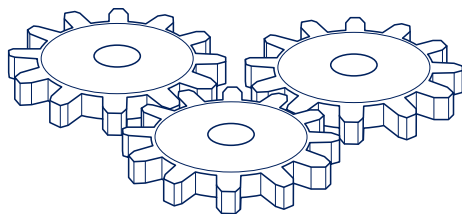


Technical Report No. 54-4

Implementation of Quality Risk Management for Pharmaceutical and Biotechnology Manufacturing Operations

Annex 3: Case Studies in the Manufacturing of Biotechnological Bulk Drug Substances

PCMO[®]
Paradigm Change in
Manufacturing Operations[®]



2014



Implementation of Quality Risk Management for Pharmaceutical and Biotechnology Manufacturing Operations

Annex 3: Case Studies in the Manufacturing of Biotechnological Bulk Drug Substances

Authors

Ruhi Ahmed, Chair, Ph.D., RAC, Ultragenyx
Pharmaceutical Inc.

Derek Blaettler, Genentech

Ursula Busse, Ph.D., Novartis

Eric Dolinski, Biogen Idec

Thomas Genova, Ph.D., Johnson & Johnson

Frank Hallinan, University College Cork

Scott Rudge, Ph.D., RMC Pharmaceutical Solutions Inc.

Raman Srinivasan, Biocon

Abdul Wajid, Ph.D., XOMA

Contributors

Patrick Swann, Ph.D., Biogen Idec

Anurag Rathore, Ph.D., Biotech CMZ

Disclaimer: This technical report annex 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 Task Force and are not necessarily views of the organizations they represent.

Implementation of Quality Risk Management for Pharmaceutical and Biotechnology Manufacturing Operations

Annex 3: Case Studies in the Manufacturing of Biotechnological Bulk Drug Substances

Technical Report No. 54-4

ISBN: 978-0-939459-73-5

© 2014 Parenteral Drug Association, Inc.

All rights reserved.



Paradigm Change in Manufacturing Operations (PCMO®)

PDA launched the project activities related to the PCMO program in December 2008 to help implement the scientific application of the ICH Q8, Q9 and Q10 series. The PDA Board of Directors approved this program in cooperation with the Regulatory Affairs and Quality Advisory Board, and the Biotechnology Advisory Board and Science Advisory Board of PDA.

Although there are a number of acceptable pathways to address this concept, the PCMO program follows and covers the drug product lifecycle, employing the strategic theme of process robustness within the framework of the manufacturing operations. This project focuses on Pharmaceutical Quality Systems as an enabler of Quality Risk Management and Knowledge Management.

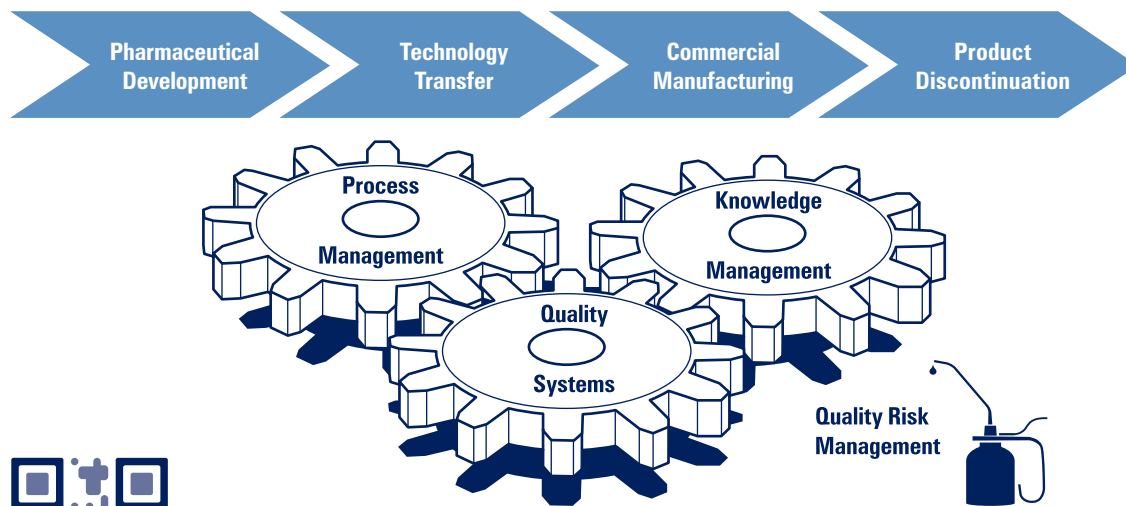
Using the Parenteral Drug Association's (PDA) membership expertise, the goal of the Paradigm Change in Manufacturing Operations Project is to drive the establishment of 'best practice' documents and /or training events in order to assist pharmaceutical manufacturers of Investigational Medicinal Products (IMPs) and commercial products in implementing the ICH guidelines on Pharmaceutical Development (ICH Q8, Q11), Quality Risk Management (ICH Q9) and Pharmaceutical Quality Systems (ICH Q10).

