## Index

#### а

b

bar-code 237

Barium 48

abbreviated 510(k) 239, 240 Abbreviated New Drug Application (ANDA) 123-124, 182 acceptable daily intake (ADI) 148 active pharmaceutical ingredient (API) 49, 51, 89, 245, 246, 252 adverse event reporting 97, 223, 296 advertising and promotion 297 analytical methods 7, 77, 140, 152, 265 anatomical therapeutic chemical (ATC) classification system 50 Animal and Plant Health Inspection Service (APHIS) 39, 163 annual safety report 98 anti-HIV drug target 52 apixaban 81, 82 asthma 60 Asthma inhaler 20 audit findings and consequences 286 - 289automatic identification and data capture (AIDC) 237 AZT (zidovudine) 52

binding assays 58 bioavailability 73-74, 82, 113, 158, 179, 181, 182 biologics license application (BLA) 110, 135 **Biologics Price Competition and** Innovation Act (BPCI Act) 185 biopharmaceutical products 61, 63, 73, 78, 183 biosimilars EU regulations 184, 185 US regulations 185-189 biotech products/biopharmaceuticals 135

# breath test 20, 48

С

carcinogenicity tests 76, 143 case report forms (CRFs) 97, 117 Center for Biologics Research and Evaluation (CBER) 102 Center for Drug Evaluation and Research (CDER) 36, 102 Center for Veterinary Biologics (CVB) 39, 146, 158, 163 Center for Veterinary Medicine (CVM) 39, 146, 158 chemical substances 58 chemotherapy drugs 2

Medical Product Regulatory Affairs: Pharmaceuticals, Diagnostics, Medical Devices, Second Edition. John J. Tobin and Gary Walsh. © 2024 WILEY-VCH GmbH. Published 2024 by WILEY-VCH GmbH. cleaning validation 266-267 clinical evaluation plan 221, 222 clinical performance study plan (CPSP) 225, 226 clinical trial authorisation 95 clinical trials definition 85 design 88-90 good clinical practice 90 in EU adverse event reporting 97 amendments 97 annual safety report 98 authorisation 95 case report forms 97 end of trial 98 ICH efficacy guidelines 92 Independent Ethic Committees 96.97 informed consent 94 investigational medicinal product dossier 94 investigational medicinal products 95 investigator 94 Investigator's Brochure 93 monitoring of trials 98 protocol 94 sponsor 93 trial master file 98-100 phase I trials 86 phase II trials 86-87 phase III trials 87 process 87 in US clinical trial information 105 communication with FDA 104 federal regulations 100, 101 Institutional Review Board 103 - 104investigational drugs 105

Investigational New Drug Applications 100–103 **Clinical Trials Information System** (CTIS) 92 Code of Federal Regulations (CFR) 4, 15, 16, 101, 163, 247, 250, 263, 268 combination product 191–192 Committee for Advanced Therapies (CAT) 32, 129 Committee for Medicinal Products for Human Use (CHMP) 31, 128-130 Committee for Orphan Medicinal Products (COMP) 166 **Common European Submission** Portal (CESP) 133 common specifications (CS) 222, 235 common technical document (CTD) 109 clinical study reports 116-118 Drug Master File 116 EU 121-123 module structure 112 non-clinical study reports 116 quality 113-115 quality overall summary 120 region specific 120 structure and hierarchy 110, 111 US 123-127 competent authorities 30, 32-34, 95, 98, 112, 121, 128, 129, 132, 133, 138, 145, 146, 156, 178, 179, 231, 236, 238, 243, 276-278, 280, 288, 290, 292–295, 298, 299 competitive inhibitors 54, 71 Complete Response Letter 137 computer systems validation 262-265 computerised topography (CT) scans 48

confirmatory trials 88, 89, 174 conformity assessment procedures 232-233 EU (self) declaration of conformity 236 EU type-examination 235 EU verification 235-236 production quality assurance certification 235 quality management system 233-235 technical documentation 233-235 coordination group for mutual recognition and decentralized procedures-human (CMDh) 132 corrections/removals of devices 300 Council Directive 90/385/EEC 12 Council of the European Union 4 COVID-19 pandemic 2, 53 COVID vaccines 53, 174 crossover trial designs 89 Cryo-Electron Microscopy 58 current Good Manufacturing Practice (cGMP) 248 cytochrome P450 enzymes 73

