

Table of Contents

Section I: Quality Management Systems

Chapter 1	Setting up a Quality Management System	1
	By Abhishek Harde, PMP, RAC	
Chapter 2	Medical Device Quality Management Systems	35
	By Gert Bos, MSc, PhD, FRAPS	
Chapter 3	Canadian Medical Device Quality System Requirements	47
	By Karen Fan, MSc, RAC, Peng, Charles Tam, MBA, and Danuta Zylka	
Chapter 4	Quality Systems and Inspectorate Process for Pharmaceuticals	63
	By Siegfried Schmitt, PhD	
Chapter 5	Regulatory Requirements for Design and Process Validation	85
	By Robert V. Packard and Leo Lagrotte	
Chapter 6	Quality Risk Management—A Gateway to Quality by Design.....	93
	By Peter Schiemann, PhD and Beat Widler, PhD	
Chapter 7	Product Lifecycle Management Guidance	105
	By Ajay Babu Pazhayattil, Naheed Sayeed-Desta, and Queenia Lee	

Section II: Laboratory Testing

Chapter 8	Good Laboratory Practice for Nonclinical Laboratory Studies.....	113
	By Navneet Sekhon	
Chapter 9	Nonclinical Laboratory Testing.....	121
	By Dorota Grabowska, PhD and Peter A. Takes, PhD, RAC, FRAPS	
Chapter 10	Medical Device Preclinical Testing	135
	By Jan-Paul van Loon, MSc, PhD and Gert Bos, MSc, PhD, FRAPS	

Chapter 11	Preclinical Testing and Good Laboratory Practice Regulations	145
	By Anu Gaur, PhD, MBA, MSRA, RAC	

Chapter 12	Good Laboratory Practice Regulations	155
	By Kurt Stahl and Jennifer G. Brown, PhD, RAC	

Section III: Production

Chapter 13	Manufacturing	169
	By Andrea Armando, RAC	

Chapter 14	Current Good Manufacturing Practices and Quality System Design	177
	By Joscelyn Bowersock, MS-RA and Richard Vincins, CQP, MCQL, CBA, CQA, RAC	

Chapter 15	Canadian Good Manufacturing Practices and Establishment Licensing	197
	By Bocar Guisse, MSc and Fraidiane Sévigné	

Chapter 16	Impact of Good Manufacturing Practices on Printed Packaging Components	215
	By Debra Goetchius	

Chapter 17	CMC Regulatory Strategy	237
	By Stephen Antonelli and Michael Craig	

Chapter 18	Fundamental Principles for Labeling and Promotion of Prescription Medical Products	247
	By Joanne S. Hawana, MS, JD, Bethany J. Hills, MPH, JD, and Benjamin M. Zegarelli, MS, JD	

Section IV: Clinical Studies

Chapter 19	Clinical Trials, Good Clinical Practice, Regulations, and Compliance	295
	By Anu Gaur, PhD, MBA, MSRA, RAC, Bettina Merz-Nideroest, MPharm, and Andrea Zobel, PhD	

Chapter 20	Canadian Clinical Trial Applications, Good Clinical Practices	313
	By Mahdis Dorkalam, MSc, RHN, and Navneet Sekhon	

Chapter 21	EU Clinical Evaluation and Clinical Investigations	325
	By Loes Pelgrim, MSc and Gert Bos, MSc, PhD, FRAPS	

Chapter 22	Clinical Trials: GCPs, Regulations and Compliance for Drugs, Biologics and Medical Devices	333
	By Monique Carter, MS, RAC and Samantha Zappia, MS, RAC	

Section V: Inspection, Compliance, and Enforcement

Chapter 23	Compliance and Enforcement	377
	By David W. Husman, PhD, ASQ CPGP, RAC and John Rossman, MBEE, RAC	
Chapter 24	FDA Inspection and Enforcement.....	399
	By Robert Rogers, MS, RAC	
Chapter 25	Components of a REMS: Communication Plans and Implementation Systems.....	411
	By Edward Tabor, MD	
Chapter 26	Components of a REMS: Elements to Assure Safe Use	413
	By Edward Tabor, MD	
Chapter 27	Components of a REMS: REMS Assessment.....	419
	By Edward Tabor, MD	
Chapter 28	Risk Management in the Medical Device and Food Industries	423
	By Salma Michor, PhD, MBA, CMgr, CQA, RAC	

