

Table of Contents

Section I: General Information

Chapter 1: Healthcare Landscape and Drug Development.....	1
Ruchi Gupta, MS	
Chapter 2: The Drug Development Continuum, Preclinical to Market Access.....	5
Darlene Rosario, MBA, RAC-US; Pragnesh Donga, MPharm, MBA, RAC-Drugs; Kathrin Schalper, PhD, RAC-US, RAC-EU, RAC-Canada, RAC-Devices	
Chapter 3: International Harmonization via ICH, WHO, and other Global Initiatives.....	19
Anu Gaur, PhD, MBA, MSRA, RAC-US, RAC-Global	

Section II: Nonclinical Studies

Chapter 4: Principles of Good Laboratory Practice and Nonclinical Development.....	29
Kurt Stahl, BS; Jennifer G. Brown, PhD, RAC-US	
Chapter 5: Safety Pharmacology Studies	37
Charlene F. Barroga PhD, DABT; Brian M. Roche, PhD, DSP, DABT; Simon Authier, DVM, PhD, MSc, MBA	
Chapter 6: Pharmacokinetic and Toxicokinetic Studies	53
Tyler Vandivort, PhD, RAC-Drugs, DABT	
Chapter 7: Genotoxicity Studies	63
Tyler Vandivort, PhD, RAC-Drugs, DABT	
Chapter 8: Carcinogenicity Studies	73
Tyler Vandivort, PhD, RAC-Drugs, DABT	
Chapter 9: Developmental and Reproductive Toxicity Assessments	85
Charlene F. Barroga, PhD, DABT; Alan M. Hoberman, PhD, DABT, ATS	
Chapter 10: Regulatory Environmental Risk Assessment of Human Pharmaceuticals.....	99
Margaret L. Fleming, PhD; Jennifer K. Saxe, PhD	

Section III: Chemistry, Manufacturing, and Controls

Chapter 11: The Global Regulatory Process for the Registration of Active Substances	111
Darlene Rosario, MBA, RAC-US; Yuwei Zhang, MD, PhD, MPH, MBA; Robert Falcone, PhD, FRAPS, FTOPRA	
Chapter 12: Coordinating Drug Supply for Clinical and Nonclinical Development	125
Ajay Babu Pazhayattil, DBA, MPharm; Payal Shah, MS, RAC-US	
Chapter 13: Pharmaceutical Development Studies and Manufacturing Experience	141
Komalkumar Patel, MS; Nikolaos Zacharias, MSc; Kingman Ng, PhD; Beat U. Steffen, MSc, MBA, FRAPS; Nicole Beard, PhD, MSc	
Chapter 14: Analytical Development – Testing and Stability	159
Blaine Van Leuven, MS, RAC-Global; Nidhi Kotecha, MPharm, PhD, RAC-Drugs	

Section IV: Clinical Trials

Chapter 15: Conducting Clinical Trials: Drug Application Types, Data Requirements and Obtaining Marketing Approval	167
Sharry Arora, MPharm, RAC-Drugs; Viktória Pásztor, MS; Bayan A. Arar, BPharm, RPh	
Chapter 16: Phases of Development (1,2,3,4)	177
Rowena Cook, MS, RAC-Global; Amanda McEwen, MRes; Shuli Cui, MS, RAC-US; Stefanie Fasshauer, MBA	
Chapter 17: Enhancing Diversity in Clinical Trials	215
Monique Carter, MS, RAC, FRAPS; Zaida Recinos-Vasquez, MSPS, MSRAQA; Leonor Pessanha Saldanha, PhD, MSc	
Chapter 18: Health Authority Interactions	231
Chauneen Leah Wood, MS, RAC-US; Azzurra Ravizza, MS	
Chapter 19: Pediatrics	255
Linda McBride, RPh, RAC-US	
Chapter 20: Regional-Specific Studies	271
Mantej (Nimi) Chhina, PhD, JD, MSc; Marjorie Zettler, PhD, MPH	

