PQLI®

Guide Series

Product Quality Lifecycle Implementation (PQLI®)
from Concept to Continual Improvement

Part 3 – Change Management System as a Key Element of a Pharmaceutical Quality System



AVA Documents
Document Sharing Hub

Full document details: ISPE Guide Series PQLI Part 3 - Change Management System as a Key Element of a Pharmaceutical Quality System 2012

Documents
Document Sharing Hub

Full document details: ISPE Guide Series PQLI Part 3 - Change Management System as a Key Element of a Pharmaceutical Quality System 2012

PQLI®
Guide Series

Product Quality Lifecycle Implementation (PQLI®)
from Concept to Continual Improvement

Part 3 – Change Management System as a Key Element of a Pharmaceutical Quality System

Disclaimer:
This Guide aims to describe potential product lifecycle approaches to a change management system within a Pharmaceutical Quality System. ISPE cannot ensure and does not warrant that a system managed in accordance with this Guide will be acceptable to regulatory authorities. Further, this Guide does not replace the need for hiring professional engineers or technicians.

Limitation of Liability
In no event shall ISPE or any of its affiliates, or the officers, directors, employees, members, or agents of each of them, be liable for any damages of any kind, including without limitation any special, incidental, indirect, or consequential damages, whether or not advised of the possibility of such damages, and on any theory of liability whatsoever, arising out of or in connection with the use of this information.

© Copyright ISPE 2012. All rights reserved.

No part of this document may be reproduced or copied in any form or by any means – graphic, electronic, or mechanical, including photocopying, taping, or information storage and retrieval systems – without written permission of ISPE.

All trademarks used are acknowledged.

ISBN 978-1-936379-46-0

Documents
Document Sharing Hub

Full document details: ISPE Guide Series PQLI Part 3 - Change Management System as a Key Element of a Pharmaceutical Quality System 2012

Preface

The ISPE Product Quality Lifecycle Implementation (PQLI) Good Practice Guide (GPG): Change Management System is Part 3 of the ISPE Guide Series: PQLI from Concept to Continual Improvement, which is a product of the ISPE PQLI program.

The modern pharmaceutical quality system described in ICH Q10 is a holistic approach which helps to facilitate the consistent development and production of high quality pharmaceutical products. The ISPE PQLI GPG: Change Management System describes potential product lifecycle approaches to the change management system element of a pharmaceutical quality system. These approaches can help to achieve the opportunities described in ICH Q10.

AVA Documents
Document Sharing Hub
Full document details: ISPE Guide Series PQLI Part 3 - Change Management System as a Key Element of a Pharmaceutical Quality System 2012

Acknowledgements

This Guide was produced by an individual Task Team led by Rob Hughes of AstraZeneca (Chair). The work was supported by the ISPE PQLI Technical Committee.

Change Management Core Team

Rob Hughes (Chair)	AstraZeneca	United Kingdom
Lilian Hamilton	AstraZeneca	Sweden
Claire Myles	formerly of AstraZeneca	United Kingdom
Susan L. Schebler	Eli Lilly	USA
Mike James	GlaxoSmithKline	United Kingdom
Ron Taticek	Genentech, Inc.	USA

Corresponding Team

Michael Choi	Teva Pharmaceutical	USA
Bernd Boedecker	Trade & Industry Inspection Agency (German Inspectorate)	Germany
Gregory Tewalt	Samsung BioLogics	South Korea
Takeshi Takashima	Powrex Corp. / ISPE Japan	Japan

ISPE PQLI Technical Committee

Gretchen Allison	Pfizer Inc.	USA
Joanne Barrick	Eli Lilly	USA
John Berridge	Consultant	USA
Bruce Davis	Bruce Davis Global Consulting	United Kingdom
Ranjit Deshmukh	MedImmune	USA
Joe Famulare	Genentech, Inc.	USA
Rob Hughes	AstraZeneca	United Kingdom
John Lepore	Merck & Co., Inc.	USA
Line Lundsberg-Nielsen	NNE Pharmaplan	United Kingdom
Roger Nosal	Pfizer Inc.	USA
Chris Potter (Co-Chair)	Consultant and PQLI Technical Project Manager	United Kingdom
Steve Tyler (Chair)	Abbott Laboratories	USA

