Table of Contents

SECTION I: Fundamentals of US Pharmaceutical and Biologics Regulations

Chapter 1  History of Food, Drug and Cosmetic Laws.................................................................1
  Updated by Meredith Brown-Tuttle, RAC, FRAPS

Chapter 2  Overview of Drug, Biologic, Device, Combination Product or Food Regulatory Pathways ..........13
  Updated by Michael R. Hamrell, PhD, RQAP-GCP, CCRA, FACRP, RAC, FRAPS

Chapter 3  Clinical Trials: GCPs, Regulations and Compliance for Drugs, Biologics and Medical Devices ....45
  Updated by Monique Carter, MS, RAC and Samantha Zappia, MS, RAC

Chapter 4  Current Good Manufacturing Practices and Quality System Design.................................83
  Updated by Joscelyn Bowersock, MS-RA, and Richard Vincins, CQP, MCQL, CBA, CQA, RAC

Chapter 5  Prescription Product Drug Submissions ...........................................................................99
  By Shyamala Jayaraman, PhD, Lean Six Sigma Black Belt and Glen D. Park, PharmD, MSJ

Chapter 6  Postapproval Submissions and Compliance: Prescription Drugs and Biologics.....................121
  Updated by Emily Rapp, RAC and Dar Rosario, MBA, RAC

Chapter 7  Generic Drug Submissions ...............................................................................................141
  Updated by Amrita Ghosh, RAC and Sharry Arora, MPPharm

Chapter 8  Patents and Exclusivity .....................................................................................................153
  Updated by Kurt R. Karst, JD

Chapter 9  Over-the-Counter (Nonprescription) Drug Products .......................................................167
  Updated by Valerie Ramsey, DRSc, MS, RAC

Chapter 10 Prescription Drug Labeling, Advertising and Promotion ..............................................177
  Updated by Anu Gaur, PhD, MBA, MSRA, RAC

Chapter 11 Pharmacovigilance and Risk Management ....................................................................191
  Updated by Stacy Woeppe, MBA and Robert Falcone, PhD

Chapter 12 Biologics Submissions ..................................................................................................205
  Updated by Jocelyn Jennings, MS, RAC

Chapter 13 Biologics Compliance ....................................................................................................233
  Updated by Anne Marie Woodland, MS, RAC
Chapter 14  Biosimilars .................................................................................................................. 245

Updated by Nathalie Innocent, MS, RAC and Jennifer Wilhelm, MSc, MBA, RAC

Chapter 15  Biologics Labeling, Advertising and Promotion .......................................................... 267

By Kathrin Schalper, PhD, RAC

Appendices

Glossary of Terms.......................................................................................................................... 279
Index of Laws and Guidances ....................................................................................................... 303
Index by Subject ........................................................................................................................... 307

Figures

Figure 2-1.  Decision Tree for Drug and Device Development and Approval When FDA Premarket Review 
is Required ........................................................................................................................................ 21
Figure 2-2.  CTD Organization ....................................................................................................... 27
Figure 3-1.  Types of Pharmaceutical and Biologic Clinical Trials and Typical Pathway .................. 54
Figure 3-2.  Types of Medical Device Clinical Trials and Typical Pathway .................................... 67
Figure 4-1.  Quality System Documentation Elements .................................................................. 85
Figure 4-2.  Design Control “V” Model Process Flow ................................................................. 86
Figure 5-1.  FDA IND Review Process .......................................................................................... 105
Figure 5-2.  Diagram of the ICH Common Technical Document (CTD) ........................................ 111
Figure 5-3.  Timeline and Product Review Clock ......................................................................... 114
Figure 6-1.  Summary of Reporting Categories for Postapproval Changes ................................. 126
Figure 6-2.  Example of a CMC Index .......................................................................................... 132
Figure 9-1.  Example of an OTC Drug Facts Label .................................................................... 174
Figure 14-1. Number of Biosimilar INDs Received by CDER by Fiscal Yeara .................................. 249
Figure 14-2. Number of Biosimilar Type 1–4 Meetings Held by CDER by Fiscal Yeara .................. 249

