 cost estimating relationship 497 cost per tablet savings 388-9 cost-benefit analysis 503 cost-benefit assessment 381-2 costs and continuous fermentation 231, 232 immobilization of yeast cells 239 and continuous manufacturing 274-5 of drug development 502 of drugs, reduced 11 in early decision-making 494, 502 analysis of categories 492-3 deriving heuristics for 495-7 equipment costs 497-8 of fermentation methods compared 241 of investment, reduced 10 reduction through CM 370, 389

savings, with PCMM platforms 397, 400

costs (cont'd) see also economic issues: investment costs: manufacturing costs counter-current loading 262 counter-current mode 14 counter-rotating twin-screw extruders 346-7 CPPs (critical process parameters) 272, 409, 423 in closed loop systems 432, 442 in LDT machines 560 and open loop performance 427, 428 CPV (continued process verification) 110, 117 - 18CQAs (critical quality attributes) 9, 109, 237, 272 in the absence of true steady-state operation 453-4 in closed loop systems 432, 440, 441 running entire process 442 in control architecture 434 and design of systems 409, 423 for LDT 563-5, 569-70 and startup and shutdown procedures 465 critical material attributes see CMAs critical process parameters see CPPs critical quality attributes see CQAs cryogenic conditions 132 crystallization 173-80, 471-7 control strategies 210-13 importance of 169-70 process development 180-5 see also continuous crystallization crystallizers 171-3, 185-207 see also reactors CSTRs (continuously stirred-tank reactors) 22, 173 for cell cultivation 254, 255-6 cultivation systems, comparison of 229-32 current Good Manufacturing Practices see cGMP customization 526 3D printing in 542 see also personalized medicine Cutter Laboratories, Berkeley 248 cybersecurity hazards 521 cyclosporine 193, 198 cystic fibrosis, drug for 3, 486 Darunavir (HIV drug) 3

data acquisition and process control systems 364-5

data availability in decision-making 486-7, 491, 503 data characterisation approaches 307 data management tools 43, 439 data mining of biological databases 508 data processing for HME 362, 363 decentralization 10 decision-making chain 487 decision-making, early stage 485-503 deferasirox 187, 189 Delta V control platform 439, 440 DEM (discrete element method) 19, 44, 45, 49 blenders 58, 59 drying 75 feeders 53 particle-scale simulation using 305-7 powder compaction 64 roller compaction 317, 333 roller compactors 67, 68 tablet presses 63 twin-screw granulation 298 wet granulation 72-3 Demonstration of Uniformity of Dosage Units using Large Sample Sizes 520 depth filtration 258-9, 260, 268 design computerized drug design 514-15, 518 and continuous bioprocessing 377-81 of control architecture 431, 432-6 of integrated continuous manufacturing systems 405-43 model-based 447, 452 rough conceptual design 406-10 design of experiments see DoE desktop flexography 540-1 diafiltration 266, 267 dielectric heating 134-5 dielectric spectroscopy 234 differential balances 15 differential scanning calorimetry 215 dimensioning 27-8 2,2-dimethylchromenes, synthesis of 156, 158 direct compaction 407, 410, 412 direct costs 494 direct delivery to patients 4, 5 see also patient-centred medicine direct shaping of final product 350-2 discontinuous mode of phase contact 13 discrete element method see DEM dispersed phases 12

dispersive mixing 345 disposable equipment 274 see also single-use technology distillation 140-2 distributive mixing 345 disturbances 460 control implications 460-4, 465 and buffer tanks 466-8 see also abnormal events; impurities documentation, regulations on 124 DoE (design of experiments) 181, 271-2, 388, 389, 391-2 integrated continuous manufacturing systems 428, 429, 440, 441 twin-screw granulation 307 dosage forms 511 dosage units, new terminology for 520 dosing in LDT manufacture 560-3 imaging to check 564-5 downstream manufacturing 38 see also secondary manufacturing downstream processing in biopharmaceutical manufacture 248-9, 257 - 66and continuous melt extrusion 349-56 disposable unit operations in 268-70 and flow technology 139-42 hot melt extrusion products 338 monitoring and control 272-3 streamlining, in tablet manufacture 452 downtime at design stage 408 in fermentation 230, 231, 232 Drexel University 545 driving force 174, 176, 179 drop on demand inkjet systems 527, 528, 529 piezoelectric see piezoelectric inkjet printers thermal see thermal inkjet (TIJ) printers drop formation, ink 531-2 drug delivery systems (DDS) flexographic printing in 537, 538 printing technologies for 525, 533-5 prototype fabrication 540-1 drug development, costs of 502 drug therapies, personalized 507-21 drug-eluting stents 533 drugs anti-inflammatory 155, 158-9 development, and flow technology 160-1 dosage forms 511

and early stage decision-making 485-503 erectile dysfunction, orodispersible films for 538 future medicines, personalized 507-21 and genetic factors 509 low dose 551-74 orodispersible films for 514, 538 poor water-solubility 534-5, 539 printing technologies for 525-46 solid see tablets see also product dry granulation 313, 407 dryers 38, 39, 42 drying, models for 75-6 DSM Pharma Chemicals 161 dual microdispenser system 535 dynamic models 48 dynamic process simulations 465 dynamic sensitivity analysis method 87 dynamic vapour sorption 214

early stage decision-making 485-503 economic issues 5, 387-95 biopharmaceutical manufacturing 274-5 continuous bioprocessing 377-81 continuous versus batch manufacturing 426 technical-economic evaluation methodology 486-503 see also costs Egalet technology 514 Ehrfeld 3, 161 Eisai 155 elderly/geriatric populations 507, 509 electric heating 135-6 electrospinning drugs 477, 478 Eli Lilly and Company 158 Emerson Process Management 439 empirical models 35, 47-8, 51-2 for blenders 62-3in crystallization 211-12 and feeders 55-6 for fermentation 235 emulsion embedded hydrophobic drugs 472-4 energy balance models for drying 76 energy balances 18-19 engineering models 46-7 for drying 76 for milling 77 for roller compactors 68-71 tablet presses 65-7

