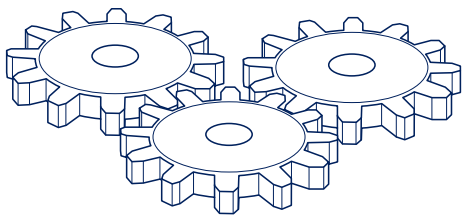
Technical Report No. 68

Risk-Based Approach for Prevention and Management of Drug Shortages

PCMO®
Paradigm Change in Manufacturing Operations®

2014



PDA®
Parenteral Drug Association

www.pda.org/bookstore

PDA Risk-Based Approach for Prevention and Management of Drug Shortages Technical Report Team

Authors

Emabelle Ramnarine, Genentech, (Chair)

Maik Jornitz, G-CON Inc.

Michael A. Long, Dr.LP., Concordia ValSource

Kevin O'Donnell, Health Products Regulatory Authority (formerly Irish Medicines Board)

Stephan Rönninger, Dr.-Ing., Amgen

Christopher Smalley, Merck Sharp & Dohme

Anders Vinther, Ph.D., Sanofi Pasteur

Disclaimer: This technical report is part of the inter-association collaborative contribution to the EMA (European Medicines Agency) Initiative on medicinal product shortages caused by manufacturing and GMP compliance issues. The content of this technical report represents a consensus and not necessarily the views of the organizations that employ the team members.

Risk-Based Approach for Prevention and Management of Drug Shortages

Technical Report No. 68

ISBN: 978-0-939459-71-1

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.

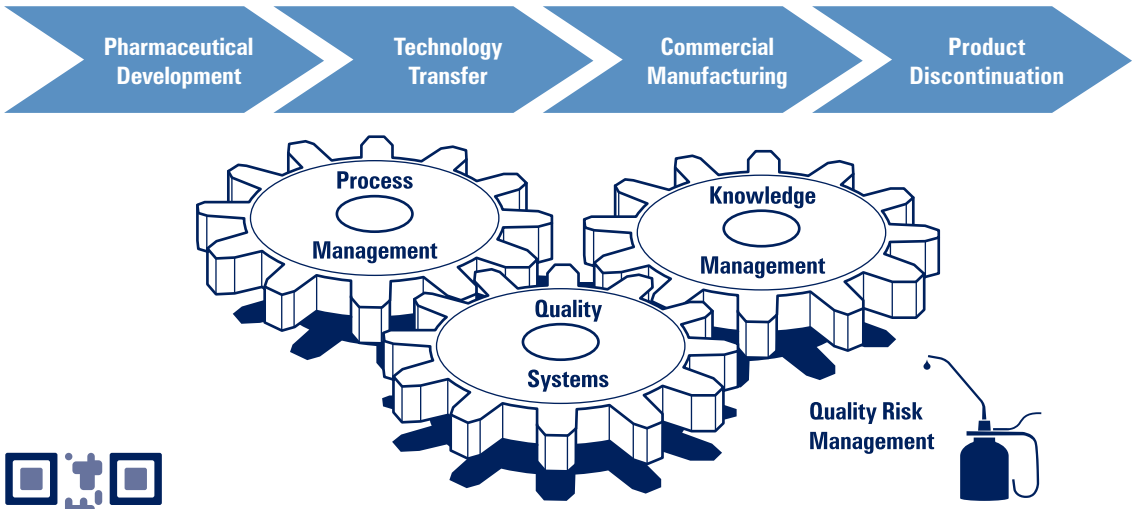
Using the Parenteral Drug Association's (PDA) membership expertise, the goal of the Paradigm Change in Manufacturing Operations Project is to drive the establishment of 'best practice' documents and /or training events in order to assist pharmaceutical manufacturers of Investigational Medicinal Products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

FIGURES AND TABLES INDEX

1.0 Introduction

Sustainable access to safe, efficacious, high-quality products every time a patient needs them is just as important as the tremendous therapeutic advances that have transformed the lives and survival of patients worldwide. The International Conference on Harmonization (ICH) quality guideline on risk management, Q9, defines harm as "damage to health, including damage that can occur from loss of product quality or *availability*" ***(1).*** Ensuring *uninterrupted* availability of and access to products, especially medically necessary products that do not have effective alternatives, is essential.