# d

decentralised marketing authorisation process 133 decentralised or mutual recognition procedures 128, 132–133, 182 decision making process 130, 131, 300 de novo 510(k) notification procedure 240 design changes 218 design input 214–218 design qualification (DQ) 261 design review 214, 217, 218 design validation 216–218

design verification 216, 217 Device Master Record (DMR) 268 diagnostic drugs 20, 48 Diagnostics Directive 98/79/EC Two new Regulations 12 Directive 2001/82/EC 7-9, 11, 110 Directives/Regulations 5,6 DNA nucleotide thymidine 52 DNA sequence 52, 78 documentation 25-27, 80, 96, 99, 112, 134, 157, 224, 225, 229, 233-237, 249, 257-259, 278, 280, 281 drug approval 81, 85, 175, 180, 296 drug authorisation 8, 165–194 drug binding interactions 49 drug categorisation drug discovery 51 lead discovery, validation and optimization 57, 58 mode of action 48, 49 physical properties 48 prescription status 47, 48 target discovery and validation 52-57 therapeutic use 49, 50 drug delivery drug characteristics 60, 61 location 60 speed and duration of 62–63 stability 63 drug development 58–59, 63, 65, 77, 80, 93, 105, 140, 167 drug discovery 47–63, 77 Drug Master File 116, 124 drug products 2, 19, 20, 38, 47, 53, 62, 63, 65, 72, 73, 78, 87, 95, 113, 115, 116, 139, 146, 159, 165, 177, 179, 180, 182, 245-248, 259 drugs and medical devices 1, 15

308 Index

#### е

economic operators and devices 238 510(k) pre-market notification process 239 electronic common technical document (eCTD) 109, 111 electronic signatures 26, 121, 263 Eliquis 81 EMA's Paediatric committee (PDCO) 32.170 emergency use authorization (EUA) 174, 175 emgality 105, 106 end of trial 98 Enterprise Resource Planning (ERP) systems 263 enzyme supplements 20 essential documents 98, 99 eSubmission Gateway 121, 129 EUDAMED 30, 224, 225, 238, 278, 298, 299 EU (self) declaration of conformity 236 EudraVigilance database 97, 292, 293 EudraVigilance IT system 290–293 EU legislation 5, 7–12, 15, 29, 35, 78, 176 EU legislative process 4-6 EU Marketing Authorisation Application form 122 EU regulations 5, 7, 30, 110, 122, 177, 181-182, 184-185, 218, 231, 276 European Commission 4, 29–31, 132, 152, 157, 158, 167, 177, 178, 200, 224, 280, 290, 294

European Economic Area (EEA) agreement 130 European GMP regulations 247, 281 European legislation Regulation (EC) No 1924/2006 19 European Medicines Agency (EMA) 30-32, 170, 171, 276 European Norms (EN) 200 European Parliament 4, 5, 7, 31, 91 European Pharmacopoeia (Ph.Eur) 7, 39, 40, 77, 192 European Public Assessment Report (EPAR) 81, 106, 130, 137 European Union (EU) 1, 4, 30, 31, 39, 44, 92, 110, 132, 147, 149, 156, 170, 175, 208, 246, 247, 290 EU type-examination 235 EU verification 235, 236 Expression proteomics 56 Extensible Markup Language (XML) 112

# f

factorial trial design 90 FDA Adverse Event Reporting System (FAERS) 296 FDA MedWatch system 296 Federal Food, Drug, and Cosmetic Act (FDC Act) 12, 36, 210, 211, 246, 288 Field Safety Corrective Action (FSCA) 298, 299 Food and Drug Administration (FDA) 12, 35, 36, 39, 105, 146, 278 Food Safety and Inspection Service (FSIS) 159

# g

Generally Recognised as Safe and Effective (GRASE) 193 generic drugs definition 181

**EU** Regulations 181, 182 US Regulations 182 genetic engineering 48, 135, 183 genome 55, 56 genome sequencing 56 Good Automated Manufacturing Practice (GAMP) 263 good clinical practice (GCP) 25, 90, 91, 141-146, 222 good manufacturing practice (GMP) 95 essential requirements complaints 259 documentation 257, 258 emergency un-blinding 259 personal hygiene 248–249 premises and equipment 249-257 production 257-258 quality assurance system 248. 254 quality control 258, 259 recall product 259 self-inspection 259, 260 work contracted out 259 regulations and guidance 245-247, 252 requirements 268, 272 validation cleaning 266, 267 computer systems 262–265 facilities and equipment validation 261 methods 265-266 process capability 261, 262 process validation 262 sterilisation procedures 267, 268 typical system 260, 261 water purification systems 268 good pharmacovigilance practice (GVP) 290, 291