engineering models (cont'd) wet granulation 74-5 for wet granulation 74-5 engineering principles 11-28 environmental issues 11, 555, 572-3 enzymes, industrial production of 227, 242, 251 equilibrium and crystallization 174 equilibrium saturation solubility curve 174, 175 equipment in continuous manufacture of solid drugs 39-44 in early decision-making 492, 497-8 overall equipment effectiveness (OEE) 489, 490, 491 and regulatory environments 112-13, 122 erectile dysfunction drugs 538 ethanol 227, 228, 238-9, 242 ethnical populations 507, 508 7-ethyltryptopol 158-9 etodolac 158-9 Eucreas (Novartis) 366 European Consortium for Continuous Manufacturing 3 European Medicines Agency (EMA) 110 European Pharmacopeia monograph 2.9.47 520 European Union 8, 110 evaluation of models 90-1, 423 evaporative crystallization 176 excipients 4, 5, 6 in downstream manufacturing 38 in hot melt extrusion 337 for inkjet and flexography 539 in innovative manufacturing 516 and roller compaction 328, 330 experimental data and modified Johanson model 320 and PBM framework 301 pressure distribution in roller compactors 322-4 for twin-screw granulation 298, 300, 302, 308 extractables and leachables 268-9 extruders 41, 338-41 feeding 341-5 operation points 347-9, 350 twin-screw 345-7, 348 extrusion 3D printers use 543-5 co-extrusion 354-6 hot melt see hot melt extrusion in innovative manufacturing 516

and innovative product design 513-14 twin-screw 345-7 fabbster (3D printer) 545 facility design 379-81 see also layout of installations failure modes 113 FBRM (focused beam reflectance measurement) 210 FDA (Food and Drug Administration) 371, 396, 518 categorisation of sensors 270 cGMP 53, 115-16, 372, 553-4 definitions by 207, 372 guidance 109, 568 meetings with manufacturers 410 and PAT 36, 142, 207, 233 promotes continuous manufacturing 248, 410, 486, 568 QbD requirements 237 regulations see Code of Federal Regulations site visits by 111 FDM (fused deposition modeling) 534, 542, 543 - 4feedstock material for 544-5, 546 fed-batch production biopharmaceuticals 274-5 comparison with perfusion systems 377, 378 - 9fermentation 230-1, 232, 242, 243 for ethanol 238 feed frames 63-4, 80, 81 feedback 436, 460-3, 468-9 feeders 38, 39, 40 and design of systems 413-14 in flowsheet modeling 78, 79-81 loss in weight 341-5, 412-15 models for 48, 53-6for roller compactors 314-15 see also feeding feedforward control 434-5, 460, 461 feeding 341-5, 420-1 multiple ingredients 408-9 see also feeders feedstock 400 for FDM printing 544-5, 546 felodipine, dispersion of 534 FEM (finite element method) 44, 49 powder compaction 64 roller compaction 67, 317, 321, 326, 327, 333

fenofibrate 472-4, 475, 533 fermentation, continuous 227-43 systems operation 229-37 FFF (fused filament fabrication) printing 527, 542, 543-4 film extrusion 354 films 474-7, 513, 538 orodispersible 514, 538 filtration, continuous 258-60, 268 finite element method see FEM first principle models 35, 44, 49 for blenders 58 for drying 75 Fitzpatrick (roller manufacturer) 313 flash chemistry 132 FLEX (fused layer extrusion) 545 flexibility 399-400 and design of systems 408 increased by CM 8 lack of, in continuous processes 406 flexible dosing 510-13 flexographic printing 526, 527, 535-8 pharmaceutical applications 525, 537-9 flocculation 259, 260 flow aid mechanical unit 48, 53 flow intensification 128 flow modes 13-14 flow rate 55-6, 111, 119 flow reactors 130, 131 continuous oscillatory flow reactors 199 oscillatory flow reactors 171, 172 plug flow reactors 171, 198-206 flow technology 127-62 industrial applications 160-1 larger-scale synthesis 156-60 micro flow technology 128-50 flow visualisation 293, 295 flowsheet modeling 36, 37 design of integrated systems 425, 432, 436, 437 and early decision-making 494, 495 in solid drug product manufacture 77-81 and tablet presses 67 FlowStart Evo 131 FlowSyn (Uniqsis) 131, 155 Flublok manufacture 251 flufenamic acid 202 fluidized beds for drying 75 fluorescence spectroscopy 234

focused beam reflectance measurement (FBRM) 210 folic acid, nanosuspensions of 534-5 Food and Drug Administration see FDA footprint, reduced 108, 128 see also space formulation 266 at plant design stage 406-7 of hot melt extrusion product 337-8 for inkjet and flexography 538-9 and liquid dispensing technology 555-6 properties, and process maps 307-8 and roller compaction 328, 330 Freund-Vector 313 friction in powder densification 316 and pressure gradient on rolls 317, 320, 321 FTIR spectroscopy 144, 146, 147 mid FT-IR 214 fused deposition modeling see FDM fused filament fabrication see FFF fused layer extrusion (FLEX) 545 fused-bicyclic isoxazolidines 158 Future Chemistry 3 future health care scenario 513-21 future medicines, personalized 507-21 future performance 470-1 FutureChemistry 131, 161

G-CON Manufacturing Inc 396, 398 GAMP 5 guidelines 362, 364 gastrointestinal stromal tumors 154 GC/LC-MS 215 GCG-70 (Glatt) 417, 420 gCRYSTAL 184 GE-Healthcare 270 GEA Group 3, 284-7, 396, 398 generic twin-screw granulation 300, 302-7 genetic factors 509 Genzyme 248 Gericke GCM-250 blender 417 Gerteis (roller manufacturer) 314 Ghent University 3 Glatt 3, 417, 420 GlaxoSmithKline (GSK) 3, 161, 381, 396 and continuous manufacturing 486 liquid dispensing technology 552-3, 554, 555, 574 air monitoring by 570-1 patent rights 557