The Task Teams wish to thank the PQLI Chair, Chuck Hoiberg, for his valuable contribution during the preparation of this document and ISPE for technical writing and editing support by Chris Potter (ISPE Technical Consultant), Gail Evans (ISPE Guidance Documents Writer/Editor), and Sion Wyn (ISPE Technical Consultant).

Documents
Document Sharing Hub
Full document details: ISPE Guide Series PQLI Part 3 - Change Management System as a Key Element of a Pharmaceutical Quality System 2012



Connecting a World of
Pharmaceutical Knowledge

ISPE Headquarters
600 N. Westshore Blvd., Suite 900, Tampa, Florida 33609 USA
Tel: +1-813-960-2105, Fax: +1-813-264-2816

ISPE Asia Pacific Office
73 Bukit Timah Road, #04-01 Rex House, Singapore 229832
Tel: +65-6496-5502, Fax: +65-6336-6449

ISPE China Office
Suite 2302, Wise Logic International Center
No. 66 North Shan Xi Road, Shanghai, China 200041
Tel +86-21-5116-0265, Fax +86-21-5116-0260

ISPE European Office
Avenue de Tervueren, 300, B-1150 Brussels, Belgium
Tel: +32-2-743-4422, Fax: +32-2-743-1550

www.ISPE.org

Documents
Document Sharing Hub

Full document details: ISPE Guide Series PQLI Part 3 - Change Management System as a Key Element of a Pharmaceutical Quality System 2012

Table of Contents

1 Introduction 7
1.1 Background 7
1.2 Purpose 8
1.3 Scope 9
1.4 Benefits 9
1.5 Key Concepts 9
1.6 Structure of this Guide 10

2 Alternative Models of a Pharmaceutical Quality System 11
2.1 PQS Based on CGMPs 11
2.2 PQS Based on ICH Q10 11
2.3 PQS Based on ISO 9001 12

3 Change Management System 15
3.1 Introduction 15
3.2 Change Management System Principles 15
3.3 Change Management System Model 16
3.4 Change Management in the Product Lifecycle 27
3.5 Change Management of Design Space and Control Strategy 33

4 Appendix 1 – High Level Change Proposal or Change Request 37

5 Appendix 2 – ICH Q10 Product Lifecycle Case Studies 39
5.1 Pharmaceutical Development 40
5.2 Technology Transfer 41
5.3 Commercial Manufacturing 42
5.4 Product Discontinuation 44

6 Appendix 3 – References 47

7 Appendix 4 – Glossary 49
7.1 Acronyms 50
7.2 Definitions 50

AVA Documents
Document Sharing Hub
Full document details: ISPE Guide Series PQLI Part 3 - Change Management System as a Key Element of a Pharmaceutical Quality System 2012

Documents
Document Sharing Hub

Full document details: ISPE Guide Series PQLI Part 3 - Change Management System as a Key Element of a Pharmaceutical Quality System 2012

1 Introduction

1.1 Background

The modern Pharmaceutical Quality System (PQS) described in ICH Q10 [1] is a holistic approach which helps to facilitate the consistent development and production of high quality pharmaceutical products. It also aims to support innovation and continual improvement of products, processes, and methodologies in accordance with the concepts described in ICH Q8 (R2) [2] using knowledge management and quality risk management, (see ICH Q9) [3].

A modern PQS is considered key to enabling the effective implementation of ICH Q8 (R2) and Q9.

