

Contents

Foreword	iii
Author Acknowledgments.....	v
Chapter 1: Driving Successful Commercial Product Launches.....	1
<i>Flora Sandra Siami, MPH</i>	
Chapter 2: Elements to Consider When Developing a Global Regulatory Strategy	13
<i>Thomas Hutchinson, MS, CQA, CMDA, CMQ/OE, RAC-US, FRAPS</i>	
Chapter 3: Core Development Teams	19
<i>Anuja Yardi, MS-RA, MSPM, MPharm, RAC-US</i>	
Chapter 4: Components of Regulatory Strategy – The Basics.....	47
<i>Melissa Walker, MS, RAC-US, FRAPS</i>	
Chapter 5: Setting up a Quality Management System.....	59
<i>Susumu Nozawa, RAC-EU, RAC-US, FRAPS</i>	
Chapter 6: Risk Management Strategies for Device Design and Development Processes	83
<i>Shannon Hoste, MSM, MSSE</i>	
Chapter 7: Global Medical Device Labeling Strategies	99
<i>Foram Shukla, PharmD, MS-RA</i>	
Chapter 8: Manufacturing.....	115
<i>Andrea Armando, MS</i>	
Chapter 9: Nonclinical Laboratory Testing.....	123
<i>Dorota Grabowska, PhD, and Peter A. Takes, PhD, RAC-US, FRAPS</i>	
Chapter 10: Global Medical Device Clinical Strategy	135
<i>Dawn N. Norman, MS</i>	
Chapter 11: In Vitro Diagnostic Medical Devices	143
<i>Jocelyn Jennings, MSRA, RAC-Devices, RAC-Drugs, RAC-US, RAC-Global, FRAPS</i>	
Chapter 12: Combination Products.....	155
<i>Allyson B. Mullen, JD</i>	
Chapter 13: Global Regulatory Processes.....	165
<i>Manuel Urena, Xianjun Chen, MS; and Brian Young</i>	
Chapter 14: Global Regulatory Process – Third-Party Point of View	179
<i>Gert Bos, PhD, MSc, FRAPS</i>	

Chapter 15: Use of Standards in Medical Device Global Regulatory Strategy	187
<i>Susumu Nozawa, RAC-EU, RAC-US, FRAPS</i>	
Chapter 16: Global Medical Device Marketing Strategy	207
<i>Charles Tam, MBA, EP</i>	
Chapter 17: Regulatory Resources for Strategy Development	225
<i>Gretchen E. Parker, PhD, CIP, RAC-US</i>	
Chapter 18: Global Postmarketing Regulatory Strategy	249
<i>Scott D. Dickerhoff, MBA, and Samata Veluvolu, MBA, RAC-US</i>	
Chapter 19: Borderline Regulation of Stem Cell Technologies: Therapies, Devices, and Combination Products	275
<i>Beat U. Steffen, MSc, MBA, RAC-Devices, FRAPS, and Andrea Lopes, PhD</i>	
Chapter 20: Patents and Intellectual Property	287
<i>Stanley F. Chavvire, PharmD, JD, and Sean D. Detweiler, JD</i>	
Chapter 21: Software	299
<i>Philip Desjardins, JD</i>	
Chapter 22: Cybersecurity	309
<i>Colin Morgan, MS, CISSP, CISM</i>	
Index	321