Gleevee (imatinib mesylate) 154-5 L-glutamic acid 191-2, 202, 203 glycine 206 GMP 3, 362, 390, 568 pilot LDT machine 557, 558, 567 see also cGMP gOMATLAB 438 Good Automated Manufacturing Practices (GAMP 5) 362, 364 good manufacturing practices see cGMP; GMP GPCC drying batch system 3 gPROMS 33, 78, 79, 332, 438 optimization routine of 437 simulation software 436 granulation 38, 39, 41-2roller compactors for 38, 39, 41, 67 twin-screw 283-308 wet see wet granulation granulation time 288-91 granule characteristics on regime maps 303, 304 granule production rate 333 granule size and energy input 304 evolution 294-7 and roller compaction 328, 330 and shape dynamics 295, 296 granule size distribution (GSD) and energy input 304 in twin-screw granulators 287, 288 link with RTD and liquid distribution 295, 297 and shape dynamics 295, 296 and solid-liquid mixing 293-4 tracking 300-2 gravimetric controllers 413 gravimetric feeding 341-2 gravure printing 526, 535 Graz University of Technology 3 green chemistry 127, 162 Green Chemistry Institute (GCI) 127 growth 174, 175, 176-9 GSD see granule size distribution GSK see GlaxoSmithKline Guidance for Industry PAT-A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance 109 Guidance for Industry Process Validation: General Principles and Practice 109, 568

Guideline on NIR 110 Guideline on Real Time Release Testing 110 Guidelines for Process Validation 110 H-Cube reactor (ThalesNano) 131, 155 health care, future scenario for 513-21 heat, speeding up reactions with 132-7 heat transfer intensification 129 Heckel equation 65 Heinrich-Heine University 3 HER-2 positive tumors 509 Herceptin 509 heterogeneous nucleation 176, 177 hierarchical viewing 455-6, 457, 465 high volume/low value 392-3 high-potency products 552-3, 570-3 HIV, drug for 3 HME see hot melt extrusion holding vessels 451 see also buffering homogenous primary nucleation 176-7 hoppers 48, 53, 314 in hot melt extrusion 342-4 modeling of 44, 45 hot die-face cutting 353-4 hot melt extrusion (HME) 337-66 continuous manufacturing with 356-60 extruders 338-41 feeding 341-5 twin-screw extrusion 345-7 hot-stage microscopy 215 5HT1B antagonist, synthesis of 155 human genome 508, 510 hybrid control strategies in crystallization 212-13 hydrodynamics of flow 129 hydrophobic drugs, emulsion embedded 472-4 6-hydroxybuspirone 159-60 hydroxypyrrolotriazine, synthesis of 156, 157-8 hyperspectral imaging NIR (near-infrared) 540 hypertension, drugs for 151 ibuprofen, micro flow technology for 153-4 iCellis 254 ICH (International Conference on Harmonisation) 108, 110

publications 108–9, 115, 117, 124, 372, 567 ICI 2 ideal plug-flow systems 21–2, 23 ideally-mixed systems 22

cascade of 22-3 imaging 88 and innovative manufacturing 516, 518 on LDT machines 560-1, 563-5, 574 near infrared hyperspectral imaging 540 see also spectroscopy imatinib mesvlate (Gleevee) 154-5 immobilization of yeast cells 238-9 immunoglobulin 263 impellers and impeller blades 416-18, 419, 420 impinging jet crystallizers 206-7 impinging jet mixers 171 implementation strategies 393-5 impurities 263, 458-60, 472 see also abnormal events: disturbances in situ measurement 142 see also in-line measurement/monitoring in-line measurement/monitoring 270, 375 applied to crystallization 207, 208 in continuous manufacture of aliskiren hemifumarate 468-9 in hot melt extrusion 357 of roller compaction process 326-8, 329, 333 soft sensors for 469-70 and state of control 357 see also at-line monitoring; in situ measurement; in-process controls; on-line monitoring in-process controls (IPCs) 111, 113, 120 and regulations 110 and systems design 430 see also in-line measurement/monitoring in-process material, regulations for 119 indirect costs (overheads) 494 see also overheads individualized manufacturing 6, 7, 10 individualized medicine 5 individualized needs 508-9 indomethacin, nanosuspensions of 538 induction time in nucleation 177 inductive heating 136-7 industrial applications of flow technology 160-1 industry see pharmaceutical industry infliximab 242 information technology computerized drug design 514-15, 518, 519 computerized systems, process integration into 362-5 and innovative flexible pharmaceutical products 521

see also modeling information transfer 426-7 infrared see IR inhibition 230, 231, 232 injection molding (IM) 351-2 inkjet printing 514, 515, 516, 517, 526, 527-35 combined with flexography 537 and LDT compared 554 pharmaceutical applications of 525, 533-5 inks 531-2, 535 formulation of 538-9 innovative flexible pharmaceutical products 513-18, 520 innovative products 513-18, 520 flexible dosing with 510-13 supply chain 520-1 inoculation 228 Inovelop 155 insect cells 251 inspection 422-3, 563-5, 569 see also in-line measurement/monitoring instability of low dose drugs 551-2, 556 installation layouts 383-7 see also facility design insulin 227, 229, 242 integral balances 15 integrated continuous manufacturing of biopharmaceuticals 247-76 full process train 270 process monitoring and control 270-3 design of systems 405-43 integrated model 424-7 integration of unit operations 447-80 intensification 128, 129, 131-8 intermediates 411, 452 buffer tanks for 465 in continuous melt extrusion 352-6and regulations 112, 119 International Conference on Harmonisation see ICH International Society for Pharmaceutical Engineering (ISPE) 362, 364 International Symposium on Continuous Manufacturing of Pharmaceuticals 2 intra-uterine devices 546 inverse gas phase chromatography 214 investment 382, 389 rational basis for decisions 488 strategies 388 investment costs 10, 408

investment costs (cont'd) see also costs IPCs see in-process control IR FTIR spectroscopy 144, 146, 147, 214 MIR (mid-infrared spectroscopy) 234 NIR see NIR (near-infrared); NIR (near-infrared) spectroscopy isoxazolidines, fused-bicyclic 158 ISPE (International Society for Pharmaceutical Engineering) 362, 364 IT see information technology itraconazole, nanosuspensions of 538 Johanson model 68-71, 316, 317-19, 332 modified 319-22Johnson and Johnson 486 K-Tron KT-20 feeder 416, 420 Kawakita model 65-6, 67 Kenics mixers 202 ketoconazole 202 kinetics and crystallization 176, 177, 179, 213 models 211 nucleation and growth 183-5 semi-empirical kinetic models 209-10 see also rate Kogenate 242, 376 Kolbe-Schmitt reaction, speeding up 132-3 Kuentz and Leuenberger model 66, 67 laboratory LDT machine 557 laboratory simulator 557, 559 lactic acid 239, 242 lactose 204-6 Lang factor 498 large scale flow reactors 130 laser diffraction 214 layout of installations 383-7 see also facility design LDT see liquid dispensing technology leachables 268-9 Lennox-Gastaut syndrome 155 leukaemia 154 level controllers 466-8 levothyroxine 552 lipoic acid-nicotinamide 199-200 liquid chromatography (LC), higher throughput 468-9 liquid dispensing cell 560-3