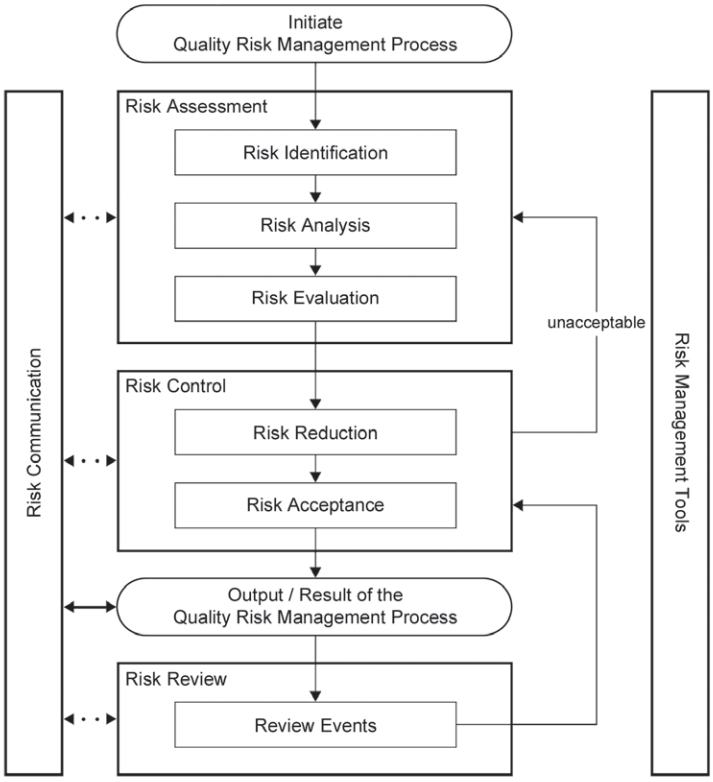
As part of the approach to support the implementation of modern quality thinking and design strategies, ICH Q8 (R2) aims to allow manufacturers to apply more effective control over the management and implementation of changes for drug products which have been developed using the principles of Q8 (R2). It also encourages the assessment of process performance and monitoring of product quality.

ICH Q8 (R2) is one in a suite of complementary ICH guides that define and encourage a modern approach to pharmaceutical quality management. It defines key concepts such as design space and control strategy, and is considered a key enabler in the acquisition, development, and transfer of knowledge for drug products.

ICH Q11 [4] provides further clarification on the principles of ICH Q8 (R2), ICH Q9, and ICH Q10 as they relate to the development and manufacture of drug substance (API).

ICH Q9 provides guidance on the principles of quality risk management and the use of quality risk management tools. These tools can enable more effective and consistent risk-based decisions across the product lifecycle (see Figure 1.1).

Figure 1.1: Overview of a Typical Quality Risk Management Process (from ICH Q9)



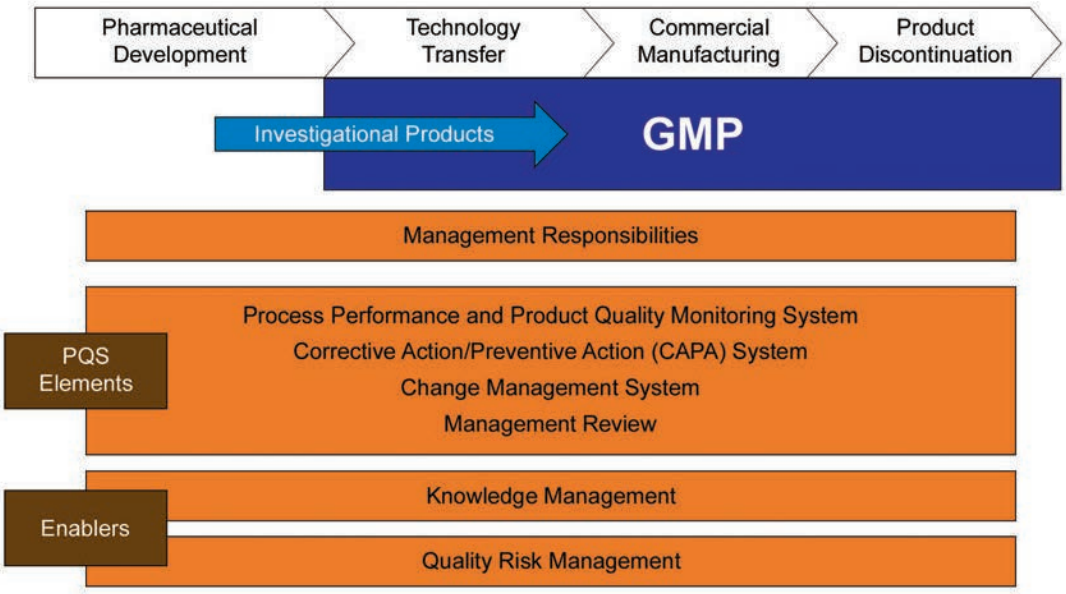
Documents
Document Sharing Hub
Full document details: ISPE Guide Series PQLI Part 3 - Change Management System as a Key Element of a Pharmaceutical Quality System 2012

