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Technical Report No. 56 (Revised 2016)

Application of Phase-Appropriate Quality System and cGMP to the Development of Therapeutic Protein Drug Substance (API or Biological Active Substance)

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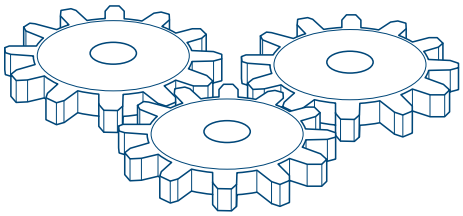

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PDA Application of Phase-Appropriate Quality System and cGMP to the Development of Therapeutic Protein Drug Substance (Revised 2016) Technical Report Team*

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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 life cycle, 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.

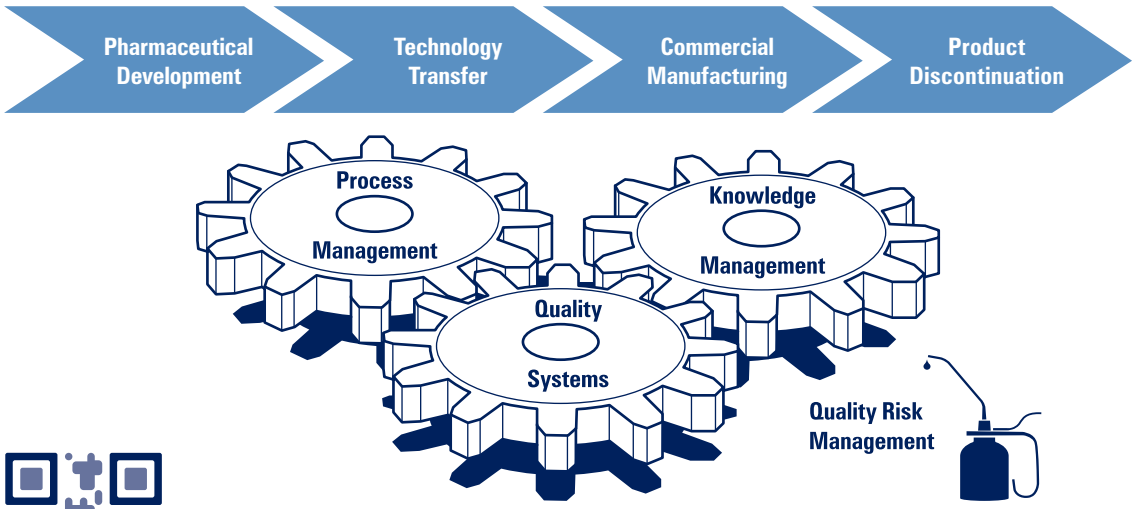
Using the Parenteral Drug Association's (PDA) membership expertise, the goal of the Paradigm Change in Manufacturing Operations Project is to drive the establishment of 'best practice' documents and /or training events in order to assist pharmaceutical manufacturers of Investigational Medicinal Products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



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1.0 Introduction

This technical report provides an overview of the ideal state for good manufacturing practices (GMPs) throughout the product life cycle. GMPs become more stringent as a product progresses through the discovery/R&D stage, the clinical trial phases, and commercial launch. This is described as a "Graded-" or "Phase-Appropriate" approach.

This report also describes a basic framework for clinical trial manufacturing for sites where full commercial development and/or manufacturing may not be the organizational goal (e.g., university/grant-funded investigators, start-up biotech firms). The graded, phase-appropriate approach should enable sponsors to supply safe clinical materials for studies in humans while maintaining manufacturing flexibility at noncommercial scales, and during scale-up and process transfer to commercial facilities. Some companies find benefit in creating a development, or R&D, quality system that is specifically tasked with oversight of the quality and compliance of clinical materials and the control and documentation processes associated. This report is not intended to serve as a regulatory guidance.

1.1 Purpose and Scope

The purpose of this technical report is to define current GMP, or cGMP, principles for the manufacture of premarketing therapeutic bulk drug substance and provide examples of approaches for cGMP compliance during clinical studies. The examples provide an overview of the expectations across regulatory authorities as a drug substance proceeds from the discovery/R&D stage through completion of Phase 3 clinical trials.

The scope of this technical report covers phase-appropriate cGMP during the manufacturing of therapeutic protein drug substance (biological active substance) from the R&D stage through completion of Phase 3 clinical trials ***(1).*** The scope also includes implementation of a pharmaceutical quality system that ensures the safety and quality of products intended for use in clinical trials ***(2).*** Finally, it provides the basis for subsequent assurance of the equivalence of products used in trials to products submitted for marketing approval. This report will focus on current best practices. The term "CGMP" is applied in this technical report to regulatory requirements, guidance, assessment and practice of current GMP, while the use of "CMC (Chemistry Manufacturing and Controls)" is applied to differentiate manufacturing systems, areas, materials, QC testing and stages of product development.

The implementation of a phase-appropriate cGMP compliant Quality System ensures that CMC submission/dossier requirements for therapeutic proteins at the premarketing phase are addressed as needed ***(3,4).*** For additional information, see **Section 8.0** Recommended Reading. Although the scope of this document describes cGMP requirements, there are many critical CMC related issues that must be addressed during the phases of clinical development of a biopharmaceutical; especially in the area of cell line development and safety (refer to **Section 6.0).** The Development Quality System provides a framework for properly addressing both cGMP and CMC requirements on a regular basis during the clinical phases.

cGMP requirements for finished drug product manufacturing are outside the scope of this report.

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