The PCMO program facilitates communication among the experts from industry, university and regulators as well as experts from the respective ICH Expert Working Groups and Implementation Working Group. PCMO task force members also contribute to PDA conferences and workshops on the subject.

PCMO follows the product lifecycle concept and has the following strategic intent:

- Enable an innovative environment for continual improvement of products and systems
- Integrate science and technology into manufacturing practice
- Enhance manufacturing process robustness, risk based decision making and knowledge management
- Foster communication among industry and regulatory authorities

The Product Life Cycle



For more information, including the PCMO Dossier, and to get involved, go to www.pda.org/pcmo

Table of Contents

1.0 INTRODUCTION	1		
1.1 Purpose and Scope	1		
2.0 GLOSSARY OF TERMS	3		
3.0 APPLICATION OF QUALITY RISK MANAGEMENT IN BIOPHARMACEUTICAL MANUFACTURING PROCESSES	5		
3.1 Raw Materials Supply and Excipients	5		
3.1.1 Associated Risks	5		
3.1.2 Suppliers	5		
3.1.3 Critical Raw Materials	5		
3.1.4 Identification and Lot-to-Lot Consistency ...	5		
3.1.5 Storage	6		
3.1.6 Excipients	6		
3.1.7 Raw Material Inventory Management	6		
3.1.8 Summary	8		
3.1.9 Case Study: Raw Materials Associated with Cell-Culture Media	8		
3.1.9.1 Risk Assessment	8		
3.1.9.2 Risk Control	10		
3.1.9.3 Risk Review	10		
3.1.9.4 Risk Communication	10		
3.2 Cell Banking	10		
3.2.1 Process Description	11		
3.2.2 Associated Risks	12		
3.2.2.1 Presence of Infective Agents, Mycoplasma, Virus, Transmissible Spongiform Encephalopathy, and Bovine Spongiform Encephalopathy	12		
3.2.2.2 Facilities and Equipment	13		
3.2.2.3 Personnel	13		
3.2.2.4 Process	13		
3.2.2.5 Testing/Characterization and Documentation of Cell Banks	13		
3.2.3 Summary	13		
3.2.4 Case Study- Process Failure During Cell Banking	13		
3.2.4.1 Risk Assessment	14		
3.2.4.2 Risk Control	14		
3.2.4.3 Risk Review	17		
3.2.4.4 Risk Communication	17		
3.3 Fermentation/Cell Culture	17		
3.3.1 Process Description	17		
3.3.1.1 Seed Culture Expansion in Disposable Shake Flasks	18		
3.3.1.2 Seed Culture Expansion in Bioreactors (Disposable and Fixed Stirred Tank Bioreactors)	18		
3.3.1.3 Production Bioreactor/Fermenter	18		
3.3.2 Associated Risks	19		
3.3.2.1 COAs	19		
3.3.2.2 WCB and MCB	19		
3.3.2.3 Seed Culture Expansion (Shake Flask/Intermediate Bioreactor) ...	20		
3.3.2.4 Production Bioreactor	20		
3.3.2.5 Clarification of Harvest	20		
3.3.3 Summary	21		
3.3.4 Case Study- Bioreactor Operation	21		
3.3.4.1 Risk Assessment	21		
3.3.4.2 Risk Control	23		
3.3.4.3 Risk Review	24		
3.3.4.4 Risk Communication	25		
3.4 Downstream Processes	25		
3.4.1 Process Description	25		
3.4.2 Associated Risks	26		
3.4.2.1 Centrifugation	26		
3.4.2.2 COAs, Operating Parameters, and In-Process Controls for Centrifugation ..	27		
3.4.2.6 COAs, Operating Parameters, and In-Process Controls for Viral Inactivation	33		
3.4.3 Summary	43		
3.4.4 Case Study: Capture Chromatography FMEA for a Protein Therapeutic	43		
4.0 ADDITIONAL APPLICATIONS OF QRM IN BIOPHARMACEUTICAL MANUFACTURING PROCESSES	47		
4.1 Primary Contact Surfaces	47		
4.1.1 System Components and Process Description	47		
4.1.2 Associated Risks	49		
4.1.3 Case Study: Primary Contact Surfaces	51		
4.1.3.2 Risk Control	53		
4.1.3.2 Risk Review	53		
4.1.3.4 Risk Communication	54		
4.2 Extractables/Leachables	54		
4.2.1 Process Description	55		
4.2.2 Associated Risks	57		
4.2.3 Case Study: Extractables and Leachables ...	59		
4.2.3.1 Risk Assessment	59		
4.3 Environmental Controls	60		
4.3.1 Process Description	60		
4.3.1.1 Facility Design	61		
4.3.1.2 Process Flows	61		
4.3.1.3 Facility Access	61		
4.3.1.4 Personnel Hygiene	61		