Section V: Marketing Authorization

Chapter 21: Framework for Benefit-Risk Assessment	283
Cristina Damatarca, MD, PgDip	
Chapter 22: eCTD and Digital Applications	295
Amrita Ghosh, RAC-US; Danini Marin, MSc; Katelyn Mulligan, MS	
Chapter 23: Expedited Approval Pathways	305
Yingying Liu, MS; Kathrin Schalper, PhD, RAC-CAN, RAC-Devices, RAC-EU, RAC-US; Ching Li, PhD; Christinne V. Villanueva, MS; Hongbo Pan, MBA; Grzegorz Podrygajlo, PhD	
Chapter 24: Dossier Requirements	353
Jesshanie Tabaniag, RPh; Kholoud Mamdouh Abdelfattah, MSc; Stefanie Fasshauer, MBA; Danini Marin, MSc; and Prashant Bhatia, MSc	

Section VI: Postmarketing Authorization

Chapter 25: Postauthorization Commitments	395
Linda McBride, RPh, RAC-US	
Chapter 26: Transfers and Renewals	405
Linda McBride, RPh, RAC-US	
Chapter 27: Product Extensions, Variations, and Supplements	425
Linda McBride, RPh, RAC-US	
Chapter 28: Compliance	447
Siegfried Schmitt, PhD; Barbara Rusin, MS; Anne Marie Woodland, MS, RAC-EU, RAC-US	
Chapter 29: Recalls	463
Siegfried Schmitt, PhD	

Chapter 30: Postmarket Surveillance.....	467
Linda McBride, RPh, RAC-US	
Chapter 31: Advertising and Promotion	481
Timothy A. Candy, PharmD, MS, BCPS	
Chapter 32: Market Access: Reimbursement and Pricing.....	499
Anu Gaur, PhD, MBA, MSRA, RAC-US, RAC-Global; Parvarsha Nafees, PharmD	

Appendices

Regulations and Guidelines Across Chapters – Comparative Matrix	543
Abbreviations and Acronyms	577
Glossary of Terms.....	605
Index.....	627

Case Studies

Case Study 5-1	47
Case Study 5-2	47
Case Study 6-1	59
Case Study 9-1	95
Case Study 16-1	203
Case Study 16-2	204
Case Study 17-1	225
Case Study 20-1	271
Case Study 20-2	272
Case Study 20-3	275
Case Study 20-4	276
Case Study 20-5	277
Case Study 20-6	278
Case Study 23-1	346
Case Study 31-1	492

Figures

Figure 2-1. The Medicinal Product Development Continuum.....	5
Figure 2-2. Traditional de novo product development process vs. product repurposing	7
Figure 2-3. Phase Transition Duration from Phase 1 through NDA/BLA Authorization	8
Figure 2-4. Phases of Clinical Research	11
Figure 2-5. CTD Triangle	14
Figure 2-6. Communicating value to healthcare stakeholders.....	15
Figure 2-7. Relationship between Pricing, Reimbursement, and Market Access.....	16
Figure 3-1. ICH Process of Harmonization	22
Figure 4-1. Final Study Report Items	32
Figure 4-2. Nonclinical Safety Evaluation Goals	33
Figure 5-1. Continuum of Safety Pharmacology Assessments from Acute to Chronic Toxicity Studies	45
Figure 6-1. Drug Exposure Parameters Derived from PK Data.....	54
Figure 8-1. Genotoxic versus Nongenotoxic Dose-Response Curves.....	74