Tables

Table 1-1. Key Differences Between ISO 9001 and ISO 13485	1
Table 1-2. Similarities Between ISO 9001 and ISO 13485.....	2
Table 1-3. Comparison of ISO 13485:2003 and ISO 13485:2016.....	6
Table 1-4. Applicability of ISO 13485 in Various Global Jurisdictions.....	12
Table 1-5. Benefits and Barriers to Certification	20
Table 1-6. Certification Body QMS Assessment Objectives, Scope and Criteria	20
Table 1-7. Audit Duration for Medical Device ISO 13485 Audits Based on Staff Numbers	22
Table 1-8. Factors That May Increase or Reduce Audit Durations	22
Table 4-1. PIC/S Member States	78
Table 6-1. Traditional Quality Management vs. QRM Approach.....	101
Table 9-1. The Universal Elements of GLP.....	123
Table 9-2. Examples of GLP Violations From FDA Warning Letters	124
Table 9-3. Sources of Device Risk	125
Table 9-4. Biocompatibility Tests	125
Table 9-5. Medical Device Classification Based on the Nature of Body Contact and Contact Duration	126
Table 9-6. Basic Animal Study Protocol Elements.....	127
Table 9-7. Animal Models for In Vivo Medical Device Assessment.....	129
Table 9-8. International Animal Research Laws, Policies and Guidelines	129
Table 9-9. Useful Web Resources for Planning and Conducting Animal Studies in Accordance With the Three Rs' Principles	130
Table 9-10. Questions a Company Should Consider When Selecting a CRO	132
Table 16-1. Select Resources on Pictogram Use.....	222
Table 17-1. Centralised Procedure Requirements Based on Product Type.....	239
Table 17-2. Regulatory Authorities by Country	239

Table 18-1. Selected FDA Regulations for the Labeling of Prescription Drugs	248
Table 18-2. Selected FDA Regulations for Device Labeling.....	249
Table 18-3. FDA's Categorization of Promotional Materials (21 CFR 202.1(l)).....	250
Table 18-4. Summary of PI Sections Under the PLR, Including Relevant Regulations and Available Guidance	257
Table 18-5. Other Product Claim Types	266
Table 18-6. Risk-Related Sections of the PI Ranked From Most to Least Important.....	271
Table 19-1. Regional Regulatory Authorities	302
Table 19-2. Trial Master File Essential Documents	310
Table 20-1. Contents of a CTA Submission Package.....	317
Table 20-2. Quality Changes-Biologics and Radiopharmaceuticals.....	318
Table 20-3. Quality Changes—Pharmaceuticals.....	319
Table 20-4. Postapproval Requirements	322
Table 22-1. Significant Legislation Relevant to Clinical Trials in the US	335
Table 22-2. Comparison of 21 CFR and ISO-GCP Requirements for Protocol Deviations in Medical Device Clinical Trials..	341
Table 22-3. Comparison of 21 CFR and ISO GCP Requirements for Investigator Responsibilities in Medical Device Clinical Trials..	367
Table 22-4. Comparison of 21 CFR and ISO-GCP Requirements for Recordkeeping in Medical Device Clinical Trials	370
Table 22-5. Comparison of 21 CFR and ISO-GCP Requirements for Device Accountability in Medical Device Clinical Trials ...	370
Table 23-1. Applicability of GxPs to Standardized Market Authorization Application Formats	388
Table 24-1. FDA Enforcement Actions	405
Table 26-1. ETASUs Approved Per Year	414
Table 28-1. Content Deviations Between ISO 14971:2007 and Directive 93/42/EEC on Medical Devices	424

Figures

Figure 1-1. Basic Process Model	3
Figure 1-2. PDCA Cycle in Resource Management.....	4
Figure 1-3. Mandatory Procedures and Documents for ISO 13485:2003.....	11
Figure 1-4. Implementing an ISO 13485:2016 QMS.....	13
Figure 1-5. Sample Schedule for QMS Implementation	15
Figure 1-6. QMS Documentation Defining Responsibilities.....	16
Figure 1-7. Typical QMS Document Hierarchy	17
Figure 1-8. Iterative PDCA Cycle	20
Figure 1-9. ISO 17021 QMS Certification Cycle.....	21
Figure 1-10. Design Process	27
Figure 2-1. Process Flow of Interrelated QMS Processes	36
Figure 2-2. PDCA Methodology.....	37
Figure 2-3. Requirements Clauses in ISO 13485:2016.....	38
Figure 2-4. Design and Development Control Steps	40
Figure 2-5. Influence of Design Controls on the Design Process.....	40
Figure 2-6. Process Validation Decision Tree	43
Figure 2-7. Key Activities for Supplier Control	45
Figure 3-1. MDSAP Audit Sequence	55
Figure 3-2. MDSAP Nonconformity Grading Overview	57
Figure 3-3. MDSAP Nonconformity Grading Matrix	58
Figure 3-4. MDSAP Post-Audit Activities and Timeline.....	59
Figure 4-1. Drug Lifecycle Regulations	63
Figure 4-2. Assessors and Inspectors.....	64