ICH Q10 describes a lifecycle approach to a PQS, from development through product discontinuation. The knowledge about a pharmaceutical product and the processes required to reliably produce that product starts with product and process development. An effective PQS uses the knowledge acquired throughout the lifecycle of the product, builds on that knowledge, and applies it to:

- Other stages of the product lifecycle
- Other product lifecycles

A change management system is an important element of a PQS as seen in Figure 1.2 – reproduced from ICH Q10, [1], which illustrates the major features of the ICH Q10 PQS model over the product lifecycle.

Figure 1.2: Diagram of the ICH Q10 Pharmaceutical Quality System (from ICH Q10)



The ICH Q10 model also describes management responsibilities and specifies the four elements of a PQS (ICH Q10 Section 3.2) as:

1. Process Performance and Product Quality Monitoring System
2. Corrective Action and Preventive Action (CAPA) System
3. Change Management System
4. Management Review of Process Performance and Product Quality

A change control system which is a GMP requirement is described in ICH Q7 [5]; however, a change management system which is discussed in ICH Q10 is considered much broader in scope.

1.2 Purpose

The purpose of this Guide as a key element of a pharmaceutical quality system is to describe potential product lifecycle approaches to the change management system element of a PQS (ICH Q10 Section 3.2). These approaches can help to achieve the opportunities described in ICH Q10.

AVA Documents
Document Sharing Hub
Full document details: ISPE Guide Series PQLI Part 3 - Change Management System as a Key Element of a Pharmaceutical Quality System 2012

The principles described in this Guide also can be applied to alternative PQS approaches that organizations may choose to implement.

The Guide aims to:

1. Describe different interpretations of PQSs, based on regional GMPs, ICH Q10 guidance, and ISO standards, to help meet regulatory expectations.

2. Provide clear guidance on achieving compliant change management systems.

3. Describe how to implement compliant change management systems within a PQS with example case studies.

4. Demonstrate the inter-relationship between ICH Q8 (R2), ICH Q9, and ICH Q10.

1.3 Scope

This Guide aims to provide descriptions of good practices for change management.

Good practices can apply to products and processes developed using minimal or enhanced, Quality by Design (QbD) approaches as discussed in Appendix 1 of Q8 (R2) [2]. Changes may occur as a response to a problem-solving activity or due to a corrective action resulting from an investigation, even when using the minimal QbD approach. Some form of change management system is required regardless of the type of quality system used.

Note: good practices described in this Guide also may be applied to drug substance (API) manufacture as given in the change control Section 13 of ICH Q7, Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients [5].

1.4 Benefits

The benefits of this Guide as applied to products and processes developed using minimal or enhanced, QbD approaches as discussed in ICH Q8 (R2) and Q11 include:

1. Facilitating a compliant and consistent approach to the implementation of change management.

2. Provision of practical guidance on the use of ICH Q9 in the context of change management within a modern PQS.

3. Description of approaches to change management within a PQS which are consistent with GMP regulations and ISO standards.