liquid dispensing technology (LDT) 551-74 machines 555-9 design details 559-66 inspection systems 563-5 overview of 553, 555-9 program goals 554-5 real-time release 567-70 scale-independence of 566-7 liquid medicines 511 liquid systems, modelling of 34-5 liquids, mixing see solid-liquid mixing LIW see loss in weight (LIW) feeders location flexibility 400 Lonza 161 loperamide hydrochloride, printing of 534 loss in weight (LIW) feeders 341-5 and design of systems 412-15 see also feeders lot, definitions of 124, 249-50 low aqueous solubility APIs 472-4 low dose drugs, manufacture of 551-74 low potency drugs 551, 552 low volume/high value 392-3 mAb (monoclonal antibody) 255-6

magnesium ammonium phosphate 191 maintenance factor 496 malaria, artemisinin for 151 mammalian cells 228, 229, 242 continuous production of 251-2 proteins from 248 and virus removal 259 manipulated variables 357 manufacturing batch see batch manufacturing continuous see continuous manufacturing (CM) for innovative flexible pharmaceutical products 513-18 low dose drug products 551-74 paradigm shift required 513 route type, and design of systems 407 solid drug products 33-94 equipment for 39-44 processes in 38-44 manufacturing costs 388, 496, 503 see also costs manufacturing on demand production units 508 market segment 382 market size and fermentation products 228

mass balances 16-18 and fermentation 230, 231, 232 see also population balance equations mass flow rate, synchronization of 330-2 mass spectroscopy 150 mass transfer 129 mass transfer intensification 129 material carry-over 120 material diversion 120 material hold-up 417, 418, 419, 420 material transport 287-94 materials characterising unit operation with 412-21 and design of continuous systems 410-11 as input and output for models 423-4 traceability see traceability see also raw materials Mathematica 425 mathematical models see modeling; models MathLab (The MathWorks Inc, UK) 332 MatLab 425, 438, 440 mechanistic description 284, 307, 308 mechanistic models 35, 44 for blenders 58, 59 for drying 75 for feeders 53 for fermentation 235 for milling 76 of powder compaction 64 for roller compactors 67-8 for wet granulation 72-3 medicines see drugs; product melting points 215 melts, crystallization from 174 membrane filtration 258, 259-60, 261, 268 membrane-based separators 142 Merck Millipore 270 mesoscale flow reactors 130 metabolism of microorganisms 227 metastable zone width (MSZW) 174, 175, 176, 177.184 micro distillation 140-1 micro flow reactors 131 micro flow technology 128-50 in API multi-step synthesis 150-6 reaction activation tools 130-9 see also flow technology micro scale flow reactors 130 micro-indentation 324-5 microbiological testing 365

microcapsules, formation of 535 Microchip (flow reactor) 131 microdosing dispenser head 534-5 microfluidics 207, 515 micromixing 129-30 microorganisms 227, 238, 239 in single cell protein production 240-1 microparticles, drug-loaded 535 microwave heating 134-5 Mikrotechnik BTS 161 milling/co-milling 315 comil 40, 78, 79, 80, 81 models for 76-7in solid drug product manufacture 40, 43 mini extruder deposition (MED) 545 mini-tablets 513, 514 miniaturization 397, 399, 515 MIR (mid-infrared spectroscopy) 234 MIT (Massachusetts Institute of Technology) 2, 3, 248, 381, 382, 472 see also Novartis-MIT Centre mixed suspension mixed product removal see MSMPR mixers see blenders (mixers) mixing back mixing 416, 419 in blenders 416-20 continuous blenders 415-21 in continuous crystallization 170 in extruders 341, 345 micromixing 129-30 solid-liquid see solid-liquid mixing in twin-screw granulators 291-4, 295 mobile health apps 521 MODCOS system 3 mode of operation, categorizing by 14-15 model integration basics 425 model predictive control (MPC) 24, 470-1 model predictive controllers see MPC controllers model-based analysis of twin-screw granulation 298-302, 307-8 model-based control 24 algorithms 24 in crystallization 210-11, 212-13 model-based design and control 447, 452 model-free control in crystallization 211-13 ModelBuilder 78, 79 modeling 44-8 and bioprocesses 234-7

modeling (cont'd) for control applications 234-5 of fermentation 235-6 flowsheet see flowsheet modeling of liquid systems 34-5 for out of specification material 358 process, fundamentals of 15-16 process chains 489-90 of solids 35 of twin-screw granulation 284, 298-300, 305 - 7see also models; simulation models 34 calibration models for analytical sensors 411 of compaction 64 coupled with experimental data 298, 300 for crystallizers 209 for drying 75-6 engineering see engineering models inferring process variables through 470-1 integration of 77-81 Johanson Model 316, 317-19, 332 modified 319-22 of open loop systems 424-7 phenomenological see phenomenological models population balance see population balance models (PBMs) for roller compaction 316-22, 332-3 semi-empirical kinetic 209-10 types of, solid drug manufacture 34-6 unit operation 48-81, 422-4 see also modeling; regime maps; simulation modified Johanson Model 319-22 modifiers in formulations for inkjet and flexography 538-9 modular design 451 momentum balances 16, 19 monitoring of biopharmaceutical manufacture 270-3 of fermentation processes 232-4 of roller compaction process 326-8, 329 see also process monitoring monitoring tools 88 see also PAT; sensors mouse myeloma (SP2/0) 251 MPC algorithm 440 MPC controllers 37, 83-4, 88-9, 92-3, 332, 435, 436 MPC-PID hybrid model 438