guidance documents 7, 29, 30, 36, 41, 42, 44, 69, 90, 112, 211, 281, 291

### h

HAZOP analysis 262 health foods 19 Health Level Seven Individual Case Safety Reporting system (HL<sub>7</sub>ICSR) 300 heating, ventilation and air conditioning (HVAC) systems 249 hepatitis B 53 high-efficiency particulate air (HEPA) filters 255 homeopathic medicines 192 homeopathic remedies 19 hormone replacement therapy 48 human factor Xa 81, 82 Human Immunodeficiency Virus (HIV) 52 human medicines 8, 9, 33, 34, 47, 139, 140, 156, 157, 181, 190, 191, 289, 290, 294, 296 human prescription drugs 48 Humanitarian Device Exemption (HDE) application 243 humanitarian use device (HUD) 243

# i

ICH Q5 guidelines 78 Independent Ethic Committees 96 informed consent 94, 96, 145, 223, 225, 227 inspection audit findings and consequences 286–289 techniques 280–286 installation qualification (IQ) 27, 261 Institutional Review Board (IRB) 103–104, 145, 227 International Electrotechnical Commission (IEC) 200 International Harmonisation Bodies 40-41 International Medical Device Regulators forum (IMDRF) 43, 44, 280 International Standards Organisation (ISO) 200 **Investigational Medicinal Product** Dossier (IMPD) 94 investigational medicinal products 85, 91, 93-95, 98, 246, 293 Investigational New Drug Applications (INDs) 100–103, 174 investigator 89, 93-98, 101, 104, 124, 145, 147, 223, 229 Investigator's Brochure (IB) 93, 223 in vitro models 73 in vitro tests 75, 76 in vivo animal studies 73 in vivo bioavailability studies 74

# j

Joint Expert Committee on Food Additives (JECFA) 148 judicial branch function 4

# l

labelling requirements 124, 236–238, 241, 243 licensing requirements, additional 279

#### m

magnetic resonance imaging (MRI) 48 manufacturing authorisation of medicinal products in the EU

documented information 276 registration of economic operators for medical devices 278 wholesale distribution of medicinal products 276-277 marketing authorization 156 common technical document clinical study report 116-118 Drug Master File 116 EU 121-123 module structure 112 non-clinical study report 116 quality 113-115 quality overall summary 120 region specific 120 structure and hierarchy 110, 111 US 123-127 submission and review process, in EU decentralised procedure 132, 133 decision making process 130 - 132mutual recognition procedure 134 national authorisations 132 plasma master files and vaccine antigen master files 134 scientific evaluation process 129, 130 union authorisation 128–129 submission and review process, in US 134–137 market vigilance 23, 24, 34, 275, 289-303 market vigilance & oversight of drugs EudraVigilance IT system 290 market vigilance in the EU 298 periodic reports 296–297

pharmacovigilance and marketing authorization holders 293-294 pharmacovigilance and reporting in US 295-296 pharmacovigilance in EU 289 - 290pharmacovigilance inspections and audits 294-295 Pharmacovigilance Risk Assessment Committee (PRAC) 290-293 renewal of marketing authorisations 295 mass spectrometry (MS) 56 Master Production and Control Record 257, 268 maximum residue limits (MRLs) 29, 139, 147-149, 154 Measles 2 medical conditions 19, 52, 53 Medical Device Coordination Group (MDCG) 30, 201, 231 medical device reporting 299-300 Medical Device Single Audit Program (MDSAP) 44, 280 medical device vigilance in the US 299 medical devices development of drugs and devices design & development planning 214 design changes 218 design controls 213-214 design input 214-216 design output 216 design review 217 design validation 216-217 design verification 216-217 risk analysis 218 in EU

conformity assessment procedures 232-236 economic operators and devices 238 labelling requirements 236–238 Notified Bodies 230–232 production quality assurance certification 235 requirements versus risk 244 technical documentation 236. 237 in Europe clinical evaluation 221, 222 clinical investigations 222-225 performance evaluation of IVDs 225 performance studies of IVDs 225, 226 regulatory strategy, EU classification 201-210 MDR vs. IVDR 196–199 standards 200-201 regulatory strategy, US 210-212 in US abbreviated 510(k) 239 abbreviated requirement investigations 227 de novo 510(k) notification procedure 240 exempted investigations 227 510(k) pre-market notification process 239 humanitarian use device 243 IDE investigations 227–231 labelling devices 229, 243 notification and review procedures 240 PMA-approved device 241–243 pre-market approval 240, 241 requirements versus risk 244 special 510(k) procedure 239 - 240

medical devices (*contd*.) traditional 510(k) notifications 239 Medical Devices Directive 93/42/EEC 12 Member States concerned 95, 97 methods validation 113, 265–266 Minor Use and Minor Species (MUMS) amendments 176 monitoring of trials 98 Mumps 2 mutual recognition procedure 128, 132, 134, 182