1.5 Key Concepts

The key concepts in this Guide include:

1. The lifecycle approach, as promoted in ICH Q10; using a consistent change management model throughout.

2. The role of the change process steward and how that can be applied in national and multi-national settings.

3. ICH Q10 and ISO 9001 quality systems and how they can be applied to assist GMP compliance in a modern PQS setting.

AVA Documents
Document Sharing Hub
Full document details: ISPE Guide Series PQLI Part 3 - Change Management System as a Key Element of a Pharmaceutical Quality System 2012

1.6 Structure of this Guide

The Guide is structured as follows:

1. Introduction
2. Description of Alternative Models of a Quality System
3. Change Management System
4. Case Studies
5. Glossary

Documents
Document Sharing Hub
Full document details: ISPE Guide Series PQLI Part 3 - Change Management System as a Key Element of a Pharmaceutical Quality System 2012

2 Alternative Models of a Pharmaceutical Quality System

The range of Pharmaceutical Quality Systems (PQSs) that could be implemented should be evaluated to determine which best meets the need of the respective company. These systems may range from a PQS based on CGMP requirements to a system based on ISO 9001. The PQS selected can affect prospective change management system options, as well as other features of the PQS which also may affect the change management system (see Table 2.1).

PQSs must remain in compliance with regional GMP requirements. These requirements and guidance provided in ICH Q7 provide a foundation for ICH Q10-based PQSs.

In an ISO 9001 quality system, selected business processes should be mapped and agreed. Personnel should be trained in these selected business processes. In an organization operating an ISO 9001 system, these business processes (e.g., financial management) are made transparent.

The main differences between a PQS based on ICH Q10 and a PQS based on ISO 9001 or CGMPs relate to the extent of:

- Continual improvement initiatives
- Senior management responsibilities

A change management system is a GMP requirement regardless of the PQS used, but the extent of application of a change management system will depend on the PQS.

2.1 PQS Based on CGMPs

A PQS based on CGMPs is the traditional approach operated by the pharmaceutical industry. It consists of complying with a set of regional GMPs that are applied by regulatory authorities worldwide. Although the details of GMPs may vary between regulatory authorities, the basic principle is to ensure patient safety through application of the GMPs. Organizations must comply with the GMP requirements of the countries or regions to which they are supplying product; therefore, compliance with regional GMPs sets a minimum standard for a PQS. Organizations may choose to set higher standards, e.g., in the case of ICH Q10.

2.2 PQS Based on ICH Q10

The key benefit of implementation of an ICH Q10-based PQS across a product lifecycle is that it helps to implement the Quality by Design (QbD) concepts of ICH Q8 (R2). An ICH Q10 quality system:

- Strengthens the links between pharmaceutical development and commercial manufacturing activities
- Helps to facilitate innovation and continual improvement

Organizations that implement an ICH Q10-based PQS should be able to demonstrate an improved understanding of the development and manufacturing processes that impact product quality. This insight should enable more effective evaluation of the potential impact of change and may allow organizations to make changes under their PQS, without necessarily having to file a post approval regulatory application/supplement. In addition, ICH Q10 describes the role that senior managers have in assessment and review of the PQS.

AVA Documents
Document Sharing Hub
Full document details: ISPE Guide Series PQLI Part 3 - Change Management System as a Key Element of a Pharmaceutical Quality System 2012

In an ICH Q10-based PQS, continual improvement is focussed on development and manufacturing processes that have a direct impact on product quality. Underlying business processes that may indirectly impact quality (e.g., the full development process, the process for financial management) may not be mapped within an ICH Q10 PQS; therefore, senior management responsibilities do not include these business processes.