Tables

Table 1-1.  Electronic Resources for US Laws and Regulations ......................................................... 3
Table 1-2.  Other Laws, Regulations and Guidelines ................................................................... 10
Table 2-1.  Title 21 CFR Parts ....................................................................................................... 20
Table 2-2.  Key Questions in a Drug Development Program ....................................................... 23
Table 2-3.  IND Safety Reporting Timeframes ............................................................................ 29
Table 2-4.  Summary of Device Classification System .................................................................. 36
Table 3-1.  Significant Legislation Relevant to Clinical Trials in the US ........................................ 48
Table 3-2.  Comparison of 21 CFR and ISO-GCP Requirements for Protocol Deviations in Medical Device Clinical Trials .................................................................................................................. 52
Table 3-3.  Comparison of 21 CFR and ISO GCP Requirements for Investigator Responsibilities in Medical Device Clinical Trials .................................................................................................................. 73
Table 3-4.  Comparison of 21 CFR and ISO-GCP Requirements for Recordkeeping in Medical Device Clinical Trials .................................................................................................................. 74
Table 3-5.  Comparison of 21 CFR and ISO-GCP Requirements for Device Accountability in Medical Device Clinical Trials .................................................................................................................. 75
Table 8-1.  180-Day Exclusivity Forfeiture Snapshot .................................................................... 161
Table 8-2. Differences Among Applications Submitted and Approved Under FD&C Act Section 505 .... 162
### Table 9-1. OTC Monograph Therapeutic Category Subtopics Evaluated as Part of the OTC Review Process

<table>
<thead>
<tr>
<th>Subtopic</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acne Drug Products: Benzoyl Peroxide</td>
<td>171</td>
</tr>
<tr>
<td>NDA vs. OTC Drug Monograph</td>
<td>172</td>
</tr>
<tr>
<td>PLR Format, Associated Regulations and Guidance Documents</td>
<td>182</td>
</tr>
<tr>
<td>PLR Format, Associated Regulations and Guidance Documents (cont’d.)</td>
<td>183</td>
</tr>
<tr>
<td>Safety Reporting Requirements for Drugs/Biologics</td>
<td>200</td>
</tr>
<tr>
<td>Safety Reporting Requirements for Medical Devices</td>
<td>201</td>
</tr>
<tr>
<td>Key Milestones in the Regulatory Oversight of Biologics</td>
<td>209</td>
</tr>
<tr>
<td>Applications Regulated by PHS Act</td>
<td>210</td>
</tr>
<tr>
<td>Applications Regulated by the FD&amp;C Act</td>
<td>211</td>
</tr>
<tr>
<td>Biologics Controlled by CDER and CBER</td>
<td>212</td>
</tr>
<tr>
<td>Submissions With Specific Regulatory Mandated Timelines (e.g., SPAs) or FDA Established Timelines (e.g., Reviews of Proposed Pediatric Study Requests)</td>
<td>214</td>
</tr>
<tr>
<td>Safety-Related Submissions</td>
<td>216</td>
</tr>
<tr>
<td>IND Drug Development Submissions</td>
<td>218</td>
</tr>
<tr>
<td>IND Drug Development Submissions (cont’d.)</td>
<td>219</td>
</tr>
<tr>
<td>Other Submission Types</td>
<td>220</td>
</tr>
<tr>
<td>Key CMC Guidance for Biological Product Development</td>
<td>222</td>
</tr>
<tr>
<td>Key CMC Guidance for Biological Product Development (cont’d.)</td>
<td>223</td>
</tr>
<tr>
<td>NDA/BLA Standard and Priority Review Process (PDUFA VI)</td>
<td>226</td>
</tr>
<tr>
<td>BsUFA Fees Financial Year 2019a</td>
<td>248</td>
</tr>
<tr>
<td>Meetings Between FDA and Biosimilar Biological Product Sponsors</td>
<td>250</td>
</tr>
<tr>
<td>Comparison of Development Programs Between Chemical Drugs and Biological Products</td>
<td>254</td>
</tr>
<tr>
<td>FDA-Approved Biosimilars</td>
<td>259</td>
</tr>
</tbody>
</table>

## SECTION II: Fundamentals of Canadian Pharmaceutical and Biologics Regulations

### Chapter 1
Health Canada Organization and Its History of Regulating Health Products in Canada

*Updated by Hetal Mokashi, MBA and Penny Wilks, ND, RAC*

### Chapter 2
Good Laboratory Practice for Nonclinical Laboratory Studies

*Updated by Navneet Sekhon*

### Chapter 3
Clinical Trial Applications, Good Clinical Practices

*By Mahdis Dorkalam, MSc, RHN, and Navneet Sekhon*

### Chapter 4
Good Manufacturing Practices and Establishment Licensing in Canada

*By Bocar Guisse, MSc and Fraidianie Sévigné*

### Chapter 5
New Drug Submission Process

*Updated by Susanne Picard and Janice Weiler*

### Chapter 6
Postmarketing and Other Activities

*Updated by Janice Weiler and Danny Germain, RAC*
Chapter 7  
Health Product Vigilance and Risk Management .................................................................69
*Updated by Christopher Antonio, Roshni Celeste, Jenna Griffiths, Carole Légaré, Marc Poitras, Tanya Ramsamy, Thanh Vu, Bruce Wozny and Raymond Yang*