Figure 8-2. ICH S1B(R1) Schema for Determining the Added Value of a 2-Year Carcinogenicity Study.....	80
Figure 9-1. Stages of the Reproduction and Development Cycle (A to F) as described in ICH S5(R3)	85
Figure 9-2. Scheme for Fertility and Early Embryonic Development Studies, Embryo-fetal Development Studies, and Combined Studies	87
Figure 9-3. Scheme for Pre- and Postnatal Development Studies and Enhanced Studies	87
Figure 9-4. Scheme for Enhanced Pre- and Postnatal Development Studies in Rabbit for Vaccines.....	94
Figure 9-5. Scheme to Determine if Standard Models for Hazard Assessment of Developmental Toxicity can be used for Molecules that produce Anti-Drug Antibodies (ADA).....	95
Figure 10-1. FDA Categorical Exclusion for Drug Approval – Small Molecules	101
Figure 10-2. FDA Studies Required for Drug Approval.....	102
Figure 10-3. EU ERA Process for Drug Approval.....	103
Figure 10-4. FDA Categorical Exclusion for Drug Approval – Biologics.....	106
Figure 11-1. Top 10 Pharmaceutical Markets	111
Figure 11-2. Percent of Global Pharmaceutical Sales by Economic Blocks	111
Figure 11-3. Brazil API Background Regulations.....	119
Figure 11-4. China API Registration Procedure	120
Figure 11-5. Japan API Process Review	121
Figure 12-1. Clinical Supply	129
Figure 12-2. Routine Challenges in Clinical Supply.....	132
Figure 12-3. US Marketed Products API Supply.....	133
Figure 12-4. Cold Chain Lifecycle.....	133
Figure 12-5. An Example Sample Kit Label and Bottle Label	135
Figure 13-1. Product requirements	142
Figure 13-2. Factors impacting product requirements – Ishikawa (fishbone) diagram.....	142
Figure 13-3. QbD Elements Flow Chart.....	143
Figure 13-4. Possible Leachables from a Plastic Bottle	150
Figure 14-1. Analytical Method Life Cycle and Links to Product Development	160
Figure 16-1. Clinical Trial Lifecycle.....	179
Figure 16-2. Russian Approval Process	191
Figure 16-3. Primary Hyperoxaluria Integrated Clinical/Regulatory Development Plan: Phase 1/2 to Start of Phase 2/3.....	204
Figure 16-4. OPTIC Study Design	208
Figure 17-1. Contributing Factors of Clinical Trial Underrepresentation	215
Figure 17-2. Demographic Diversity of Global Clinical Trials Participation for New Drugs Approved by the FDA	216
Figure 17-3a. Distribution of Clinical Trial Participants – US Compared to the Rest of World	217
Figure 17-3b. Global Distribution of Clinical Trial Participants by Country vs US	217
Figure 17-4. Clinical Trial Sex, Race, Age, and Ethnicity Distribution in the US	218
Figure 17-5. Percentage of Trials with Participant Levels Above Census	218
Figure 17-6. Representation in Pfizer Trials vs. US Census Level.....	219
Figure 17-7. OMB Minimum of Race and Ethnicity Categories	221
Figure 17-8. Intrinsic and Extrinsic Ethnic Factors	224
Figure 18-1. CHMP SA Process.....	238
Figure 18-2. Parallel Scientific Advice (FDA-EMA).....	240
Figure 18-3. NICE Standard Scientific Advice Process	247
Figure 18-4. NICE MHRA Scientific Advice Process	248
Figure 18-5. NICE CADTH Scientific Advice Process	248
Figure 18-6. NICE HTA-EMA Scientific Advice process	249
Figure 20-1. Requests for Local Clinical Data and Different Therapeutic Areas	272
Figure 20-2. Representative Schematic of Potential Approaches to Conducting Regional-Specific Studies	273
Figure 20-3. Clinical Development Strategies Employing Local vs. MRCT Strategies (Adapted from ICH E17).....	274
Figure 21-1. Continuous Benefit-Risk Assessment for Defining and Maintaining the Safety Profile of Drugs Through the Development Lifecycle.....	284
Figure 21-2. BRAT Six-Step Process.....	288
Figure 21-3. EMA Eight-Step PrOACT-URL.....	289
Figure 21-4. FDA's Benefit-Risk Framework for New Drug Review.....	290
Figure 22-1. History of Regulatory Submission Tools	295

