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

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Paradigm Change in Manufacturing Operations®

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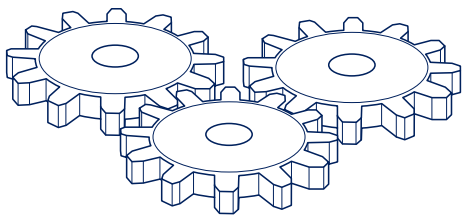

PDA®
Parenteral Drug Association

Implementation of Quality Risk Management for Pharmaceutical and Biotechnology Manufacturing Operations

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

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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.

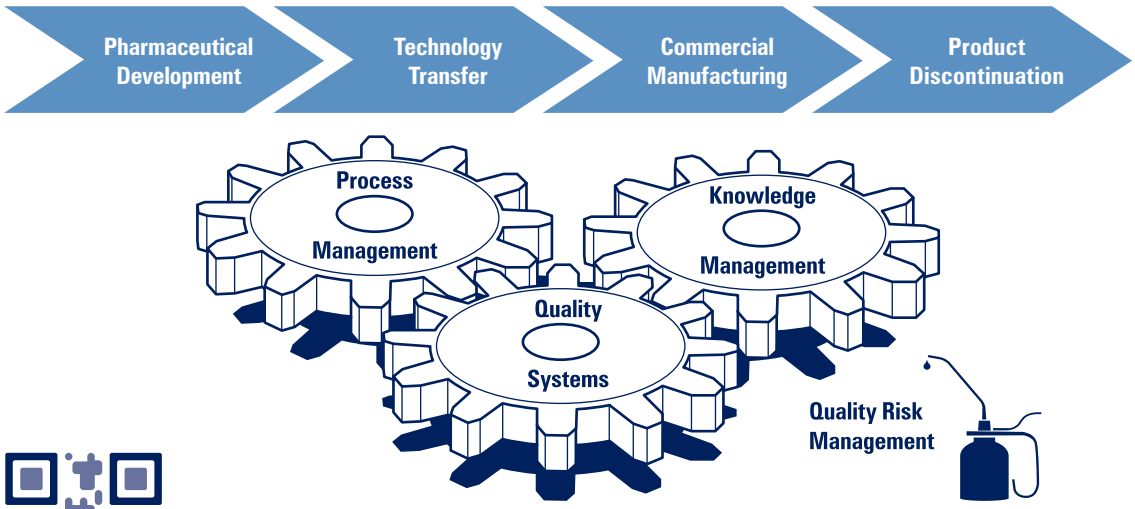
Using the Parenteral Drug Association's (PDA) membership expertise, the goal of the Paradigm Change in Manufacturing Operations Project is to drive the establishment of 'best practice' documents and /or training events in order to assist pharmaceutical manufacturers of Investigational Medicinal Products (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

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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.

The goal of this Technical Report is to provide detailed examples of characteristic operations and case studies that demonstrate the value of implementing QRM to effectively manage risks during pre-commercial manufacturing operations. Each section of this technical report begins with an overview of a stage of the biopharmaceutical manufacturing process and the typical risks associated with that stage, followed by a case study demonstrating how to apply a QRM tool to control, mitigate, and/or eliminate risks during that stage of production. This report also includes a section on the application of QRM to additional factors that can affect biopharmaceutical manufacturing, such as primary contact surface for drug substance, extractables/leachables in the process stream, and environmental controls.

QRM applications that are related to manufacturing/contract manufacturing, supply chain, labeling/packaging, shipping, technology transfers and post-approval changes are out of scope for this annex.

Since every product and process is unique, it is not possible to provide case studies and examples that fit every aspect of biotechnological manufacturing. Furthermore, although there are many risk management tools available, the choice of a QRM tool used by the authors is guided by many factors, such as, type of risk, phase in the manufacturing process, company culture, or experience with methodology, resources available, etc. ***(1).*** The examples in this technical report are not all-inclusive (or exclusive) and are not meant to replace or redefine regulatory guidance and expectations. They are for illustrative purposes only and are not to be used as regulatory standards.