Unfortunately, drug shortages have become more frequent and severe globally since the early 2000s for a variety of reasons ***(2).*** As globalization of the industry increases, the complexity of supply chains grows, global and regional regulatory expectations continue to evolve, and economic and business motivators change. The drivers behind drug shortages in different geographic areas and countries vary, and causes are usually multifactorial. The range of causes includes financial, economic, and business concerns, increased or unanticipated market demand, evolving regulatory expectations, manufacturing, quality, good manufacturing practice, capacity, lack of redundancy, and supply chain issues ***(2,3).*** A high percentage of drug shortages are related to sterile injectable products especially at specialized facilities such as those preparing toxic (oncolytic) products—and a majority of these shortages in the United States are caused by manufacturing and quality issues ***(4-7).***

The emerging global challenge of supply disruptions is drawing greater focus from the pharmaceutical industry, regulators, legislators, healthcare providers, patient organizations, and patients. Drug shortages are also now covered to a much larger extent in the public press. The legislation and regulatory processes for shortage-related issues are continuing to evolve. In 2012, the European Medicines Agency (EMA) published a reflection paper and an implementation plan for drug shortages that affect patients ***(8,9)***. In 2013, the United States Food and Drug Administration (FDA) established a Drug Shortage Task Force, which published a strategic plan for preventing and reducing drug shortages ***(10).*** Notification of a potential drug shortage to relevant health authorities is a legal requirement in many countries. Early and timely notifications have had a positive impact in reducing the number of shortages by enabling manufacturers and health authorities to jointly take steps to reduce supply disruption ***(10).***

It is essential for the executive management of a firm to have control of and be accountable for ensuring uninterrupted supply of their products. Their decisions can not only impact a firm's ability to cause shortages, but also to prevent and recover from shortages in an expedient manner. Principles of quality risk management (QRM) are fundamental for proactive prevention of drug shortages and to enable risk-based decision-making by both companies and health authorities.

Moving beyond timely notification requirements, the health authorities and pharmaceutical industry are now undertaking more proactive efforts to prevent drug shortages. As a follow-up to EMA's reflection paper, an EMA workshop was held in October 2013 involving many stakeholders. From this workshop an inter-associations drug shortages team was formed to work on solutions to address prevention and communication of drug shortages caused by manufacturing and quality related disruptions.

- The Parenteral Drug Association (PDA) and the International Society for Pharmaceutical Engineers (ISPE) were chartered to deliver proposals and plans for the prevention of drug shortages caused by manufacturing and quality problems. PDA and ISPE both represent individual members from across the pharmaceutical industry.
- The industry trade associations European Federation of Pharmaceutical Industries and Associations (EFPIA), European Generic Medicines Association (EGA), Association of the European Self-Medication Industry (AESGP) and Plasma Protein Therapeutics Association (PPTA) were chartered to deliver harmonized communication principles and a reporting framework between the marketing authorization holder and the regulatory authorities. The trade associations represent the industry with corporate memberships; EFPIA also represents domestic associations in European countries.

1.1 Purpose and Scope

As a contributor to the inter-associations drug shortage project mentioned above, PDA has developed this technical report. The following aspects for proactive prevention of drug shortages will be addressed in this report:

1. A holistic, risk-based framework at a product level for prevention and management of drug shortages caused by manufacturing and quality issues.

2. A risk triage model that can be used to assess drug shortage risks and implement appropriate controls in the end-to-end value chain for manufacturing and distribution of a product.

3. Templates for developing a Drug Shortage Risk Register and a Drug Shortage Prevention and Response Plan at a product level.

The framework provided in this report also supports and enables marketing authorization holders and manufacturers to meet the requirements of Section 506C of the Federal Food, Drug and Cosmetic Act ***(11)*** and Article 13 of the EU GMP Directive 2003/94/EC ***(12),*** to notify relevant health authorities in the event of a drug shortage.

Development of PDA's risk-based approach for prevention and management of drug shortages started in 2012 as part of the Paradigm Change in Manufacturing Operations (PCMO®) project. An overview of the risk-based approach was published in April 2014 in a *PDA Letter* article ***(13)*** and is elaborated in detail in this technical report. PDA also held a drug shortage workshop in September 2014; key outcomes from the workshop have been incorporated into this technical report. Additionally PDA's *Technical Report No. 54* series of best-practice and companion case study documents, *Implementation of Quality Risk Management for Pharmaceutical and Biotechnology Manufacturing Operations* ***(14)*** provide detailed guidance and practical application on how to implement QRM for management of product quality risks in manufacturing operations, supply chains, and operations of third parties (e.g., suppliers, contract manufacturers). PDA *Technical Report No. 59: Utilization of Statistical Methods for Production Monitoring* describes additional risk-based activities that use statistical methodologies for quality control and manufacturing ***(15).***