Figures

Figure 1-1. Market Access External Stakeholders	2
Figure 1-2. PDP Internal Stakeholders and Collaborators	3
Figure 1-3. Reimbursement for Medical Devices	6
Figure 4-1. Comparison of Target Market Release Timelines	55
Figure 5-1. Basic Process Model	61
Figure 5-2. PDCA Cycle in Resource Management	61
Figure 5-3. Implementing an ISO 13485:2016 QMS	65
Figure 5-4. Sample Schedule for QMS Implementation	67
Figure 5-5. QMS Documentation Defining Responsibilities	68
Figure 5-6. Typical QMS Document Hierarchy	69
Figure 5-7. Iterative PDCA Cycle	70
Figure 5-8. ISO 17021 QMS Certification Cycle	72
Figure 5-9. Design Process	77
Figure 6-1. Framework Developed by the Presidential Commission 1997 Report	85
Figure 6-2. NIST Cybersecurity Framework 2.0 Governance is Designed to be a Cross-Cutting Function to Inform and be Infused throughout the Other Five Elements. ¹²	86
Figure 6-3. NIST AI RMF Governance is Designed to be a Cross-Cutting Function to Inform and be Infused throughout the Other Three Elements	87
Figure 6-4. High-Level Summary of Some Key Steps in Product Risk Management	90
Figure 6-5. Comparison Example of Top-Down Hazard Analysis and Bottom-Up FMEA Tools.	92
Figure 7-2. Example of a Medical Device Label for Use in Multiple Regions	102
Figure 9-1. Strategy for Performing Animal Studies	129
Figure 15-1. Document Hierarchy	192
Figure 21-1. Rule 11 of Annex VIII of EU MDR	306
Figure 22-1. Product Security Framework From the JSP	311
Figure 22-2. AAMI TIR57 and ISO14971 Crosswalk	313

Tables

Table 1-1. Main Type of Coding in the US Healthcare Reimbursement System	8
Table 3-1. Example Development Phases	24
Table 3-2. Regulatory Pathway Assessment Elements	36
Table 3-3. Regulatory Strategy and Plan Elements.....	37
Table 3-4. Ebb and Flow of Core Team Member Involvement.....	42
Table 4-1. GRS Simplified Element Table.....	48
Table 4-2. Regulatory History Considerations.....	51
Table 4-3. Tools or Treatment	52
Table 4-4. Expanded Example of the GRS Element Table.....	56
Table 4-5. Regulatory Submission Requirements.....	57
Table 4-6. Summary of Regulatory Risks.....	57
Table 5-1. Key Differences Between ISO 9001 and ISO 13485	59
Table 5-2. Similarities Between ISO 9001 and ISO 13485.....	60
Table 5-3. Applicability of ISO 13485 in Various Global Jurisdictions.....	64
Table 5-4. Benefits and Barriers to Certification.....	71
Table 5-5. Certification Body QMS Assessment Objectives, Scope, and Criteria.....	72
Table 5-6. Audit Duration for Medical Device ISO 13485 Audits Based on Staff Numbers	73
Table 5-7. Factors That May Increase or Reduce Audit Durations	73
Table 6-1. Project Risk Mitigation Strategies	88
Table 6-2. Overview of Tools Used within Risk Management.....	91
Table 6-3. IMDRF Code Mapping to ISO 14971.....	95
Table 7-1. Comparison of Terminology “Label vs. labeling” in the US and EU	100
Table 7-2. Key Medical Device Labeling Regulations in the US: Code of Federal Regulations	100
Table 7-3. Key Medical Device Labeling Regulations in the EU MDR.....	102
Table 7-4. ISO FDIS 20417: Medical Devices—Information to be Supplied by the Manufacturer	103
Table 9-1. The Universal Elements of GLP.....	124
Table 9-2. Examples of GLP Violations From FDA Warning Letters	125
Table 9-3. Sources of Device Risk.....	126
Table 9-4. Biocompatibility Tests	127
Table 9-5. Medical Device Classification Based on the Nature of Body Contact and Contact Duration	128
Table 9-6. Basic Animal Study Protocol Elements.....	128
Table 9-7. Animal Models for In Vivo Medical Device Assessment.....	130
Table 9-8. International Animal Research Laws, Policies and Guidelines	131
Table 9-9. Useful Web Resources for Planning and Conducting Animal Studies in Accordance with Three Rs Principles.....	131
Table 9-10. Questions a Company Should Consider When Selecting a CRO	132
Table 16-1. Example of a CV Medical Device Company Product Development Matrix	208
Table 16-2. Country-Specific Information from the Handbook of Pharma and MedTech Compliance.....	214
Table 16-3. High-Level Marketing and Advertising Information for Countries in Asia-Pacific.....	215
Table 16-4. High-Level Marketing and Advertising Information for Countries in Europe	216
Table 16-5. High-Level Marketing and Advertising Information for Countries in Latin America and South America.....	217
Table 17-1. African and Middle Eastern Regulatory Agencies	229
Table 17-2. Asia/Pacific Regulatory Agencies	231
Table 17-3. European National Competent Authorities	232
Table 17-4. Eastern European Agencies.....	233
Table 17-5. Latin American Regulatory Agencies	234
Table 17-6. North American Regulatory Agencies	234
Table 17-7. Global Regulatory Professional Trade Organizations.....	236
Table 17-8. Miscellaneous Resources	240
Table 17-9. African/Middle Eastern Intelligence Resources.....	242
Table 17-10. Asia/Pacific Intelligence Resources	242
Table 17-11. European Intelligence Resources.....	242
Table 17-12. Latin American Intelligence Resources.....	243