## n

National Authorisations 127, 132. 178 National Committee for Clinical Laboratory Standards (NCCLS) 200 national legislation 5, 6, 133 New Animal Drug Application (NADA) 158–162, 182 New Drug Application (NDA) 110, 123, 135, 136, 193 nexviazyme (avalglucosidase alfa-ngpt) 137 NMR spectroscopy 58 non-clinical study bioavailability and bioequivalence 73,74 carcinogenicity studies 76 chemistry, manufacturing and control development (CMC) 77 clinical trial and marketing authorisation phases 66 genotoxicity studies 75, 76 good laboratory practice (GLP) 78-80

ICH harmonised safety and quality guidelines 67 pharmacological studies 69–71 pre-clinical phase of drug development 65 quality by design (QbD) 77 reproductive toxicology studies 76.77 safety and preliminary efficacy indications 65 stability studies 78 toxicity studies 74, 75 non-polar drug 60, 72 notification and review procedures 240 Notified Bodies 31, 34-35, 44, 80, 195, 199, 201, 224, 230-233, 235–238, 240, 243, 278, 280, 298

# 0

Office of Orphan Products Development (OOPD) 166 Omeprazole 54, 55 open-label trial 89 operational qualification (OQ) 27, 261 Organisation for Economic Cooperation and Development (OECD) 78 orphan drugs 12, 13, 165–168, 190, 193, 243 over-the-counter (OTC) 40, 47, 48, 191, 193, 259 OvuGel 157, 158

# р

paediatric investigation plans (PIPs) 92, 170 paediatric legislation 170 patented medicines 59 peptic ulcers 53 performance qualification (PO) 27, 261 Periodic Adverse Drug Experience Reports (PADERs) 296 periodic reports 243, 296–297 periodic safety update reports (PSURs) 236, 294 personal hygiene 248 pest control programme 251 Pharmaceutical Inspection Cooperation Scheme (PICS) 44, 45, 276, 281 pharmaceutical manufacture, in Europe 247 pharmacological studies pharmacodynamic studies 70, 71 pharmacokinetic/toxicokinetic studies 72, 73 pharmacovigilance and marketing authorisation holders 293, 294 pharmacovigilance & reporting, in US 295, 296 pharmacovigilance, defined 289 pharmacovigilance inspections and audits 294, 295 Pharmacovigilance Risk Assessment Committee (PRAC) 32, 128, 290 - 293pharmacovigilance systems, in Europe 289 photostability 78 Plan-Do-Check-Act (PDCA) 201 plasma master files & vaccine antigen master files 134 Portable Document Format (PDF) files 112 post-authorisation safety studies (PASS) 290, 293 post-market clinical follow-up (PMCF) data 221, 303

post-market surveillance 222, 224, 236, 278, 298, 299, 302-303 pre-market approval process (PMA) 240, 241 prescription-only medicines (POM) 47 process validation 113, 115, 262, 273 processing changes in EU extension applications 178 major variation (type II) 178, 179 minor variation (type IA/IB) 179 in US major changes 180 manufacturing change supplements 180 minor changes 181 moderate changes 180, 181 product development 23, 175, 212 production quality assurance certification 235 product manufacture 23, 24, 262 product safety 1, 287 proton pump inhibitors 54, 55 Public Health Services (PHS) Act 15

### q

quality assurance system 25, 248, 254
quality by design (QbD) 77
quality control 59, 93, 214, 249, 251, 257–259, 276, 281
quality management system 201, 202, 213, 233–235, 268, 273, 294, 298
quality management system regulation (QMSR) 213, 268
Quality System Inspection Technique (QSIT) 286

Quality System Regulation (QSR) 211, 213, 268, 270, 280, 287 quantitative proteomics approach 57