Figure 23-1. Outcome of PRIME Eligibility Requests by Therapeutic Area	311
Figure 23-2. Expedited Pathways in Different Development Stages in China.....	321
Figure 23-3. Standard Marketing Authorization Application Procedures and Expedited Pathways.....	321
Figure 23-4. General Timeframe of SAKIGAKE	327
Figure 23-5. SAKIGAKE Designation Procedure.....	328
Figure 23-6. Standard Review, Conditional Early Pathway, Priority Review and Orphan Drugs in Japan	328
Figure 23-7. Conditional Early Pathway Procedures in Japan.....	329
Figure 24-1. ASEAN CTD	367
Figure 28-1. How Good Practices Align with the Product Lifecycle.....	447
Figure 28-2. China Drug Regulatory Legislative System.....	455
Figure 28-3. China Drug Regulatory Landscape	456
Figure 29-1. Recall of Clinical Trial Supplies Process Flow.....	465
Figure 31-1. Example of a Reminder Ad	484
Figure 31-2. Ad for a Boxed Warning Drug	484
Figure 31-3. General Timeline View of Pre-submission Requirements for Subpart E/H Products.....	485
Figure 31-4. Issuance of Enforcement Action Letters Over Time (1997–2022).....	489
Figure 32-1. Factors Influencing Medicinal Product Pricing	500
Figure 32-2. Timeline of US “HTA Like” Bodies.....	503
Figure 32-3. Overview of the Canada Public System Reimbursement Decision Pathway.....	506
Figure 32-4. Process Map for France.....	509
Figure 32-5. Process Map for Germany	510
Figure 32-6. Mean Length of Time From EMA Authorisation to HTA Decision for Oncology Products	511
Figure 32-7. Overview of ERP Across Europe (2013).....	512
Figure 32-8. Types of Cost Containment Policies Adopted by Member States	513
Figure 32-9. Process Map for England.....	514
Figure 32-10. Process Map for Scotland	515
Figure 32-11. German Pricing for Medicinal Products Under AMNOG	520
Figure 32-12. Map of Australian Government HTA Processes for Market Entry and Reimbursement Processes.....	527
Figure 32-13. Framework for Pricing Drugs and Devices in Japan.....	529
Figure 32-14. Flow Diagram of HTA in South Korea.....	530
Figure 32-15. Historical MaHTAS Milestones	530

Tables

Table 2-1. Pharmacology Studies – Overview.....	10
Table 2-2. Toxicology Studies – Overview	10
Table 3-1. Current Members and Observers of the ICH Association.....	21
Table 3-2. Members and Observers of the International Pharmaceutical Regulators Programme.....	24
Table 5-1. Cardiac Ion Channels Assessed by In Vitro Assay in Chinese Hamster Ovary (CHO) Cells and Human Embryonic Kidney 293 (HEK293) Cells.....	38
Table 5-2. Cardiovascular (CV) Study Designs and Endpoints.....	39
Table 5-3. Stand-Alone Cardiovascular or Combined Cardio-Respiratory Telemetry Studies – Latin Square (4x4) Study Design	41
Table 5-4. Integrated Cardiovascular or Cardio-Respiratory Telemetry Endpoints in a Non-rodent, Repeat-Dose, Toxicology Study Design.....	41
Table 5-5. Stand-Alone Rodent Respiratory or CNS (FOB or modified Irwin) Parallel Study Design	42
Table 5-6. Combined Respiratory and CNS (FOB or modified Irwin) Study in Rodent Repeat Dose Toxicology Study Design.....	42
Table 5-7. Safety Pharmacology Strategies for Pharmaceuticals and Biopharmaceuticals	44
Table 6-1. Parameters for Comparing Drug Exposure Across Studies.....	55
Table 6-2. Global Implementation of Major ICH Guidance Relevant to Pharmacokinetic and Toxicokinetic Studies	56
Table 6-3. Preclinical Case Study: ZILRETTA®.....	59
Table 7-1. ICH S2(R1) Recommendations for In Vitro Genotoxicity Testing	66
Table 7-2. ICH S2(R1) Recommendations for In Vivo Genotoxicity Testing.....	68
Table 7-3. Overview of Common In Vitro and In Vivo Genotoxicity Testing Assays.....	70
Table 8-1. Global Implementation of Major ICH Guidance on Carcinogenicity.....	75
Table 8-2: Key Weight of Evidence Factors for Integrated Assessments of Carcinogenic Potential.....	81