4.3.1.5 Cleaning, Sanitization, and Decontamination	61
4.3.1.6 Pest Control	62
4.3.1.7 Environmental Monitoring	62
4.3.2 Associated Risks	62
4.3.3 Case Study: Environmental Monitoring.....	62
4.3.3.1 Risk Assessment.....	63
4.3.3.2 Risk Control	65
4.3.3.3 Risk Review	66
4.3.3.4 Risk Communication.....	69

5.0 CONCLUSION.....	70
6.0 REFERENCES.....	71

FIGURES AND TABLES INDEX

Table 3.1.7-1 Risk Factors for Raw Materials and Excipients.....	7	Table 3.3.4-1 Risk Assessment Tool for Ranking Risk.....	21
Table 3.1.9.1-1 Criteria for Severity Categories	8	Table 3.3.4.1-1 QRM Study of Production Bioreactor for the Production of BDS.....	22
Table 3.1.9.1-2 Criteria for Detection Categories	9	Table 3.3.4.2-1 Partial Experimental Design for Cell-Culture Process	24
Table 3.1.9.1-3 Criteria for Occurrence Categories	9	Figure 3.3.4.2-1 Effect of High DO Level and Agitation Speed on CQA Acidic Variants	24
Table 3.1.9.1-4 Rankings Assigned to Different Ranges of RRR Values	9	Table 3.4.1-1 Example of a Process Risk Map for Downstream Operations	26
Table 3.1.9.1-5 Results of Raw Material Risk Assessment	10	Table 3.4.2.2-1 Disk-Stack Centrifuge Operating Parameters and Associated Failure Modes	28
Table 3.2.2-1 Characterization Tests Typically Recommended for MCBs and WCBs	12	Table 3.4.2.2.1-1 Operating Parameters and Associated Failure Modes for Microfiltration	31
Table 3.2.4.1-1 Criteria for Classifying Risk Components	14	Table 3.4.2.3.1-1 Operating Parameters and Associated Failure Modes for Low-pH Viral Inactivation.....	33
Table 3.2.4.1-2 Example of RRR Calculation	14	Figure 3.4.2.4-1 Effect of Equilibration/Wash Buffer Conductivity and Load pH on HCP Removal	35
Table 3.2.4.2-1 Relative Risk Rankings for Causes of Process Failure in a Cell Banking Process	15	Table 3.4.2.4.1-1 Operating Parameters and Failure Modes for Chromatography Columns .	36
Table 3.2.4.2-2 Filtering and Risk Control for Causes of Process Failure in Cell Banking Process	16	Table 3.4.2.5.1-1 Operating Parameters and Failure Modes for Ultrafiltration	39
Figure 3.3.1-1 Steps in Mammalian Cell-Culture and Bacterial Fermentation Process	18	Table 3.4.2.6.1-1 Operating Parameters for VF	41
Table 3.3.2.1-1 COAs Typically Impacted by Cell-Culture Conditions.....	19		
Table 3.3.2.5-1 Classification of Upstream Unit Operations and Their Risk Assessment	20		

