



Technical Report No. 54-5

Quality Risk Management for the Design, Qualification, and Operation of Manufacturing Systems

Currently in preview, click buy full version



PDA Quality Risk Management for the Design, Qualification, and Operation of Manufacturing Systems Technical Report Team

Authors

Ghada Haddad, MBA, Merck & Co./Merck Sharp & Dohme, (Chair)

Harold S. Baseman, Valsource, LLC

David Calvaresi, Valsource, LLC

Liza Lamb, Wright Medical Technology

Lori Richter, Genentech Inc/Valsource, LLC

Christopher J. Smalley, PhD, Merck & Company

William Stelzenmuller, Johnson & Johnson

Kelly Waldron, Sanofi and Dublin Institute of Technology

Steve Wisniewski, Commissioning Agents Incorporated

Disclaimer: This technical report was developed as part of PDA's Paradigm Change in Manufacturing Operations (PCMO) project. The content and views expressed in this Technical Report are the result of a consensus achieved by the authorizing Technical Report Team and are not necessarily views of the organizations they represent.

Quality Risk Management for the Design, Qualification, and Operation of Manufacturing Systems

Technical Report No. 74-5

ISBN 978-0-939459-96-4

© 2011 Parenteral Drug Association, Inc.

All rights reserved.



Table of Contents

1.0 INTRODUCTION	1	7.3 Qualification.....	30
1.1 Purpose	1	7.4 Developing the Commissioning and Qualification Strategy.....	31
1.2 Scope.....	1		
1.3 Overview	1		
2.0 GLOSSARY AND ABBREVIATIONS	2	8.0 QUALITY RISK MANAGEMENT IN QUALITY SYSTEMS.....	32
2.1 Acronyms.....	5	8.1 Quality Risk Management for Discrepancy Management System	34
3.0 QUALITY RISK MANAGEMENT BEST PRACTICES..	6	8.1.1 Risk-Based Approach to Categorization of the Discrepancy	35
3.1 Developing the Risk Question	6	8.1.2 Risk Evaluation	36
3.2 Cross-functional Risk Management.....	7	8.2 Risk Assessment to Determine Corrective and Preventive Actions.....	37
3.3 Considerations for Effective and Efficient Risk Assessment	8	8.2.1 Tool Selection	37
3.4 Considerations for Effective and Efficient Risk Control.....	9	8.2.2 Defining Scope and Boundaries	38
3.5 Considerations for Effective and Efficient Risk Review.....	10	8.2.3 Risk Identification.....	38
3.6 Considerations for Effective and Efficient Risk Communication	11	8.2.4 Risk Analysis	38
		8.2.5 Risk Evaluation.....	39
4.0 QUALITY RISK MANAGEMENT APPLICATIONS FOR STRATEGIC PLANNING AND PROJECT INITIATION	13	8.2.6 Risk Documentation	40
4.1 Project Charter	14	8.2.7 CAPA Effectiveness.....	40
4.2 Project Execution Plan.....	14	8.3 Quality Risk Management for Change Management	41
4.3 Quality Risk Management Plan	15	8.3.1 Risk-Based Approach to Categorizing the Change	42
5.0 DEFINING REQUIREMENTS	16	8.3.1.1 Risk Evaluation	42
5.1 User Requirement Specification	16	8.3.1.2 Risk Assessment Activities.....	43
		8.3.1.3 Tool Selection	43
6.0 MANUFACTURING SYSTEM DESIGN	17	8.3.1.4 Risk Assessment	43
6.1 Manufacturing System Characterization	17	8.3.1.5 Risk Evaluation Post Assessment	44
6.1.1 System Characterization by Process Risk Assessment.....	17	8.3.1.6 Risk Documentation	44
6.1.2 System Characterization by System Risk Assessment	21	8.4 Quality Risk Management for Ongoing Monitoring of Manufacturing Systems.....	45
6.1.3 Choosing an Approach to Characterize the System	23	8.4.1 Focus of Ongoing Monitoring.....	45
6.2 Design Risk Assessment	24	8.4.2 Frequency of Ongoing Monitoring	47
6.3 Requirements Traceability Matrix.....	25	8.4.3 Alert/Action Limits	47
6.3.1 Requirements Section.....	26	8.4.4 Investigation and CAPA.....	47
6.3.2 Design Qualification Section	26	8.5 Quality Risk Management for Periodic Assessment/Requalification	48
6.3.3 Commissioning and Qualification Section..	26	8.5.1 Risk Review.....	49
6.4 Design Review in the Quality Risk Management Lifecycle	27	8.5.2 System Robustness	49
		8.5.3 Periodic Assessment and Risk Review Criteria Development.....	51
7.0 QUALITY RISK MANAGEMENT APPLICATION FOR COMMISSIONING AND QUALIFICATION	28	8.5.4 Assessment and Risk Review	51
7.1 Commissioning	28	8.5.5 First- and Second-line Data.....	52
7.2 Risk-based Approach to Determine Appropriate Carry-forward of Testing.....	28	8.5.6 Risk Review.....	53
		8.5.7 Fitness for Intended Use.....	53
		8.5.8 Requalification	54
		8.5.9 Quality Risk Management Application for Decommissioning	54
		9.0 TOOLS AND TEMPLATES	54
		10.0 CONCLUSION.....	61