Table 9-1. DART Strategy for Pharmaceuticals and Biologics Depending on Relevant Species.....	89
Table 9-2. Embryo-fetal Development (EFD) Study Design Parameters for Rodent, Rabbit and Non-human Primate Species	89
Table 9-3. Considerations for Design of a Pre- and Post-Natal Development (PPND) Toxicity Study in Rats.....	91
Table 9-4. Considerations for the Design of an Enhanced Pre- and Post-Natal Development Toxicity Study in Nonhuman Primates	92
Table 9-5. Potential Species for DART Studies (relative percentages used from a 10-year period at a contract testing facility).....	93
Table 10-1. Studies Required During the EU Environmental Risk Assessment Process	104
Table 11-1. Global Regulatory Active Substances Filing Requirements	112
Table 11-2. Master File Classifications	116
Table 11-3. Type of Fee (Active Substance Manufacturers)	118
Table 11-4. Type of Fee (Active Substance Importers and Distributors).....	118
Table 12-1: Standards and Guideline Types That Apply in Clinical Supply	126
Table 12-2: Standards and Guideline Types That Apply in Non-Clinical Supply.....	126
Table 12-3. Components of Clinical Supply Chain Strategy	127
Table 12-4. Clinical Development Stages	127
Table 12-5. FDA Regulations Relating to GCP and Clinical Trials	130
Table 12-6. Comparing Clinical and Non-Clinical Material Supply	131
Table 12-7. Factors to Consider When Selecting Excipients	133
Table 13-1. QbD regulatory guidance comparison in major markets.....	144
Table 13-2. Container Content/Volume Label Claim/Extractable Volume Test Regional Comparison	146
Table 13-3. Dosage Form Compatibility Cases.....	149
Table 13-4. Typical Packaging Suitability Considerations for Common Classes of Drug Products.....	149
Table 13-5. Modified FDA/CDER/CBER Risk-based Approach to Consideration of Leachables.....	150
Table 13-6. Dissolution Specification Setting Considerations	152
Table 13-7. Biopharmaceutics Classification System (BCS)	153
Table 13-8. Considerations for Specific Dosage Forms.....	153
Table 13-9. Applicability of Different Types of Waivers per Dosage Form.....	154
Table 13-10. Most Common Routes of Administration: Advantages and Disadvantages	155
Table 13-11. Comparison of Regulatory Guidance.....	157
Table 15-1. Key documents required for the clinical trial application submission US.....	169
Table 15-2. Changes to EU Legislation for the Conduct of Clinical Trials 2022 to 2025	170
Table 15-3. Key documents required for the initial clinical trial application submission in the EU.....	170
Table 15-4. Data requirement for clinical investigation stage in BRICS, APAC, and MENA countries.....	171
Table 15-5. Comparison of data requirements for marketing application stage per region for BRICS, APAC and MENA countries.....	171
Table 16-1. Phase I-IV Clinical/Regulatory Terminology.....	178
Table 16-2. APAC Countries and Respective Regulatory Authorities.....	192
Table 16-3. Middle East/North Africa Countries and Respective Regulatory Authorities.....	197
Table 16-4. Countries of Africa and Their Respective Regulatory Authorities	200
Table 16-5. Regulatory History of Iclusig®.....	205
Table 16-6. Clinical Studies Included in the Initial NDA	206
Table 16-7. PACE Study Patient Cohorts.....	207
Table 17-1. US Clinical Trial Participant Cross-Section Distribution by Sex, Race, and Age for Select Therapeutic Areas	218
Table 17-2. Percentage of Pfizer Inc. Studies with Participation at or Above US Census Levels Across Therapy Areas.....	220
Table 17-3. Pfizer Inc. Race and Ethnicity Diversity Plan Template	222
Table 17-4. Government of Canada Historical GBA Initiatives and Activity Timeline	224
Table 18-1. Formal Meetings Negotiated Under PDUFA (timelines).....	233
Table 18-2. Formal Meetings Negotiated Under BsUFA (timelines).....	234
Table 18-3 CADTH Scientific Advice at a Glance.....	236
Table 18-4. CADTH Scientific Advice Process	237
Table 18-5. Key Timelines for CADTH Scientific Advice Offerings.....	237
Table 18-6. Types of Questions for Scientific Advice.....	239
Table 18-7. Parallel Scientific Advice Timelines	240
Table 18-8. EU National Competent Authorities and Scientific Advice	241
Table 18-9. Simultaneous NCA Participating Countries	245
Table 18-10. NICE Advice Timelines.....	247
Table 18-11. PMDA Categories and Content of Consultations for New Medicinal Products.....	250