MS see mass spectroscopy MSMPR (mixed suspension mixed product removal) 171, 185-93 cascade 172, 193-8 optimizing 472 MSZW (metastable zone width) 174, 175, 176, 177, 184 multi-compartment systems 525 multi-dimensional population balance models 44-6, 50 multi-layer membranes 525 multi-orifice oscillatory baffled crystallizer 204-6 multi-phase balances 16 multi-stage MSMPR 172, 193-8 multilayer printing 539 multivariate data analysis software 438, 439 murine melanoma cells (NS0) 251 mutation probability in fermentation 232 Myozyme 242 nabumetone 155 nanocrystals 472 nanofibres containing drugs 477 nanofiltration, virus removal with 259 nanoparticles 515, 532 nanosuspensions 534-5, 538, 539 naproxcinod 161 National Centre for Innovative Manufacturing 161 NatureWorks 239 near infrared see NIR (near-infrared); NIR (near-infrared) spectroscopy net present value (NPW) 382, 388, 391 and batch size 392, 393 nicotinamide 199-200 NicOx 161 nip angle 315, 316, 317-19, 320, 321 measurements of 322, 323 nip region (compactors) 316 NIR (near-infrared) 215, 565 chemical imaging (NIR-CI) 326-8, 329, 333 hyperspectral imaging 540 probes using 357, 429-30 sensors using see NIR sensors NIR (near-infrared) spectroscopy 110 for continuous fermentation processes 233-4 and flow technology 144, 146 for hot melt extrusion 360 NIR probes 357, 429-30

NIR sensors 361, 376 in real time monitoring 82, 88, 89, 90, 92, 93 NIST calibration 561, 563 NIIT 2 NMR spectroscopy for crystallization 215 and flow technology 147, 149-50 non-aqueous solvent, printing of 535 non-conforming materials 119-20, 520 see also out of specification material Noracet 155 Novartis 3, 151, 154, 161, 255, 366, 381, 486 Novartis-MIT Centre 2, 85-6, 161, 471, 472, 480 see also MIT novel process windows (NPW) 130-2 Novo Nordisk 229 NPW see net present value nucleation 170 and growth 176-9 increased rates of 475-7 occupational health and high potency drugs 552-3, 572, 574 and liquid dispensing technology 570-2 see also safety issues off-line characterization 213-15 of continuous fermentation processes 233 of ribbon quality 324-6 Ohnesorge number (Oh) 532 OLUPX (online prediction engine) 440 on-demand fabrication 526 on-line monitoring of fermentation 233 on-line prediction tool 438, 439 on-line probes 233-4 on-line sensing and model design 429-30 on-line sensors 270 in situ near-infrared 376 on-line testing of PAT tools 430-1 oncology 508 OPC (OLE process control) protocol 438, 439, 440 open-loop systems 424-9, 430-1 and closed-loop compared 432, 433 operating temperature, increase in 132-7 operation points for extruders 347-9, 350 operational costs in early decision-making 494 see also costs

optical coherence tomography (OCT) 361 optical microscopy 214 optimal experimental design (OED) approach 307 Optimal Industrial Automation Ltd 439 optimization control layer 236-7 oral films 513, 538 oral solid dosage 38, 381-95 next generation 396-9 printing technology for 533 see also tablets Orkambi (cystic fibrosis drug) 3, 486 orodispersible drug formulations 514, 538 mini-tablets 513 oscillatory flow reactors (OFR) 171, 172 out of specification material 357-60, 431 see also non-conforming materials overall equipment effectiveness (OEE) 489, 490, 491 overheads 494 in early decision-making 494, 495-7 Ozurdex (Allergan) 365

packed bed reactors 131, 253-4 paclitaxel solutions, printing of 535 pad printing cell 565-7 Panzytrat OK 513 paracetamol 190, 194-5 Parkinsons disease, orodispersible films for 538 particle characteristics 213-15 particle size 211, 324, 361 particle size distribution (PSD) 171 and crystallizer type 186, 199 impinging jet crystallizers 206-7 particle-scale simulation 305-7 PAT (process analytical technology) 8, 24, 25, 36-7, 120-1 and biopharmaceuticals 272 and bioprocessing 371, 375-6, 384 PCMM platform 397, 399, 400 and continuous fermentation processes 233 continuous printing applications 539-40 and control strategies 112 and crystallization 184, 201, 207-10, 211 data management tools 91-2, 439 and flow technology 142-50, 159, 162 and hot melt extrusion 338, 357-8, 359, 360-2, 365 and real-time release testing 365 and innovative manufacturing 516, 518, 520 in integrated continuous manufacturing 468-9, 479

PAT (process analytical technology) (cont'd) in integrated system design 409, 428, 429-31, 439 and liquid dispensing technology 552, 554, 568 regulatory considerations 108, 109, 110 and roller compaction 326, 333 and twin-screw granulation 286-7 patent rights for LDT 557 Patheon 382 patient-centred medicine 507 patient-centric drug development 508 patient-centric supply chain 520 patient-specific needs 6, 7 patients direct delivery to 4, 5 groups of 507, 508-9 PBEs see population balance equations PBMs see population balance models PCMM 396-400 PCS7 control platform 439, 440 performance targets and early decision-making 488 perfusion reactors 252, 254, 371, 372-4 commercial 376 disposable 268 see also bioreactors perfusion systems 270, 273, 274-6 analytic tools 375-6 comparisons with other systems 377-9 counter-current loading 262 products 242, 247, 254-7 reactors see perfusion reactors personalized doses, printing for 534 personalized drug therapies 507-21 personalized medicine 370, 508-10 see also customization personnel procedures and training 120 perturbations 431 Pfizer 3, 381, 396, 486 pharmaceutical applications of flexographic printing 537-8 of inkjet printing 533-5 three-dimensional printing in 525, 545-6 see also drugs Pharmaceutical CGMPs for the 21st century - A Risk-Based Approach 372, 553-4 pharmaceutical industry batch processing in 33-4 continuous manufacturing 2, 161, 381-3