11.0 REFERENCES	62	13.5 Commission and Qualification Strategy	78
12.0 ADDITIONAL READING	62	13.5.1 Risk Assessment to Determine Deviation Response	80
13.0 APPENDIX I: CASE STUDY 1.....	63	13.5.2 Risk Assessment to Determine Corrective Actions.....	82
13.1 Background.....	63	13.6 QRM for Change Management and CAPA	84
13.1.1 Manufacturing Operations.....	63	13.7 CAPA Effectiveness	87
13.1.2 Project Charter.....	64	14.0 APPENDIX 2: CASE STUDY 2.....	88
13.1.3 Project Execution Plan	64	14.1 Background.....	88
13.1.4 Tool Selection	64	14.2 System Impact Assessment.....	88
13.2 Quality Risk Management Plan (QRMP)	66	14.2.1 Manufacturing System Description.....	89
13.2.1 QRM Application for System Design.....	66	14.2.2 Intended Use Summary	89
13.2.1.1 Quality User Requirements Specifications (URS)	66	14.2.3 Manufacturing System Bound.....	89
13.2.1.2 User Requirement Specification for the New Isolator	67	14.3 User Requirement Specifications.....	89
13.2.1.3 System Description.....	67	14.4 Criticality Assessment	90
13.3 System Characterization	69	14.5 Design Risk Assessment.....	91
13.4 Design Risk Assessment	74	14.6 Requirements Traceability Matrix.....	95

FIGURES AND TABLES INDEX

Figure 3.0-1	Model of Typical Quality Risk Management Process from ICH Q9.....	6	Figure 6.1.1-5	Structure of PRA in an FMEA Model .	19
Table 3.1-1	Example of Risk Question/Statement...	7	Table 6.1.1-2	Process FMEA for Saline Solution Preparation	20
Table 3.2-1	Roles and Responsibilities at the Initiation of the QRM Process.....	8	Table 6.1.1-3	HACCP for Vial Washing and Sterilization.....	20
Table 3.6-1	Example of Risk Communication Matrix	12	Figure 6.1.1-7	Hazard Analysis Structure/HACCP Model.....	20
Figure 4.0-1	ICH Q10 Pharmaceutical Quality System	13	Table 6.1.2-1	Summary of Inputs, Process, and Outputs for a System Risk Assessment (SRA)....	21
Figure 4.0-2	Manufacturing System Lifecycle and Risk Management	13	Table 6.1.2-2	Critical Aspect Identification of a Buffer Preparation System.....	23
Table 4.0-1	Risk Management Intent and Output.....	14	Table 6.1.3-1	Comparison of System Characterization Approaches.....	24
Table 4.2-1	Probability of Occurrence	15	Table 6.2-1	Design Risk Assessment	25
Table 4.2-2	Consequences or Impact.....	15	Table 6.3-1	Example of Requirements Traceability Matrix.....	27
Table 4.2-3	Risk Estimation Matrix.....	15	Table 7.2-1	Scoring Criteria for Risk Level Associated with the Critical Aspect..	28
Table 4.2-4	PEP Risk Assessment	15	Table 7.2-2	Scoring Criteria for Quality and Documentation System Robustness..	29
Table 6.1.1-1	Process QRM Approach	17	Table 7.2-3	Outcomes of Risk Level and Quality System Robustness Scores.....	29
Figure 6.1.1-1	Pharmaceutical Operations Hierarchy	18	Table 7.2-4	Score Criteria for Likelihood of System Change.....	30
Figure 6.1.1-2	Flowchart of Developmental Process	18	Table 7.2-5	Score for Likelihood of System Change.....	30
Figure 6.1.1-3	Simplified Failure Chain.....	18			
Figure 6.1.1-4	Simplified Chain of Failure Mode in the Process FMEA (Process vs. Design)	18			
Figure 6.1.1-5	Failure Mode Chain of CAs at the Component Level	18			