## r

radio frequency identification (RFID) 237 reference drug exclusivity 189–191 registration of economic operators 238.278 registration of manufacturers 275, 303 registration of producers of drugs and devices in the US 278, 279 Regulation (EC) No. 726/2004 7, 9, 170, 176, 290 Regulation (EU) 2019/6 7, 8, 145, 156, 177, 181, 246, 275, 290 Regulations EU Legislation 7–12 EU Legislative Process 4-6 guidance documents 7 legal texts 6 National Legislative Process 3.4 pharmacopoeial publications 7 principles and concepts 1 product safety 1 scope of legislation 15-20 US Legislation 12-15 Regulatory strategy EMA 30-32 European Commission 29, 30 Food and Drug Administration (FDA) 35-39 International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) 41-43 International Harmonisation Bodies 40-41

International Medical Device Regulators forum (IMDRF) 43,44 market vigilance 24 national competent authorities 32 - 34notified bodies 34, 35 Pharmaceutical Inspection Cooperation Scheme (PICS) 44,45 pharmacopoeia authorities 39,40 product development 23 product manufacture 23 quality assurance systems 25 quality assurance systems corrective and preventative action 27 documentation 25, 26 facilities and equipment 26, 27 personnel 25 US Department of Agriculture 39 validation 27, 28 veterinary medicinal products (VICH) 43 World Health Organisation (WHO) 45 relative polarity 60 renewal of marketing authorisations 295 retrospective validation 262 rheumatoid arthritis (RA) 53 risk analysis 215, 218, 230, 240, 260, 263, 264, 268, 269 **Risk Evaluation and Mitigation** Strategy (REMS system) 296 Rubella 2 **Rules Governing Medicinal Products** 30, 92, 110, 149, 156, 246, 247

### S

scientific evaluation process 129, 130

single registration number (SRN) 238, 278 special 510(k) procedure 239, 240 special drug applications accelerated access to new drug therapies emergency use authorization 174.175 EMA accelerated review and conditional marketing routes 170, 171 EU compassionate use 171 expanded access 174, 175 expedited pathways, in US 171-174 orphan drugs 165-168 paediatric applications 167–170 statistical power 89 Stents 20 sterilisation procedures 242, 267, 268 structural proteomics 56, 58 submission and review process in EU decentralised procedure 132, 133 decision making process 130 - 132mutual recognition procedure 134 national authorisations 132 plasma master files & vaccine antigen master files 134 scientific evaluation process 129, 130 union authorisation 128, 129 in US 134–137 summary basis of approval (SBC) document 137 summary of product characteristics (SPC) 94, 122, 123, 129, 134, 156, 178

Suspected Unexpected Serious Adverse Reactions (SUSAR's) 97, 293

## t

target validation 57 technical documentation 233–237, 278 therapeutic categories 49, 50 traditional fine-chemical-based pharmaceutical products *versus* biopharmaceuticals 184 traditional 510(k) notifications 239 traditional herbal medicines 19, 192, 193 Trial Master File 98, 99 tumour necrosis factor-alpha (TNF-α) 53, 57

### u

ultrasound 20, 227 union authorisations 127–129, 132, 156, 179 union marketing authorisation process 130, 131 unique device identifier (UDI) 199, 237 United States Code (USC) 12 United States Pharmacopoeia (USP) 7, 256, 257 US Legislation 12–15

### V

vaccination 2, 53, 156 Vaccine Adverse Event Reporting System (VAERS) 296 vaccine technology 53 verquvo (vericiguat) 132 veterinary biologics licence applications 158 Veterinary Feed Directive (VFD) drug 159

veterinary good pharmacovigilance practice (VGVP) guideline 290 veterinary medicinal products (VICH) 7, 29, 30, 43, 139, 146, 149, 156, 164, 177, 178, 246, 275 veterinary medicines clinical trials in EU 145-146 in US 146, 147 development process clinical trials 141 **Good Clinical Practices** 141-145 pre-clinical studies 140, 141 in EU establishment of MRLs 149-152 marketing authorisations 156 MRL applications 150 - 152MRL dossier 153 technical dossier 156, 157

maximum residue limits 147–149 in US New Animal Drug Application 158–162 veterinary biological products 163–164 Virus-Serum-Toxin Act 15, 163

#### W

water purification system 256, 268 well-established medical use products 191 wholesale distribution of medicinal products 276, 277 work contracted out 259 Working Groups (WG) 30, 41, 44 World Health Organisation (UN WHO) 41, 45, 50, 148, 171

# X

X-ray crystallography 58 X-ray equipment 20, 36