Chapter 8  
An Overview of Pharmaceutical Intellectual Property Protection in Canada..........................79
*By Junyi Chen, JD, PhD, Danny Germain, RAC, Gordon Jepson, MA, LLB, and Bhavesh Patel, CChem*

Chapter 9  
Abbreviated New Drug Submissions ......................................................................................95
*Updated by Bhavesh Patel, CChem, Bocar Guisse, MSc and Fraidianie Sevigne*

Chapter 10  
Nonprescription Drugs ........................................................................................................105
*Updated by Kristin Willemsen*

Chapter 11  
Biologics Submission, Approval and Postmarketing ..............................................................115
*Updated by Marcia Sam and Mahdis Dorkalam, MSc, RHN*

Chapter 12  
Labelling, Advertising and Promotion: Prescription Pharmaceutical Drugs, Biologics and Radiopharmaceuticals ........................................................................................................127
*Updated by Marcia Sam, Veronica Yip and Sandra Alderdice*

Chapter 13  
electronic Common Technical Document (eCTD) ................................................................133
*By Khaled Yahiaoui, MSc, RAC*

Chapter 14  
Product Lifecycle Management Guidance .............................................................................143
*By Ajay Babu Pazhayattil, Naheed Sayeed-Desta and Queenia Lee*

Index .............................................................................................................................................149

**Figures**

Figure 1-1. Health Canada ..........................................................................................................2
Figure 1-2. Branches with Responsibility for the Regulation of Healthcare Products .................3
Figure 5-1. Diagram of the NDS Submission and Approval Procedure ......................................51
Figure 5-2. Example Boxed Text for Product Approved Under the NOC/c Policy .......................52
Figure 6-1. Form IV Patent List ..................................................................................................64
Figure 13-1. Structure of a Regulatory Transaction in eCTD Format .......................................135
Figure 13-2. End-to-End Process for Preparing and Filing Regulatory Transactions in eCTD Format ......141

**Tables**

Table 1-1. Timeline—Regulating Health Products in Canada ..................................................6
Table 2-1. Examples of Studies and the Requirement for GLP Compliance ................................14
Table 3-1. Contents of a CTA Submission Package ..................................................................22
Table 3-2. Quality Changes—Biologics and Radiopharmaceuticals .........................................24
Table 3-3. Quality Changes—Pharmaceuticals .........................................................................25
Table 3-4. Postapproval Requirements ....................................................................................27
Table 4-1. Definitions for Terms in This Chapter ..................................................................30
Table 4-2. GMP Regulations Applicable to Licensable Activities ........................................33
Table 5-1. Presentation of Information in the Common Technical Document (CTD) Format .......49
Table 5-2. Target Review Times ............................................................................................53
Table 7-1. Clinical Trial Definitions ........................................................................................71
Table 7-2. Postapproval Stage Definitions ........................................................................................................... 74
Table 9-1. Target Review Times .......................................................................................................................... 102
Table 10-1. NAPRA Scheduling Factors .............................................................................................................. 110
Table 11-1. Drug Substance (Biologics and Radiopharmaceuticals) .................................................................. 118
Table 11-2. Drug Product (Biologics and Radiopharmaceuticals) ..................................................................... 119
Table 11-3. Sample Table of Contents for a Schedule D (Biological) Product Monograph (PM) .................... 120
Table 11-4. Summary of Requirements for Evaluation Groups ......................................................................... 123
Table 13-1. Localization of Main XML Files Within an eCTD Sequence ........................................................ 136
Table 13-2. Canadian eCTD Envelope Elements ............................................................................................... 136
Table 13-3. m2-m5 eCTD Attributes .................................................................................................................. 137
Table 13-4. Validation Rule Samples and Their Descriptions and Severities ................................................... 137
Table 13-5. Document Formats Health Canada Expects for Specific Documents ............................................ 138
Table 13-6. Lifecycle Management Table Template ......................................................................................... 138
Table 13-7. Lifecycle Management Table Example with Three Regulatory Activities and Related Regulatory Transactions .................................................................................................................... 139
Table 13-8. Lifecycle Management of Specific Documents ............................................................................... 140

SECTION III: Fundamentals of EU Pharmaceutical and Biologics Regulations
See Volume 2 of Fundamentals of Pharmaceutical and Biologics Regulations

SECTION IV: Fundamentals of International Pharmaceutical and Biologics Regulations
See Volume 2 of Fundamentals of Pharmaceutical and Biologics Regulations
Table of Contents

SECTION I: Fundamentals of US Pharmaceutical and Biologics Regulations
See Volume 1 of Fundamentals of Pharmaceutical and Biologics Regulations

SECTION II: Fundamentals of Canadian Pharmaceutical and Biologics Regulations
See Volume 1 of Fundamentals of Pharmaceutical and Biologics Regulations