current examples 376-7 drivers for 369-71 status and perspective 369-401 lack of advancement in 554 modernization compared to other industries 485 needs process engineering skills 442-3 supply chain of the future 395-400 pharmaceutical ingredients see APIs pharmaceutical quality system (PQS) 109, 115 pharmaceuticals see drugs pharmacogenomics 508 pharmacokinetics 509, 510 phase diagrams 174-6, 183, 184 phases, categorizing unit operations by 11-12 phenomenological models 35, 44, 46-7, 50 drying 76 milling 77 roller compactors 68-71 tablet presses 65-7 wet granulation 74-5 physico-chemical equivalence considerations 123 physico-chemical principles 11, 12 PI feedback control, pilot plant uses 460 PID control, disadvantages of 332 PID controllers 83, 88-9, 92-3, 333, 435, 436, 437, 438 PID (proportional integral derivative) 37 piezoelectric inkjet printers 528, 530-1, 537 for drug delivery 533-4, 535 ink for 531. 532 pilot plants continuous tablet manufacture 82, 83, 94, 381 design and control 452-9, 460-1, 465-7, 470 - 1operating and control user interface 440, 441 and flow technology 156, 157, 160 pilot scale LDT machine 557, 558, 567 piroxicam 535 plant cells 251 plant-wide control 236-7, 455-6 plastification units 339, 340 plug flow reactors 171, 198-206 plug-flow systems, ideal 21-2, 23 plug-flow transport in twin-screw granulators 292, 294, 300 POC (point of care) diagnostics 509-10, 521 POD systems 396, 397, 398, 399

point of care diagnostics 509-10, 521 polymers in 3D printing 544-5 biobased 239 and electrospinning drugs 477 in hot melt extrusion 337-8 in innovative manufacturing 516 in liquid dispensing technology 556 poorly soluble drugs, printing for 534-5, 539 population balance equations (PBEs) 17-18, 301 crystallization 180 population balance models (PBMs) 44, 49-51 for blenders 58-60 for crystallization 180, 210 for drying 75-6 gCRYSTAL for 184 lower dimensionality 46 for milling 76-7 multi-dimensional 44-6, 50 particle-scale modeling 305-6 for roller compactors 68 tracking granule size distribution 300-2 for wet granulation 72-4 portability 397, 399 potency high 552-3, 570-3 low 551, 552 powder compaction, models of 64 powder densification 313, 315-17 PQS (pharmaceutical quality system) 109, 115 pre-blends, feeding 408-9 pre-coat filtration 259 precipitation, continuous 263-6 precision extruding deposition (PED) 545 prednisolone 533 pressure distribution in roller compactors 317-19 experimental 322-4 modified model 320 pressure gradient on rolls 317-19 primary manufacturing 4-6, 490 see also upstream processing primary nucleation 174, 175, 176-8 printability of inks 531-2 printing technologies 535 in drug manufacturing 525-46 products 512, 514-15 probability density function (PDF) 46 probability distribution of induction time 177

process analytical technology see PAT Process Analytical Technology Team 110 process chains, modeling 489-90 process control 24-6, 36-7 basics 83-4 continuous printing applications 539-40 continuous roller compaction 332-3 hot melt extrusion 364-5 solid-based drug manufacture 81-93 systemic methodology for design 84-93 closed-loop operation 92-3 control variables 86-8 controllers and control parameters 88-90 implementation 91-2 monitoring tools 88 performance evaluation 90-1 see also control systems process design intensification 131-2 process development crystallization 180-5 and regulations 111 process drift 568 process engineering skills, need for 442-3 process and facility design comparison 379-81 process integration into computerized systems 362-5 process maps 303-4, 308 process monitoring continuous crystallization 207-10 in hot melt extrusion 358 in integrated continuous manufacturing 468-71 of biopharmaceuticals 270-3 and regulatory environments 113 process options in early stage decision-making 492-8 process performance and material properties 410-11 Process Pulse 439, 440 process simulation 34-6, 452 in early decision-making 494, 495 effect of recycling on impurities 458-60 for startup and shutdown 465 see also simulation process systems engineering (PSE) tools 34, 36 process technologies 372-7 process understanding hot melt extrusion 356 process validation 109, 110, 117-18, 568 process variables inferring with soft sensors 470

process variables (cont'd) and state of control 357 process verification, continued 568 product with continuous melt extrusion 349-56 criteria for accepting 113 flexibility 399-400, 408 from continuous upstream processing 254-7 of hot melt extrusion 365-6 launch and time to market effects 391-2 low dose, manufacture of 551-74 monitoring, production floor 120-1 out of specification see out of specification material quality and batch release 116 and regulatory environments 113 and steady-state operation 453-4 type and design of systems 406-7 product costing with activity model 495 product inhibition 230, 231, 232 product life cycle 503 product performance drivers 370 protein concentration 234 proteins cell culture products 255-6 continuous production problems 247-8 recombinant, upstream processes for 252 single cell proteins 240-1, 242 prototyping 3D printing in 542 drug delivery systems 540-1 PSD see particle size distribution PSE 425, 436 see also gPROMS Purdue University 2,86 purification processes 374-5, 377 push-mode inkjet technology 531 push/pull scheme (throughput control) 455 Python 425

QbD (Quality by Design) 8, 36, 37, 447, 486 and biopharmaceuticals 271, 272 and bioprocessing 371, 372 and crystallization 170 and design of integrated systems 409, 442 and future medicines 508 and liquid dispensing technology 553, 554 regulatory environment 108, 110, 115, 237 and roller compaction 326 quality and batch release 116, 568 in continuous manufacturing 115-23 and conventional tablet manufacturing 567-8 in hot melt extrusion 349, 350 and regulations 109, 112 quality assurance and batch release 568 real-time 4, 9, 405 Quality by Design see ObD quality control 370 and absence of steady-state operation 453-4 buffer tanks provide opportunity for 465 quality product target profile (QPTP) 486-7 quality risk management, FDA guidance on 109 quality systems, FDA guidance on 109 quasi-continuous manufacturing 1 quasi-plug flow 128 R2⁺/R4 reactor (Vapourtec) 155 radial mixing 291, 418-19 Raman spectroscopy 234 and crystallization 215 and flow technology 146, 148 for hot melt extrusion 360-1 ranking in early decision-making 498, 502 rapamycin derivative 533 rasagiline mesylate 534, 538 Rasilez (UK brand name) 151 rate of growth of crystals 179 of nucleation 177, 475-7 of reaction, increasing 132-9 rational approach 488, 503 raw materials 410-11 and crystallization 181-2 extrusion of 338-41 modeling in feeders 53-5 and regulations 112, 116, 119 variability 110, 121 see also materials RDT (residence time distribution) MSMPRs 186 React-IR DiComp probe 160 reaction activation tools 130-9 reactivity, increased 370 reactors bio- see bioreactors for continuous upstream processing 255-6 for crystallization 171-3 see also crystallizers