Table 19-1. Comparison of Pediatric Development Regulations.....	267
Table 20-1. Time to Regulatory Authority and Ethics Board Approvals in an MRCT	278
Table 20-2. Clinical Trial Applications in North America (Canada, Mexico, US)	279
Table 20-3. Clinical Trial Applications in Europe (EU, Switzerland, UK).....	279
Table 20-4. Clinical Trial Applications in BRICS Countries.....	280
Table 20-5. Clinical Trial Applications in South America (Argentina, Colombia, Chile, Peru).....	280
Table 20-6. Clinical Trial Applications in Select Asia-Pacific (APAC) Countries	281
Table 20-7. Clinical Trial Applications in Select Middle East/North Africa (MENA) Countries	281
Table 21-1. A Brief History of the Evolving BRA Initiatives, Methods, and Procedures	286
Table 21-2. UMBRA Steps and Process	291
Table 22-1. Advantages and Disadvantages of eCTD.....	296
Table 22-2. Example of Folder Names in eCTD	301
Table 22-3. Error Severity	301
Table 22-4. eCTD 4.0 Implementation Schedule as per ICH Guideline July 2022	302
Table 23-1. Overview of Expedited Approval Programs in the US.....	307
Table 23-2. Overview of Expedited Approval Pathways in Argentina	308
Table 23-3. Overview of Expedited Approval Pathways in Canada	309
Table 23-4. Overview of Expedited Approval Pathways in Mexico	310
Table 23-5. Comparison of Conditional Marketing Authorization and Marketing Authorization Under Exceptional Circumstances	312
Table 23-6. Overview of Accelerated Approval Pathways in EU, Switzerland, UK, and Turkey.....	317
Table 23-7. Overview of Expedited Approval Pathways in Brazil.....	319
Table 23-8. Summary of Expedited Approval Pathways in India.....	320
Table 23-9. Overview of Expedited Approval Pathways in China	322
Table 23-10. Overview of Expedited Approval Pathways in Australia.....	323
Table 23-11a. Overview of Expedited Approval Pathways in Japan: SAKIGAKE, Conditional Early Pathway and Priority Review	324
Table 23-11b. Overview of Expedited Approval Pathways in Japan – Orphan Drug Review, Recruitment for Unapproved Drugs and Indications, and Emergency Approval.....	325
Table 23-12. Overview of Expedited Approval Pathways in South Korea	329
Table 23-13. Overview of Expedited Approval Pathways in New Zealand.....	330
Table 23-14. Overview of Expedited Approval Pathways in Taiwan.....	332
Table 23-15. Overview of ASEAN Joint Assessment Procedure	334
Table 23-16. Overview of Approval Pathways in Brunei.....	335
Table 23-17. Overview of Expedited Pathways in Cambodia	336
Table 23-18. Overview of Expedited Regulatory Pathways in Indonesia.....	336
Table 23-19. Orphan Drug Designation in Malaysia.....	338
Table 23-20. Expedited Regulatory Pathways in Malaysia.....	338
Table 23-21. Overview of the Expedited Regulatory Pathways in Philippines	340
Table 23-22. Overview of Expedited Pathways in Singapore.....	341
Table 23-23. Eligible Criteria for a Drug to be Considered on the List of Rare Drugs in Vietnam	343
Table 23-24. Overview of Expedited Approval Pathways in Saudi Arabia	345
Table 24-1. Country Requirements	354
Table 24-2. Regulatory Authority and Country Legal Framework.....	360
Table 24-3. Content and Format Requirements.....	370
Table 24-4. Country Requirements	375
Table 24-5. Dossier Requirement for Collaborative and Reliance Procedures, ACCESS Consortium	379
Table 24-6. Country-Specific Dossier Requirements Related to Selected Described Pathways.....	380
Table 24-7. Combination Product Definitions	387
Table 24-8. Combination Product Definitions in Additional Regions.....	390
Table 25-1. Regulatory Framework for Postauthorization Studies in Major America Regions.....	396
Table 25-2. Regulations and Guidance Documents	402
Table 26-1. Postapproval Regulations in Each MENA Country	420
Table 27-1. Americas: Comparison of Regulations Across Jurisdictions	429
Table 27-2. NMRAs and Guidelines for Pharmaceuticals in African Countries	442
Table 28-1. Regulations and Guidance for GPvP Management and Reporting	448
Table 28-2. PRAC Scope of Recommendations	453