SECTION III: Fundamentals of EU Pharmaceutical and Biologics Regulations

Chapter 1  EMA and Other Regulatory Bodies.................................................................1
Updated by Ratinder Dhani, MSRA, RAC

Chapter 2  History of EU Regulations..........................................................................13
Updated by Sabina Hoekstra-van den Bosch, PharmD, FRAPS

Chapter 3  Overview of Drug and Biologic Regulatory Pathways.................................31
Updated by Kathrin Schalper, PhD, RAC

Chapter 4  Preparing for EMA Meetings Prior to Submission of a Marketing Authorisation Application.........41
Updated by Kell Cannon, Kate Dion and Cindy DiBiasi

Chapter 5  Preparing for EMA Meetings During Review of a Marketing Authorisation Application...............53
By Kell Cannon, Kate Dion and Cindy DiBiasi

Chapter 6  EU Pricing and Reimbursement..................................................................61
Updated by Anu Gaur, PhD, MBA, MSRA, RAC

Chapter 7  Health Technology Assessment (HTA).........................................................77
Updated by Azzurra Ravizza, MSc and Monique Carter, MS, RAC

Chapter 8  The Paediatric Regulation...........................................................................93
Updated by Karl-Heinz Huemer, PhD, MD

Chapter 9  Advertising and Promotion........................................................................103
Updated by Karen Zhou, JD, MS, RAC
<table>
<thead>
<tr>
<th>Chapter</th>
<th>Title</th>
<th>Page</th>
<th>Updated By</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Enforcement and Competent Authorities</td>
<td>115</td>
<td>Sabina Hoekstra-van den Bosch, PharmD, FRAPS</td>
</tr>
<tr>
<td>11</td>
<td>European Union Falsified Medicines Directive: Requirements and Implications for Multi-Stakeholder Healthcare Delivery</td>
<td>121</td>
<td>Yolanda García Barruso</td>
</tr>
<tr>
<td>12</td>
<td>Regulatory Strategy</td>
<td>135</td>
<td>Karen Fan, MSc, PEng, RAC</td>
</tr>
<tr>
<td>13</td>
<td>Overview of Authorisation Procedures for Medicinal Products</td>
<td>141</td>
<td>Sharry Arora, MPharm</td>
</tr>
<tr>
<td>14</td>
<td>Adaptive and Alternative Pathways</td>
<td>159</td>
<td>Kathrin Schalper, PhD, RAC</td>
</tr>
<tr>
<td>15</td>
<td>Preclinical Testing and Good Laboratory Practice Regulations</td>
<td>165</td>
<td>Anu Gaur, PhD, MBA, MSRA, RAC</td>
</tr>
<tr>
<td>16</td>
<td>Medicinal Product Clinical Trials</td>
<td>173</td>
<td>Ashley Clark, MSc, RAC</td>
</tr>
<tr>
<td>17</td>
<td>Registration Procedures for Medicinal Products</td>
<td>205</td>
<td>Jocelyn Jennings, MS, RAC</td>
</tr>
<tr>
<td>18</td>
<td>Quality Systems and Inspectorate Process—Pharmaceuticals</td>
<td>227</td>
<td>Treena Jackson, MS, MA, CQA, CSSGB, RAC, Siegfried Schmitt, PhD</td>
</tr>
<tr>
<td>19</td>
<td>Generic Medicinal Products</td>
<td>241</td>
<td>Nicole Beard MSc, PhD</td>
</tr>
<tr>
<td>20</td>
<td>Biosimilar Medicinal Products</td>
<td>257</td>
<td>Jocelyn Jennings, MS, RAC</td>
</tr>
<tr>
<td>21</td>
<td>Nonprescription Medicinal Products</td>
<td>267</td>
<td>Nicole Beard MSc, PhD</td>
</tr>
<tr>
<td>22</td>
<td>Marketing Authorisations for Products Derived From Biotechnology</td>
<td>277</td>
<td>Jocelyn Jennings, MS, RAC</td>
</tr>
<tr>
<td>23</td>
<td>Pharmaceutical Postauthorisation Requirements and Compliance With the Marketing Authorisation</td>
<td>287</td>
<td>Sharry Arora, MPharm</td>
</tr>
<tr>
<td>24</td>
<td>Pharmacovigilance</td>
<td>301</td>
<td>Jocelyn Jennings, MS, RAC</td>
</tr>
<tr>
<td>25</td>
<td>Regulatory Framework for Advanced Therapy Medicinal Products</td>
<td>315</td>
<td>Daniela Drago, PhD, RAC, Florence Houn, MD, MPH and James McBlane, PhD</td>
</tr>
<tr>
<td>26</td>
<td>Human Tissue Regulation</td>
<td>335</td>
<td>Nicole Beard, MSc, PhD</td>
</tr>
</tbody>
</table>
Chapter 27  Vaccines .................................................................................................................. 353  
  Updated by Frédéric Béard