Figure 4-3. EU Legal Instruments	67
Figure 4-4. Inspections as Part of the Drug Approval Process	68
Figure 6-1. Failure Mode and Effect Analysis Cycle.....	96
Figure 6-2. Three-step RPN-based Risk Evaluation	99
Figure 6-3. Example of QRM in Action	100
Figure 9-1. Strategy for Performing Animal Studies.....	128
Figure 16-1. NDC Number Example	218
Figure 16-2. Trade Bottle Label	225
Figure 16-3. Small Container Label (Small Label Exemption Rule).....	225
Figure 16-4. Folding Carton for Pharmaceutical Drug Product	228
Figure 16-5. Biologic Label.....	231
Figure 16-6. Biologic Carton Label.....	231
Figure 19-1. Acceptance of Foreign Clinical Data	301
Figure 19-2. Quality Management System	306
Figure 22-1. Types of Pharmaceutical and Biologic Clinical Trials and Typical Pathway	342
Figure 22-2. Types of Medical Device Clinical Trials and Typical Pathway.....	361
Figure 23-1. TPLC Cycle for Devices.....	379
Figure 23-2. Medical Device Design Control and Review Process	380
Figure 28-1. The Risk Management Process	425
Figure 28-2. Principal Activities for Risk Management	427
Figure 28-3. The Risk Management Process	430

Sidebars

Sidebar 18-1. Enforcement Example Mirapex 9/2008	251
Sidebar 18-2. Enforcement Example Focalin XR 5/2011	265
Sidebar 18-3. Enforcement Example Idelvion, 2/2018.....	269
Sidebar 18-4. Enforcement Example Estrin 6/2018	270
Sidebar 18-5. Enforcement Example Vantas 9/2012.....	273
Sidebar 18-6. Enforcement Example Contrave 5/2017.....	276
Sidebar 18-7. Enforcement Example Muse 5/2004 and 4/1998	277
Sidebar 18-8. Enforcement Examples MiraLax 3/2001 and Patanol 3/2001	279
Sidebar 18-9. Enforcement Example Tasigna 7/2010	284
Sidebar 18-10. Enforcement Example NCS Pearson 8/2015	289

1

Setting up a Quality Management System

By Abhishek Harde, PMP, RAC

Introduction

Building a quality management system (QMS) from scratch can be challenging, especially when the appropriate regulatory standards or compliance guidelines are not followed. Management system standards make best practices available to organizations of all sizes, in all sectors. Any organization can implement a system to improve efficiency and effectiveness and manage its way of doing things by:

- ensuring nothing important is omitted
- clearly defining who is responsible
- describing what to do, why, when, how and where
- ensuring people are not just “doing their own thing”
- ensuring the organization goes about its business in an orderly way¹

Quality management is the set of coordinated activities to direct and control an organization with regard to quality.² Quality management systems are central to the medical device regulatory process in many countries to ensure safe products entering the market perform as intended. Streamlining and automating design documentation and quality processes to align with major industry regulations and standards are key criteria for setting up a quality management system. In this chapter,

the focus is on ISO 9001 and ISO 13485,^{3,4} and subsequently, US FDA’s *Quality System Regulation (QSR)*⁵ contained in 21 CFR 820. ISO 13485:2016 *Medical Devices—Quality Management Systems—Requirements for Regulatory Purposes* is a QMS standard based on ISO 9001 *Quality Management Systems Requirements*. The ISO 9000 series, originally published in 1987, was based on the British Standards Institution’s (BSI) BS 5750 series of standards.⁶ ISO 9001 covers both product quality assurance (providing confidence that quality requirements will be fulfilled) and enhanced customer satisfaction. Key differences between ISO 9001 and ISO 13485 are shown in **Table 1-1**.⁷ Similarities between ISO 9001 and ISO 13485 are shown in **Table 1-2**. The standard can be applied to all products and services. ISO 9001 is based on the eight quality management principles:

1. process approach
2. system approach to management
3. continual improvement
4. factual approach to decision making
5. mutually beneficial supplier relationship
6. customer focus
7. leadership
8. involvement of people⁸

Table 1-1. Key Differences Between ISO 9001 and ISO 13485

ISO 9001	ISO 13485
6 documents	27 documents
Aims for customer satisfaction through continuous improvement	Does not include customer satisfaction and continuous improvement as objectives
Covers all products	Different requirements for different types of products
Basis for voluntary certification	Basis for regulatory certification