Table 28-3: EU Mutual Recognition Agreements	453
Table 30-1. MAH Reporting Requirements	470
Table 31-1. Common Scenarios Considered False, Lacking in Fair Balance, or Otherwise Misleading by FDA	483
Table 32-1. Drugs Eligible for CADTH's Drug Review Processes.....	504
Table 32-2. Summary of CADTH's Elements and Recommendation Categories	505
Table 32-3. Latin American Country-Specific HTA Overview.....	505
Table 32-4. Summary of Time From EMA Authorisation to HTA Decision and Outcome.....	507
Table 32-5. HTA and Associated Organizations in Selected EU Member States and the UK.....	511
Table 32-6. Overview of Reference Pricing and Country Baskets in Europe.....	512
Table 32-7. Comparison of HTA in Germany, France, UK, Italy, and Spain	517
Table 32-8. Summary of HTA Status in Select Asian Countries	518
Table 32-9. Regulatory Authorities of BRIC region and their Product Categories for Controlled Pricing	523
Table 32-10. Types of Drug Categories followed in Brazil for price fixation	524
Table 32-11. Types of Regulatory Programs and Reimbursement Methods in Russia.....	525
Table 32-12. 13 Selected Products for Japan MHLW 3-Year HTA Pilot Evaluation	528
Table 32-13. MaHTAS 1995–2018 Impact Overview	531
Table 32-14. Regulatory Authorities and Pricing Models in South Asia	532

Healthcare Landscape and Drug Development

Ruchi Gupta, MS

Healthcare always has been – and is even more so today – a vital aspect of human life. The healthcare landscape continues to evolve and transform hand in hand with evolution in the medicinal product development field, now highly influenced by payer reform, technology, scientific advances, consumer demand, and more.

These new realities and challenges impact how medicinal products are developed and approved. Previously, we lacked effective treatments for many life-threatening diseases; now, despite having many more treatments available, public scrutiny of healthcare has intensified. Patients and their families want new treatments sooner with accurate and understandable information on how to use them. While this has led health authorities to support innovation and advances in science and technology, it has also increased the complexity in the global regulatory landscape.

The Food and Drug Administration (FDA) and the European Medicines Agency (EMA) often are the regulators who first review these innovative treatments and lead the way in bringing efficacious and cost-effective treatments to the general and broader population.

In addition, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) plays a critical role in global drug development by developing guidelines based on scientific discussions among regulatory authorities and the pharmaceutical industry. ICH guidelines are updated continuously and applied by an increasing number of health authorities worldwide. The mission of ICH is to achieve greater harmonization worldwide and ensure that safe, effective, and high-quality medicines are developed, registered, and maintained in the most resource-efficient manner while meeting high standards.¹

Food and Drug Administration

FDA, an agency of the US the Department of Health and Human Services (HHS), is responsible for protecting the public health by assuring the safety, efficacy, and security of human drugs and biological products, as well as other products outside the scope of this book. FDA's mission includes advancing public health by supporting innovations that make medicines safer, more effective, and more affordable. The agency is tasked with providing the public with the accurate, science-based information they need to use medicinal products to maintain and improve their health. FDA plays a significant role in US counterterrorism efforts. The

agency collaborates with other US agencies, international regulators, academia, trade associations, consumer groups, and others.²

Role in Global Regulatory Landscape

Many of the medicinal products consumed by people of leading nations such as the US are produced in other countries. In the US, FDA-regulated products are produced in over 130,000 facilities in more than 150 countries.³ The agency faces challenges in determining and confirming that its standards and requirements have been applied in the manufacture, distribution, and storage of medicinal products imported into the US. Given that the manufacture of a product may involve multiple parties from different countries, there are chances for the product to be improperly formulated or packaged, contaminated, diverted, counterfeited, or adulterated. Thus, compliance and surveillance activities overseen by regulatory bodies across the product life cycle are a critical part of the drug development process.⁴

Inspections are a big part of such surveillance activities and depend on the stage of drug development. In situations where noncompliance is identified, FDA may issue one of several types of regulatory action letters, such as warning letters, administrative license action letters, and license revocation to cease practices that violate regulations and promote corrective action. If warranted, the FDA also has the authority to impose civil enforcement actions, including seizure, injunction, and prosecution.

FDA oversees the import and export of medicinal products to ensure that the FDA-regulated products comply with the requirements of the Food, Drug, and Cosmetics Act (FD&C Act) and the regulations promulgated under these statutes.⁵ Imported products regulated by FDA are subject to inspection at the time of entry by the US Customs and Border Protection (CBP). Imported products not in compliance with US regulations are subject to detention. Moreover, FDA verifies with CPB a company's licensure for imports, may perform random sampling, and will issue import alerts for noncompliant products.⁶ A foreign manufacturer must have a US license to import a biological product into the US.

FDA works closely with external organizations and foreign governments to promote product safety and regulatory consistency. Its efforts include:

- developing new enforcement and regulatory tools;
- conducting more foreign inspections;