CSTRs 22, 173, 254, 255-6 flow 130, 131, 171, 172, 198-206 types of 21-3 real-time measurements applied to crystallization 207, 208 real-time monitoring 233, 432, 435 real-time product quality information 108 real-time quality assurance 9, 109, 405 real-time quality evaluation 109 real-time release (RTR) 9, 567-70 real-time release testing (RTRT) 110, 112, 365 Rebif 376 recombinant antibodies 248-9, 274, 275 see also antibodies recombinant proteins 252 recycling 456, 458-60, 472 reduced-order models (ROM) 47-8 for blenders 62-3and feeders 55-6 refilling 342-3, 413, 414, 416 refolding processes 251 regime maps 302-5 regulatory control 236, 237 regulatory environment 8, 108-15, 271-2, 388 Code of Federal Regulations 123-4, 249, 372.568 definitions 123-4, 249-50 and innovative products 518, 520 regulatory strategy 409-10 regulatory submissions 115 Relafen 155 relative gain array (RGA) method 87 relative ribbon density 319, 320, 321, 324 as key product quality attribute 333 off-line measurements 324-6, 327 see also ribbon quality relief printing 535 see also flexographic printing Remicade 242, 376 representative stability batches 114 Research Centre for Pharmaceutical Engineering (RCPE) 3 research and development savings and costs 388, 392 to commercial production 383 research-scale inkjet models 540-1 residence time in continuous fermentation 231, 232 in transitions between unit operations 428 see also RTD

residence time distribution see RTD residence time function 20 resolution, printing 537 Reynolds number (Re) 531-2 rheumatoid arthritis 159 ribbon quality 324-8, 329 see also relative ribbon density risk assessment 422-3 and early decision-making 490-2 and regulatory environments 113 risk factors and early decision-making 488, 491 risk scores 490-1, 492 risk-based approach 108-9 roll surface 315 roller compaction 313-34 formulative aspects of 328, 330 in-line monitoring 326-8, 329 powder densification in 315-17 roller compactors 38, 39, 41 main components of 313-15 models for 67-71 pressure distribution in 317-19, 320 experimental 322-4 rough conceptual design 406-10 Roughton mixer 200, 210 RTD (residence time distribution) 20-1, 46 and blenders 60-2, 420-1 characterising using process materials 412-21 in CSTRs 22, 23 in extruders 346, 347 and feeders 53-4, 415 ideal plug-flow systems 21 impact of recycling 456, 458-60 and material traceability 119 micro flow technology reduces 128 modeling 46-7, 50-1 for tablet presses 63 in twin-screw granulators 288-90, 291-3 and liquid distribution 295, 297 modeling 298-300 RTRT (real-time release testing) 110, 112, 365 rufinamide 155-6 Rutgers University 2,85 Ryshkewitch-Duckworth equation 66 safety issues

reduced, with flow technology 128 and supercritical solvents 139 *see also* occupational health salbutamol sulfate 534 salicylic acid 200 sampling 110 of continuous fermentation processes 233 and model design 429-30 and regulatory environments 113, 114, 117 Sanofi 275 scale-down 26, 108 scale-independence 566-7 scale-out 26, 113, 127-8 scale-up 9, 26-7, 34 and bioprocessing 383, 397 and cell retention devices 254 for continuous fermentation 232 of microtechnology 161 and regulatory environments 108, 113 safety concerns 139 and stability considerations 114 scanning electron microscopy 214 science-based approach 108-9 Scottish Blood Transfusion Centre 248 screen printing 526 screw extruders 41, 338-41 twin-screw 345-7, 348 see also extruders screw feeding systems 314 Sculptify 545 seamless/straight-through processing 249 secondary manufacturing 4, 5, 6-7, 490 see also downstream manufacturing secondary metastable limit 176 secondary nucleation 174, 175, 177, 178-9 sectioning 324-5 seed crystals 174-5, 176 seeded segmented tubular flow reactor 172 seeding in fermentation 228 segmented (slug) flow reactors 171 semi-batch manufacturing 1 semi-continuous manufacturing 1, 2 semi-empirical kinetic models 209-10 sensitivity analysis 87-8, 502 sensor technology 375-6 sensors 24-6, 429-30, 436 in biopharmaceutical manufacture 250, 270-3 in closed-loop systems 435 in continuous tablet manufacture 88, 451 in control frameworks 438-9, 440 for crystallization 210, 211 FDA categorisation of 270 with hot melt extrusion 360

NIR see NIR sensors soft sensors 469-70 software sensors 308 see also PAT separation techniques 139-42 shape dynamics in granulators 295, 296 shaping calender 351 shear stresses in roller compaction 323-4 shear-mode inkjet technology 531 shearing forces in powder densification 315, 316 shutdown see startup and shutdown Siemens 439, 451 Simatic PCS7 (Siemens) 451 Simca P+ 438, 439 simulation 427, 437 for blenders 58, 59 and computerized drug design 514-15, 518, 519 for continuous roller compaction 332 for feeders 53 particle-scale 305-7 for tablet presses 63 see also process simulation simulation software 425, 426 gPROMS 436 Simulect 242 single cell proteins (SCP) 240-1, 242 single pass tangential flow filtration 260, 261 single-phase balances 16 single-use technology 266, 268-70, 371, 373 and cell separation 374 and facility design 379, 380-1 sensors 376 UV-C viral inactivation devices 375 see also disposable equipment Sintermask GmbH 545 SiPAT (PAT data management platform) 439, 440 site visits by regulators 111 slip region (compactors) 315-16 soft sensors 469-70 soft-gel manufacturing 554 software sensors 308 solid dosage pen 512 solid drug products formulations 511-13 manufacture of 33-94 process control in 81-93 processes in 38-44 see also tablets