Table 3.4.2.8-1	Scale-Up Parameters for Purification Processes.....	42	Table 4.1.3.1-2	Initial Zone Classification of RPNs....	52
Table 3.4.4.1-1	FMEA Risk Category Definitions and Scoring Scales	44	Table 4.1.3.2-1	Initial and Revised RPN Assessments	53
Table 3.4.4.1-2	FMEA of Operational (Input) Parameters for Capture Chromatography Step.....	44	Figure 4.1.3.3-1	Revised Zone Classification of RPN.	54
Figure 3.4.4.1-1	Pareto Chart of RPN Scores for Capture Chromatography Step.....	45	Figure 4.2.1-1	Relationship between Extractables and Leachables	56
Table 3.4.4.1-3	Summary of DoE Results for Capture Chromatography Step	46	Table 4.2.3-1	API X Process Disposables	59
Figure 4.1.1-1	System Components.....	48	Table 4.2.3.1-1	API X Process In-House Culture and Stability Studies	60
Table 4.1.1-1	Properties of System Components...	48	Figure 4.3.3-1	Overview of the PHA Process	63
Table 4.1.1-2	MOCs of Typical Primary Contact Surfaces	49	Table 4.3.3.1-1	Risk Levels Based on RPN	65
Table 4.1.2-1	Examples of Primary Contact Surfaces Risks to Product Quality and Related Hazards	50	Table 4.3.3.3-1	Environmental Monitoring Frequency Based on Criticality and Risk Priority Level	66
Figure 4.1.2-1	QRM Road Map for Primary Contact Surfaces	51	Table 4.3.3.3-2	Criticality Based on Hazard Severity Ranks	66
Table 4.1.3.1-1	Initial RPN Assessment for a Primary Packaging Process	52	Table 4.3.3.3-3	PHA to Establish Risk-Based Environmental Monitoring Frequency ..	68

1.0 Introduction

Biopharmaceutical manufacturing processes are highly complex. These processes make controlling risks throughout the product lifecycle challenging. When regulators and industry make decisions about the development and routine performance of such manufacturing processes, a key objective is the delivery of products with consistent yield and quality over time. This objective is recognized in ICH Guideline Q9, Quality Risk Management (QRM), which states (1):

The manufacturing and use of a drug (medicinal) product, including its components, necessarily entail some degree of risk. The risk to its quality is just one component of the overall risk. It is important to understand that product quality should be maintained throughout the product life cycle such that the attributes that are important to the quality of the drug (medicinal) product remain consistent with those used in the clinical studies.

Therefore, identification and control of risks is essential to achieve such consistency and to ensure product quality and patient safety.

QRM commences during product design and development of the manufacturing process. During this stage, QRM helps companies identify the process parameters and attributes that affect their product's quality, leading to a more thorough understanding of the manufacturing process and ensuring product quality.

QRM should extend from incoming raw materials and excipients through the distribution chain and, ultimately, to the patient. QRM can begin with the identification of the quality target product profile (QTPP) which is a summary of product characteristics that will ensure its quality, safety, and efficacy, and an analysis of user requirements. Applicable variables (e.g., raw materials or process parameters) can be explored through quality by design (QbD) developmental studies to elaborate the variables' effects and the interactions among them (2). In addition, QRM is an iterative process in which each step is driven by significant advances in knowledge that lead to more effective risk control.

It is important to distinguish QRM from QbD, as these two concepts are often confused with one another. QRM is an iterative process of evaluation and mitigation, whereas QbD is a stand-alone process applied at the beginning of an activity, such as, designing a product, developing a process, or building a facility. Like QRM, QbD can be iterative and uses critical quality attributes (CQAs) and other concepts to assess process capability. However, unlike QRM, QbD is often implemented during a "process characterization" phase, i.e., when the process has theoretically already been designed. In this context, QbD principles of exploring the design space through planned experiments to assess process capability are different from QRM, which is used to design the process so that it has certain attributes. Therefore, QbD is often employed in settings where the results of the experiments become a form of risk mitigation (through enhanced process knowledge) and the results become an important part of QRM.

Finally, QRM should become a living part of the product lifecycle. QRM documents should be maintained and updated as new knowledge is gained about the product and process. These documents should be used to improve processes and implement actions designed to minimize the occurrence of future problems.

1.1 Purpose and Scope

This document is one of the final annex to PDA *Technical Report No. 54: Implementation of Quality Risk Management for Pharmaceutical and Biotechnology Manufacturing Operations* (3). In *Technical Report No. 54 (TR No.54)*, the authors provide detailed guidance on the methodology, application and implementation of QRM throughout the product lifecycle. In particular, *TR No.54* addresses QRM application during commercial manufacturing and the integration of QRM into a pharmaceutical quality management system. The annexes to TR No. 54 consist of case studies that illustrate the various applications of QRM.