Chapter 28  Products Manufactured From Human Blood or Plasma ......................................... 365  
  Updated by Nicole Beard, MSc, PhD

Chapter 29  Orphan Medicinal Products ................................................................................... 375  
  Updated by Jocelyn Jennings, MS, RAC

Chapter 30  Combination Products ......................................................................................... 389  
  Updated by Claudia Ising, FRAPS, RAC

Appendices

Comparative Matrix of EU Legislation Across Product Lines..................................................... 399
Glossary ........................................................................................................................................ 447
Index ........................................................................................................................................... 467

Figures

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-1</td>
<td>EMA Mission</td>
<td>3</td>
</tr>
<tr>
<td>1-2</td>
<td>EMA Organisational Structure</td>
<td>9</td>
</tr>
<tr>
<td>5-1</td>
<td>Approximate Representation of Key CHMP, CAT and PRAC Feedback and Meetings Based on Standard Assessment Review Timeline</td>
<td>55</td>
</tr>
<tr>
<td>5-2</td>
<td>Example Timeline for CHMP Meeting Preparation</td>
<td>57</td>
</tr>
<tr>
<td>6-1</td>
<td>Factors Influencing Medicinal Product Pricing</td>
<td>62</td>
</tr>
<tr>
<td>6-2</td>
<td>Overview of ERP across Europe (2013)</td>
<td>64</td>
</tr>
<tr>
<td>6-3</td>
<td>Summary of Economic Evaluation Methods</td>
<td>66</td>
</tr>
<tr>
<td>6-4</td>
<td>Types of Cost Containment Policies Adopted by Member States</td>
<td>67</td>
</tr>
<tr>
<td>6-5</td>
<td>German Pricing for Medicinal Products Under AMNOG</td>
<td>70</td>
</tr>
<tr>
<td>7-1</td>
<td>Process Map for France</td>
<td>85</td>
</tr>
<tr>
<td>7-2</td>
<td>Process Map for Germany</td>
<td>86</td>
</tr>
<tr>
<td>7-3</td>
<td>Mean Length of Time From EMA Authorisation to HTA Decision for Oncology Products</td>
<td>88</td>
</tr>
<tr>
<td>8-1</td>
<td>PIP Procedure</td>
<td>98</td>
</tr>
<tr>
<td>11-1</td>
<td>Comparison of EU FMD and Other Countries’ Falsified Medicines Legislation</td>
<td>123</td>
</tr>
<tr>
<td>11-2</td>
<td>Routes in the Medicinal Product Supply Chain by Which Falsified Active Substances may Reach Patients</td>
<td>125</td>
</tr>
<tr>
<td>11-3</td>
<td>An Example of the Common Logo Online Retailers of Medicines Must Display</td>
<td>128</td>
</tr>
<tr>
<td>11-4</td>
<td>Flowchart Representing Product and Information Flow With Unique Product Identifiers and Accompanying Verification and Repository Systems</td>
<td>131</td>
</tr>
<tr>
<td>14-1</td>
<td>Product Eligibility for Adaptive Pathways Approach (Source: EMA, 2016)</td>
<td>161</td>
</tr>
<tr>
<td>16-1</td>
<td>Clinical Trial Legislative Improvements</td>
<td>176</td>
</tr>
<tr>
<td>16-2</td>
<td>Regulation (EU) 536/2014</td>
<td>177</td>
</tr>
<tr>
<td>16-3</td>
<td>Clinical Trial Authorization Procedure</td>
<td>190</td>
</tr>
<tr>
<td>16-4</td>
<td>Clinical Trial Application Scientific Assessment</td>
<td>191</td>
</tr>
<tr>
<td>16-5</td>
<td>Clinical Trial Application: Part II Assessment</td>
<td>192</td>
</tr>
<tr>
<td>16-6</td>
<td>Serious Adverse Event Reporting</td>
<td>196</td>
</tr>
<tr>
<td>17-1</td>
<td>Initial Marketing Authorisation Application Through the Centralised Procedure</td>
<td>219</td>
</tr>
<tr>
<td>17-2</td>
<td>Initial Marketing Authorisation Application Through the Decentralised Procedure</td>
<td>220</td>
</tr>
</tbody>
</table>
Table 16-3. Initial Marketing Authorisation Application Through National Procedure and Mutual Recognition Procedure ................................................................................................................................. 221
Figure 18-1. Drug Lifecycle Regulations ................................................................................................................................. 228
Figure 18-2. Assessors and Inspectors ................................................................................................................................. 229
Figure 18-3. EU Legal Instruments ........................................................................................................................................... 230
Figure 18-4. Inspections as Part of the Drug Approval Process ................................................................................................. 231
Figure 20-1. Biosimilar Development ........................................................................................................................................... 259
Figure 20-2. Stages of Development of a Biosimilar Medicine ........................................................................................................... 260
Figure 20-3. Timeline for Development of a Biosimilar Medicine ........................................................................................................... 261
Figure 20-4. Biosimilar Product Development and Marketing Approval ............................................................................................... 263
Figure 24-1. Pharmacovigilance System Master File ..................................................................................................................... 305
Figure 24-2. ICSR Expedited Submissions Requirements............................................................................................................. 309
Figure 24-3. Signal Management Lifecycle ................................................................................................................................. 311
Figure 25-1. Decision Tree for Potential Pathways and Expedited Evaluation Programs in the EU ........................................................................................................................................ 318
Figure 25-2. Decision Tree for Classification of TEPs and CTMPs ........................................................................................................... 322
Figure 25-3. Decision Tree for the Classification of GTMPs ............................................................................................................... 323
Figure 27-1. General Principles of VAMF Certification ................................................................................................................ 355
Figure 27-2. Procedure for Seasonal Influenza Vaccines in the EU (EMA/56793/2014) .................................................................................. 359
Figure 29-1. Simplified View of the Designation Criteria .................................................................................................................. 378
Figure 29-2. EMA Orphan Drug Designation Guide ......................................................................................................................... 380