Table 7.4-1	Commissioning and Qualification Strategy Considerations.....	32	Table 13.1.4-3	Example of Consequences or Impact.....	65
Figure 8.0-1	Performance Quality System Focus..	32	Table 13.1.4-4	“Living” Risk Assessment.....	66
Figure 8.0-2	Diagram of the ICH Q10 Pharmaceutical Quality System Model	33	Table 13.2.1.1-1	Factors to Determine CPPs.....	67
Table 8.0-1	Overview of Quality System Processes.....	33	Table 13.2.1.1-2	Quality Requirements for Filling Process	67
Table 8.0-2	Detailed Summary of Quality Processes, Risk Question, and Proposed Methodology.....	34	Table 13.2.1.2-1	Product Fill Specifications or Fill Line Specifications	67
Figure 8.0-3	Overall QRM Integration into PQS....	34	Table 13.2.1.3-1	Process / Product Requirements.....	68
Figure 8.1.1-1	Use of Risk Management in the Discrepancy Management System...	35	Table 13.2.1.3-2	System Design Requirements.....	69
Table 8.1.1-1	Risk Level Definition	36	Table 13.3-1	CQAs and CPPs Associated with Isolator	69
Table 8.1.1-2	Definition for Scoring Criteria	36	Figure 13.3-1	Diagram of FMEA Process	69
Table 8.1.2-1	Risk Matrix	37	Table 13.3-2	Risk Ranking Criteria	70
Table 8.1.2-2	Risk Actions	37	Table 13.3-3	Failure Mode to Create or Sustain CPP	71
Table 8.2.4-1	Detection Definition	39	Table 13.3-4	Failure Mode to Create or Sustain CPP	71
Table 8.2.5-1	Risk Level Matrix with Detection	39	Table 13.3-5	Failure Mode to Create or Sustain CPP	71
Table 8.2.5-2	Table of Risk Actions.....	40	Table 13.3-6	CAs of Isolator System	71
Figure 8.2.7-1	Use of Risk Management in CAPA....	41	Table 13.3-7	Preventative Controls	71
Table 8.3.1-1	Example of Categorization of Changes and Actions	42	Table 13.3-8	Preventative Controls/Probability of Occurrence.....	72
Table 8.3.1.4-1	Example of Severity Risk Definitions ..	44	Table 13.3-9	Detection Controls /Probability of Occurrence	72
Table 8.3.1.4-2	Example of Probability or Likelihood of Occurrence Risk Definitions	44	Table 13.3-10	Likelihood Detection Score for HEPA Filter Failure and Cause.....	72
Table 8.3.1.4-3	Example of Risk Actions based on What-if Analysis	44	Table 13.3-11	Risk Priority Number (RPN) Criteria ..	72
Table 8.3.1.6-1	Example of What-if Analysis	45	Table 13.3-12	Other Potential Risks	73
Figure 8.4.1-1	Typical Chain of Events in a QRM Paradigm	47	Table 13.3-13	Requirements Traceability Matrix (RTM)	73
Table 8.4.4-1	Example of Investigation Focus and CAPA Risk Controls for Excursions Identified during Ongoing Monitoring..	48	Figure 13.4-1	Chain for Failure Effect of Design FMEA 74	
Table 8.5.2-1	Risk Class Matrix.....	50	Table 13.4-2	Failure of the CAs.....	74
Table 8.5.2-2	Risk Priority Classification.....	50	Table 13.4-1	Failure of the CAs (HEPA Filter and In-line Particulate Monitoring).....	74
Table 8.5.2-3	Prior Review Intervals	51	Table 13.4-3	Severity of the CPP-related Failure Effects	75
Figure 8.5.4-1	Assessment and Risk Review Approach	52	Table 13.4-4	Potential CADE Failures.....	75
Table 9.0-1	Formality Spectrum for Selection of Analysis Tool.....	56	Table 13.4-5	Preventative Controls	75
Table 9.0-2	Comparison of Risk Management Tools ..	56	Table 13.4-6	Frequency of Probability of Occurrence	76
Table 13.1.1-1	Systems Requiring Modification	64	Table 13.4-7	Detection Controls for Each Failure Mode Identified.....	76
Table 13.1.4-1	Risk Estimation Matrix	65	Table 13.4-8	Detection Controls for Each Failure Mode Identified.....	76
Table 13.1.4-2	Example of Probability of Occurrence	65			