Table 17-13. North American and Other Critical Intelligence Resources	244
Table 19-1. Summary of Select Revenue-Generating Cell Therapy Products Currently on the Market	276
Table 19-2. Definitions of Manipulations Considered Minimal (US) or Not Substantial (EU)	277
Table 19-3. Summary of Regulatory Routes and Documents Applicable to Stem Cell and/or Device Products	278
Table 21-1. IMDRF SaMD Categories	301
Table 21-2. IMDRF Clinical Evaluation Process.....	302

1

Driving Successful Commercial Product Launches

Flora Sandra Siami, MPH

Introduction

In 2025, the global medical device market was valued at roughly \$570 billion and estimated to reach \$1 trillion by 2034.¹ According to AdvaMed, at 40%, the United States (US) holds the largest percentage of the global medical device market.² Companies can no longer rely solely on regulatory market authorization for their products to be competitive, as their commercial success requires pricing, reimbursement, and market adoption.

However, these elements become challenging as the healthcare delivery model continues to transform owing to continued uncontrollable cost increases, higher healthcare utilization, and increased regulatory scrutiny. Purchasing decisions have been transferred from clinical decision-makers to economic buyers. Payment models have reassigned financial risk from payers (e.g., Fee-for-Service [FSS]) to providers (e.g., Value-Based Care). Therefore, healthcare providers are focused more than ever on controlling costs, being more efficient, and delivering improved patient care.

As these foundational shifts in the healthcare system continue, medical device companies must step out of their traditional role and evolve, focusing on solutions that reduce the cost of care, increase efficiencies, and improve patient outcomes by leveraging data and building intelligence into their products as essential parts of the new device value proposition to the multiple stakeholders within the healthcare delivery system.³ A stakeholder's willingness to pay for a medical device will be tied to its impact on

patient outcomes, cost-effectiveness, and support for quality-based performance metrics.

Companies, more than ever, need to understand the fluctuating landscape for successful commercial device launches. This chapter provides readers, especially those responsible for developing and building a regulatory strategy, with a framework to achieve a successful commercial product launch. Regulatory leaders and leaders from other cross-functional departments must recognize that their strategies and tactics should not be viewed from their perspective alone. Instead, they must understand that they are part of a process that has a patient-centered and market adoption end in mind. To thrive in this transforming healthcare environment, a collaborative cross-functional market access approach must be embraced by everyone in the organization. While a considerable portion of this Chapter discusses the US reimbursement landscape since it is the most complex, the European Union (EU) and other global markets are considered.

Commercialization Through Cross-Functional Collaboration With Market Access Mindset

In the past, when it came to Product Development Plans (PDPs), most medical device manufacturers either rarely considered payment, value, or their end users or only considered some of these factors during product launch. However, in recent years, medical