Tables

Table 3-1. Differences Between Conditional Marketing Authorisation and Marketing Authorisation Under Exceptional Circumstances ................................................................................................................. 36
Table 4-1. Overview of the Key EMA Advice Meetings and Their Goals ........................................................................................... 43
Table 4-2. Overview of the Different Steps Required for Each Meeting .............................................................................................. 45
Table 4-3. Timeline for Key Meeting Steps ................................................................................................................................. 46
Table 5-1. EMA Scientific Committees: Roles ............................................................................................................................. 54
Table 6-1. Overview of Reference Pricing and Country Baskets in Europe .......................................................................................... 65
Table 7-1. HTA and Associated Organisations in Select EU Member States .......................................................................................... 82
Table 7-2. Comparison of HTA in Germany, France, UK, Italy and Spain ................................................................................................. 83
Table 7-3. Summary of Time From EMA Authorisation to HTA Decision and Outcome ........................................................................... 87
Table 11-1. Definitions of Key Terms in This Chapter ....................................................................................................................... 124
Table 11-2. Worldwide Examples of SFFC Medicines From 2008 to Present .......................................................................................... 126
Table 11-3. Different Medicinal Product Supply Chain Stakeholder Requirements Under the FMD .................................................................. 127
Table 11-4. FMD Definitions of Active Substances and Excipients .................................................................................................... 128
Table 11-5. EU Initiatives Relevant to the FMD ............................................................................................................................ 129
Table 11-6. Status of Third Country Listing Requests .................................................................................................................... 130
Table 12-1. Regulatory Key Questions During Development ............................................................................................................. 137
Table 13-1. Standard Timetable for Evaluation of a Centralised Application .......................................................................................... 148
Table 13-2. Mutual Recognition Procedure Flowchart ..................................................................................................................... 151
Table 13-3. Decentralised Procedure Flowchart .......................................................................................................................... 154
Table 16-1. Summary of Selected Significant Changes Under Regulation (EU) No. 536/2014 (ECTR) ......................................................... 178
Table 16-2. Definitions of Selected Clinical Trials Directive and ECTR Terms ..................................................................................... 180
Table 16-3. General Contents of Applications to Ethics Committees and National Competent Authorities ............... 185
Table 16-4. Contents of Clinical Trial Application Dossier per the ECTR .......................................................... 193
Table 16-5. Contents of DSUR ............................................................................................................................ 198
Table 17-1. EU Module 1 Contents ..................................................................................................................... 215
Table 17-2. EU eCTD Envelope Information ....................................................................................................... 216
Table 19-1. Legal Basis of EU Applications from Directive 2001/83/EC .............................................................. 245
Table 20-1. Data Package Required for a Marketing Authorisation Application to EMA .......................... 264
Table 21-1. Some Common Health Conditions Treated Using Nonprescription Medication .................. 269
Table 21-2. Comparison of EU MAA Procedure Advantages and Risks for Nonprescription Medicines .... 270
Table 24-1. Overview of Good Pharmacovigilance Practices ........................................................................ 303
Table 24-2. Periodic Benefit-Risk Evaluation Report (PBRER), Development Safety Update Report (DSUR) and Risk Management Plan (RMP) Interchangeable Modules .......................................................... 308
Table 25-1. EU Pathways and Expedited Evaluation Programs That Might Apply to ATMPs ................ 317
Table 25-2. ATMPs That Have Been Granted a Marketing Authorisation in the EU .................................. 319
Table 25-3. Recent Examples of CAT ATMP Classifications ........................................................................ 321
Table 26-1. Serological Donor Testing Requirements ....................................................................................... 339
Table 26-2. Structure of the Single European Code ......................................................................................... 340
Table 26-3. Qualifications and Responsibilities of the Responsible Person Under the EUTCD, Qualified Person for Human Medicinal Products and Responsible Person for Regulatory Compliance Under the EU MDR ......................................................................................................................... 343
Table 26-4. Standard Timetable for Initial ATMP Marketing Authorisation Application Evaluation Under the Centralised Procedure .......................................................................................................................... 345
Table 28-1. Medicinal Products Derived From Human Plasma and Their Indications ........................................ 367