Table 13.4-9	Risk Level of CADEs.....	77	Table 13.6-1	Categorization of Changes and Actions	85
Table 13.4-10	Requirements Traceability Matrix – Design Qualification (DQ)	78	Table 13.6-2	Categorization of Proposed Changes and Actions	85
Table 13.5-1	Requirements Traceability Matrix – C&Q.....	79	Table 13.6-3	Risk Statement to include Proposed Change.....	85
Table 13.5.1-1	Risk Statement	80	Table 13.6-4	Severity Risk Definitions.....	85
Table 13.5.1-2	Risk Associated with Deviation Event	80	Table 13.6-5	Probability or Likelihood of Occurrence Risk Definitions	86
Figure 13.5.1-1	Quality Risk Management Applications in Quality Systems.....	80	Table 13.6-6	Risk Actions.....	86
Table 13.5.1-3	Example of Severity Risk Level Definitions.....	81	Table 13.6-7	What-if Analysis	86
Table 13.5.1-4	Example of Probability or Likelihood of Occurrence Risk Level Definitions	81	Table 13.6-8	Risks Re-scored to Reflect Identifier High Risks and Mitigation	87
Table 13.5.1-5	Example of Risk Matrix	81	Table 13.6-9	Detection Controls – Reassessment Confirmed	87
Table 13.5.1-6	Example of Risk Actions.....	81	Figure 14.2.1-1	Buffer Preparation and Hold Tank....	88
Table 13.5.1-7	Discrepancy Event	82	Table 14.3-1	Requirements for Buffer Preparation and Hold Tank.....	89
Table 13.5.1-8	Risk Statement	82	Table 14.3-2	CCMP Impact Assessment Requirements.....	90
Figure 13.5.2-1	Documentation Process for Risk Assessment – CAPA.....	82	Table 14.4-1	Identification of Critical Aspects	90
Table 13.5.2-1	Risk Associated with Deviation Event (Initial Deviation Evaluation).....	83	Table 14.5-1	Severity Criteria.....	91
Table 13.5.2-2	Risk Associated with Deviation Event	83	Table 14.5-2	Probability of Occurrence	91
Table 13.5.2-3	Risk Associated with Deviation Event - Modified Detection Control	83	Table 14.5-3	Risk Matrix	91
Figure 13.6-1	Documentation Process for Risk Assessment – Change Management ..	84	Table 14.5-4	Risk Tolerance Matrix.....	92
			Table 14.5-5	Design Risk Assessment	92
			Table 14.6-1	Risk Traceability Matrix for BPH Tank .	95

1.0 Introduction



Identifying and managing risk in the pharmaceutical and biopharmaceutical industry is vital to establishing and enhancing understanding of medicinal products, processes, and production and supporting manufacturing systems to minimize potential negative impacts on patients. The industry and health authorities share the common goal of protecting the quality of the product and public health through the reliable supply of safe and effective medicines. Yet, the processes and systems involved in drug product manufacturing inherently entail some degree of risk. Left unmanaged, this could jeopardize the ability to achieve the goal of manufacturing quality and safe drug products. The application of Quality Risk Management (QRM) principles and practices can be used to ensure that high-quality medicines are available to the patient when needed.

Although ICH Guideline Q9, *Quality Risk Management (1)*, presents general principles of risk management, examples of various risk management tools and potential areas where risk management may be applied, it does not provide details on how to use QRM principles or tools to manage risks throughout the design, qualification, and operation of manufacturing systems (see *PDA Technical Report 54, Implementation of Quality Risk Management for Pharmaceutical and Biotechnology Manufacturing Operations (2)*). In applying QRM to the design, it is possible to determine the potential causes of process failure and identify control elements to manage the failure modes/hazards to an acceptable level of risk.

1.1 Purpose

This technical report provides a practical guide on how to manage quality risks throughout the manufacturing system lifecycle and illustrates concepts through two case studies, thereby bridging the gap.

1.2 Scope

The information in this technical report is applicable to both new and existing manufacturing systems for clinical and commercial drug substances and products, packaging, warehousing, and critical utility systems. It focuses on manufacturing systems determined to have an impact on product quality. The inherent assumption is that each firm will adapt this content according to its specific needs. QRM deliverables should be based on risk to product/patient, novelty, complexity, and design input (level of customization).

This technical report does not represent or replace regulatory requirements or guidances, nor does it establish legally enforceable guidelines.

1.3 Overview

ICHQ9 provides a standard approach for the application of risk management activities to the manufacturing system lifecycle:

The risk management process should be initiated prior to design of the system. Quality Risk Management can be used to focus the design and specification development effort. Process and product knowledge evolve over the course of the pharmaceutical development program. Early planning facilitates appropriate data gathering from Stage 1, Process Design, in which a quality risk assessment is performed subsequent to initially identifying the critical quality attributes and defining the manufacturing process and associated critical process parameters (3).

Due to the pace of change that may occur early in the manufacturing system lifecycle, risk assessments and identified controls may require frequent updates. Manufacturing system definition and design documents should be updated when controls/critical aspects are identified to reduce residual risk to an acceptable level.

Controls/CAs should be incorporated during the design process, verified at design review/design qualification, and verified during the installation and operational test phases of the qualification lifecycle.