solid feeding of extruders 341-2 solid freeform fabrication (SFF) 546 see also three-dimensional (3D) printing solid-liquid mixing 287, 288, 291, 293-4, 297 and modeling 304, 306-7 solids, modeling of 35 solubility 176, 214 poor 472-4, 535 solution NMR 215 solvent-free conditions 138-9 solvents and crystallization 182-3 supercritical 139 L-sorbose 192-3 space gained 391 see also footprint spectroscopy 207-9, 233-4 FTIR 144, 146, 147, 214 mass 150 mid-infrared (MIR) 234 near infrared see NIR (near-infrared) spectroscopy NMR 147, 149-50, 215 Raman 146, 148, 215, 234, 360-1 terahertz 215 UV-vis 147, 149 see also imaging; PAT spherical crystallization 195-6 spherical crystallization of benzoic acid 195-6 squeeze-mode inkjet technology 531 stability 114-15, 441-2 stacked systems 525 Standard Guide for Application on Continuous Processing in the Pharmaceutical Industry 371 startup and shutdown 453-4, 464-5 in biopharmaceutical manufacture 257 in continuous fermentation processes 236 reducing delays due to 250-1 in regulations 112, 116-17 state of control 112, 116, 117-22, 357 definition 124, 357 static mixers 171, 172 statistical modeling approaches 307 steady-state 48, 254, 273 absence of 453-4 STELARA 242 stents, drug-eluting 533 stick deposition moulding (SDM) 545 stirred tank 186

see also CSTRs strain development 228 strand cutting 352-3 Stratasys 543 Strathclyde University 2 strength of tablets 328, 330 struvite 191 substrate inhibition 230, 231, 232 supercritical fluids 176 supercritical solvents 139 superheated conditions 132-4 supersaturation 173-6, 177, 212-13 supervisory control 236, 237, 432 supply chain 8-9, 381, 393, 395 bullwhip effect 393-4 of the future 395-400 increased flexibility 370 for innovative products 520-1 surface forces in microenvironments 142 surface tension 531-2, 534, 535 for separation 142 suspension formulation 534-5 synTO (PAT data management platform) 439, 440 Syrris 3, 131, 161 system boundaries and early decision-making 488, 489 system dynamics 452-68 tablet press 38-9, 43 modeling 63-7, 78, 80 tablets 38

from films 474-7 formulation 511-13 and roller compaction 328, 330 manufacture 33-94, 381-95 critical control variables 86-7 injection molding in 35 integration of units 448-52 liquid dispensing technology in 552, 555-70, 574 novel tableting 471 processes control 81-93 processes in 38-44 roller compaction in 313, 330-2 shaping calenders in 351 next generation 396-9 printing technologies for 533, 546 properties 66 and ribbon quality 324

tadalafil, suspensions containing 538, 539 tanks in series (TIS) approach 298-300 technical feasibility 488, 490-2, 495 technical-economic evaluation methodology 486-503 techno-economic profile (TEP) 488 technology transfer 114 Tekturna 151 temperature see operating temperature TEP (techno-economic profile) 498 terahertz spectroscopy 215 ThalesNano 3, 131, 155 theophylline, printing of 533-4, 540 theoretical modeling coupled with experimental data 298, 300, 308 of twin-screw wet granulation process 284 see also modeling therapy, individualized 508-9 thermal gravimetric analysis 215 thermal inkjet (TIJ) printers 528, 529-30 for deposition of APIs 533 for drug delivery systems 534 ink for 531 thermal range with flow technology 128 thioquinazolinones 156 three-dimensional (3D) printing 514, 516, 518, 541 - 6and LDT compared 554 in pharmaceutical applications 525, 545-6 3D Systems Inc 545-6 L/D-threonine 197 time to market 391-2 total installed cost (TOT) 498 traceability 113, 116, 412, 415 tracers 20-1, 46, 415, 416 and blenders 420 in twin-screw granulator investigations 289 transient models 48 transient states 112, 116-17 transitions between unit operations 428, 430 transport model, one-dimensional 298 Tricor tablets 474 tubular blenders 415-21 tubular crystallizers 172, 185 tubular pipes as crystallizers 199 Tufts Centre for the Study of Drug Development 502 tumors 154, 509 see also cancer turbidostat operation 231, 254

turret 63 twin-screw extruders 345–7, 348 twin-screw granulation 283–308 granule size evolution in 294–7 model-based analysis 284, 298–302 twin-screw granulators (TSG) 284, 300 twin-screw loss in weight feeders 341, 342

UCB 3 ultrafiltration 260 ultrasound and crystallization 192, 193, 204 fouling reduction with 173 Umetrics, Simca P+ by 438 uncertainty analysis 502 Uniqsis 3, 131, 155, 161 unit operations 11-15, 39-44 in biopharmaceutical manufacturing 257 characterising, using actual process materials 412-21 in continuous manufacture of aliskiren hemifumarate 448-52 disposable 268-70 integration of 447-80 models 48-81, 422-7 reducing numbers of 471 roller compaction as 313, 330-2 United States 8 Food and Drug Administration see FDA University of Basel 2 University of Eastern Finland 3 University of Puerto Rico 2, 85 University of Southern California 542 Unscrambler X 438, 439 upstream processing 38 continuous 251-7, 376, 452 monitoring and control 272, 468 see also primary manufacturing US 8 FDA see FDA ustekinumab 242 UV sensors 451, 461-4 UV-C viral inactivation devices 375 UV-vis spectroscopy and flow technology 147, 149

Vapourtec 3, 155, 161 variables in model development 422–3, 434 VDI guidance 488 velocity gradient through ribbon thickness 321 verification 568 continuous process verification (CPV) 110, 117–18 continuous quality verification (CQV) 109 of control framework 438–40, 441 in model development 423 Vertex 3, 381, 486 virus inactivation/removal 248, 259, 375 viscosity of drug-containing liquids 534, 538–9 of inks 531, 532, 535 vitamin C (ascorbic acid) 192–3 volumetric efficiency 231 volumetric feeding 341, 343–4, 412–13 Weber number (We) 531–2

weighing platforms 413

weighting factors in decision-making 492, 498, 502
wet granulation 38, 39, 42
and design of systems 407
models for 71–5
scaling-up problems 26–7
twin-screw 283, 284–7
typical horizontal line 384–5
Wolfram Alpha Ltd 425
X-ray micro-computed tomography (X-ray

CT) 324–5 X-ray powder diffraction 214

yield 471, 472

Zoladex (AstraZeneca) 365