SECTION IV: Fundamentals of International Pharmaceutical and Biologics Regulations

Chapter 1 Clinical Trials, Good Clinical Practice, Regulations and Compliance ................................................. 1
Updated by Anu Gaur, PhD, MBA, MSRA, RAC

Chapter 2 International Advertising and Promotion .......................................................................................... 13
Updated by Treena Jackson, MS-QA/RA, MA, CQA, CSSGB, RAC

Chapter 3 Premarket Requirements/Dossier Requirements ............................................................................... 21
Updated by Monique Carter, MS, RAC, and Jesshanie Tabaniag

Chapter 4 Authorization Procedures for Pharmaceutical Products ............................................................. 29
By Orin Chisholm, GCULT, PhD, MTOPRA, and Monique Carter MS, RAC

Chapter 5 Stability Test Requirements .......................................................................................................... 47
By Sharry Arora, MPharm, and Rosie Dawes

Chapter 6 Quality Systems and Inspectorate Process for Pharmaceuticals ..................................................... 59
Updated by Siegfried Schmitt, PhD, CSci, CChem, FRSC

Chapter 7 Generic Drug Products .................................................................................................................. 75
Updated by Pallavi Trivedi, MPH, RAC, and Anu Gaur, PhD, MBA, MSRA, RAC
Chapter 8  Over-the-Counter (OTC) Products........................................................................................................89
  Updated by Robert Falcone, PhD
Chapter 9  Pharmaceutical Postmarketing and Compliance..................................................................................97
  Updated by Valencia Hood-Humphrey, MSRA, and Kathrin Schalper, PhD, RAC
Chapter 10  High-Risk Products: Products Derived from Biotechnology..............................................................113
  Updated by Jocelyn Jennings, MS, RAC, and Angela L. Nelson, MBA, RAC
Chapter 11  Biosimilars: Basics and Recent Developments..................................................................................129
  Updated by Pallavi Trivedi, MPH, RAC
Chapter 12  Vaccines ............................................................................................................................................161
  By Nicole Beard, MSc, PhD
Chapter 13  Products Manufactured From Human Blood and Plasma.................................................................179
  Updated by Indraneel Dasari, RAC
Chapter 14  Principles of Rare Diseases and Orphan Products Development ......................................................199
  Updated by Todd J. Banks, PharmD, RPh, Mridula Shukla, MS, RAC, and Phu Bo Chung, JD, MS, RAC
Chapter 15  Global Pediatric Drug Development .................................................................................................209
  By Lynne Georgeopoulos, RN, MSHS, RAC, and Daniela Drago, PhD, RAC

Appendices
Appendix 15-1. Timeline of Key Pediatric Initiatives Undertaken in the US ..........................................................213
Appendix 15-2. Timeline of Key Pediatric Initiatives Undertaken in the EU ..........................................................223
Comparative Matrix of Regulations Across Product Lines ..................................................................................229
Glossary...............................................................................................................................................................255
Index.....................................................................................................................................................................271

Annexes
Annex 11-1. US Biosimilar Guidelines .............................................................................................................133
Annex 11-2. Brazil Technical Guidelines, Coordination of Biological Products (CPBIH) and ANVISA ..............135
Annex 11-3. EU Product-Specific Biosimilar Guidelines .....................................................................................136

Figures
Figure 1-1. Acceptance of Foreign Clinical Data.................................................................................................5
Figure 1-2. Quality Management System ........................................................................................................9
Figure 3-1. CTD Organization ..........................................................................................................................23
Figure 6-1. Drug Lifecycle Regulations ...........................................................................................................60
Figure 6-2. Assessors and Inspectors ...............................................................................................................61
Figure 6-3. EU Legal Instruments ....................................................................................................................62
Figure 6-4. Inspections as Part of the Drug Approval Process ............................................................................63
Figure 9-1. MedDRA Coding Hierarchy .........................................................................................................107
Figure 11-1. Influence of Stakeholders as Drivers of Biosimilars ...................................................................132
Figure 11-2. Standalone vs. Abbreviated Development Programs .................................................................141
Figure 11-3. Regulation in Latin America .......................................................................................................157
Figure 13-1. Fundamentals of Pharmaceutical and Biologics Regulations

Table 12-1. Table 11-13. Table 11-12. Table 11-11. Table 11-10. Table 11-9. Table 11-8. Table 11-7. Table 11-6. Table 11-4. Table 11-3. Table 11-2. Table 11-1. Table 10-1. Table 9-1. Table 7-2. Table 7-1. Table 6-1. Table 5-6. Table 5-5. Table 5-3. Table 5-1. Table 4-1. Table 3-1. Table 2-1. Table 1-1.

Tables

Table 1-1. Regional Regulatory Authorities ................................................................. 6
Table 1-2. Trial Master File Essential Documents ...................................................... 11
Table 3-1. ACTD Format and Content ........................................................................ 27
Table 4-1. Country-Specific Regulatory Requirements .............................................. 31
Table 5-1. Climatic Zones ......................................................................................... 48
Table 5-2. WHO Recommended Stability Testing Conditions for Drug Substance and Drug Product .......... 50
Table 5-3. Recommended Stability Storage Conditions for Refrigerated and Frozen Drug Substance and Drug Product ................................................................. 51
Table 5-4. Country-Specific Climatic Zones and Stability Data Requirements for Asia Pacific Region .......... 54
Table 5-5. Country-Specific Climatic Zones and Stability Data Requirements for Latin America ............... 55
Table 5-6. Country-Specific Climatic Zones and Stability Data Requirements for SEE, Middle East and Africa ....................................................................................... 56
Table 6-1. PIC/S Member States ................................................................................ 70
Table 7-1. Comparison of Generic Product Development Regulatory Requirements in Select Countries ...... 77
Table 7-2. Comparative Study Parameter Assessment Between the US, EU and Canada .................. 81
Table 9-1. MAH Reporting Requirements .................................................................. 108
Table 10-1. Comparison of ICH CTD and ASEAN CTD Structures ............................ 124
Table 11-1. Advantages and Disadvantages of Equivalence/Noninferiority Designs for SBPs ............ 133
Table 11-2. EMA Biosimilar Marketing Approvals via the Centralised Procedure .................... 134
Table 11-3. Typical Biosimilar Product Marketing Application Dossiers and Data Requirement for Approval in the EU .............................................................................. 137
Table 11-4. FDA Approved Biosimilars Listed in Purple Book (30 August 2016) ......................... 140
Table 11-5. Typical Dossier and Data Requirements for US Biosimilar Applications ................. 142
Table 11-6. PMDA-Approved Biosimilars as of March 2016 ......................................... 144
Table 11-7. Typical Dossier and Data Requirements for Biosimilar Applications in Japan .............. 146
Table 11-8. Typical Application Dossier and Data Requirements for Biosimilar Marketing Applications and Approvals in India .......................................................... 148
Table 11-9. Typical Application Dossier and Data Requirement for Biosimilar Marketing Applications and Approvals in China ............................................................. 150
Table 11-10. MFDS-Approved Biosimilars .................................................................. 151
Table 11-11. Typical Application Dossier and Data Requirements for Biosimilar Marketing Applications and Approvals in Korea ............................................................ 152
Table 11-12. Rest of Asia Pacific ................................................................................ 155
Table 11-13. Typical Application Dossier and Data Requirements for Biosimilar Marketing Applications and Approvals in Brazil ............................................................. 156
Table 12-1. Adjuvants Licensed in the EU ................................................................... 172
Table 12-2. European Guidelines for Influenza Vaccines ............................................. 174

Fundamentals of Pharmaceutical and Biologics Regulations
Table 13-1. Overview of Products Manufactured From Blood and Their Clinical Significance ................................. 181
Table 13-2. Overview of Blood Product Approvals Obtained in the US ................................................................. 182
Table 13-3. Evidence of Infection Transmission by Human Blood .................................................................................. 186
Table 14-1. Overview of Orphan Drug Framework .................................................................................................. 202
Table 15-1. FDA Pediatric Age Categories for Labeling of Drugs and Biologics ......................................................... 212
Table 15-2. Outline of the initial Pediatric Study Plan (iPSP) ...................................................................................... 214
Table 15-3. Overview of BPCA and PREA ............................................................................................................. 216
Table 15-4. Paediatric Regulation—Key Requirements and Incentives ................................................................. 218
Table 15-5. Overview of Information Required in a PIP ......................................................................................... 222