2.3 PQS Based on ISO 9001

According to the ISO website, *"The ISO 9000 family of standards represents an international consensus on good quality management practices. ISO 9001:2008 is the standard that provides a set of standardized requirements for a quality management system, regardless of what the user organization does, its size, or whether it is in the private, or public sector. It is the only standard in the family against which organizations can be certified – although certification is not a compulsory requirement of the standard. The ISO 9001:2008 standard provides a tried and tested framework for taking a systematic approach to managing the organization's processes so that they consistently turn out product that satisfies customers' expectations."*

ISO 9001 is a widely adopted standard that is used as the basis for the ICH Q10 approach. In an ISO 9001 quality system, selected business processes are mapped, therefore helping to facilitate innovation and continual improvement across business processes that impact on customers' expectations, i.e., a broader scope than ICH Q10. Senior management responsibilities include review of these business processes.

Table 2.1 shows the relationship between ICH Q10 quality system features and whether these features would be achieved under the three different models of a GMP, ICH Q10, and ISO 9001-based PQS. As regulatory authorities adopt elements of ICH Q8 (R2), ICH Q9, and ICH Q10 the requirements for a PQS may move from the current GMP-based approach to an ICH Q10-based approach.

Documents
Document Sharing Hub
Full document details: ISPE Guide Series PQLI Part 3 - Change Management System as a Key Element of a Pharmaceutical Quality System 2012

Table 2.1: Example Differences in Requirements of a PQS

Key PQS and Business Features	PQS Based on GMP	PQS Based on ICH Q10	PQS Based on ISO 9001
Outsourcing			
• Control and review of outsourced activities included in management responsibilities.	-	√	√
Change Management			
• System should be effective, ensure continual improvement, include risk management and change of product ownership, be evaluated post implementation.	-	√	√
CAPA			
• CAPA to be implemented following specified investigations and root cause to be determined.	√	√	√
Quality Risk Management	√	√	√
Enhanced, Quality by Design Approach	-	**Optional**	**Optional**
Process Performance and Product Quality Monitoring System			
• Establish control strategy to facilitate timely feedback/feed forward, measure, analyze, identify sources of variation, and drive continual improvement.	-	**ICH Q8(R2)**	**Product Realization/ ICH Q8(R2)**
Business Process Performance	-	-	√
Knowledge Management	-	√	√
Senior Management Responsibilities			
• Accountability for PQS including governance and reviews, establish Quality Policy and Quality Objectives.	-	√	√

Notes:
1. √ indicates requirements covered in the respective PQS
2. Underlined text emphasizes specific requirements, e.g., GMPs require control of outsourcing, but do not specifically mention inclusion of outsourcing control within management responsibilities.

Documents
Document Sharing Hub
Full document details: ISPE Guide Series PQLI Part 3 - Change Management System as a Key Element of a Pharmaceutical Quality System 2012

Documents
Document Sharing Hub

Full document details: ISPE Guide Series PQLI Part 3 - Change Management System as a Key Element of a Pharmaceutical Quality System 2012

3 Change Management System

3.1 Introduction

Change management is one of the four PQS elements described in ICH Q10. This Chapter provides guidance on how a change management system is operated within an ICH Q10-based PQS.

The change management system principles and model are described, based on ICH Q10. This model can be applied to each stage in the product lifecycle. This Chapter also describes how the enablers, knowledge management, and quality risk management can apply to each step of a change management system.

3.2 Change Management System Principles

The principles of an effective change management system apply, regardless of the type of PQS or the stage within the product lifecycle. For example, when using a minimal approach to development and a PQS which is based only on compliance with GMPs, a change management system is still required to evaluate and implement changes. In this case, changes may occur, e.g., from resolution of troubleshooting exercises or from complaint investigations. Where a pharmaceutical system is required to support products and processes developed using an enhanced, Quality by Design (QbD) approach and the principles described in ICH Q8 (R2), [2], an effective change management system is considered essential.

ICH Q10 [1] (Section 3.2.3) describes four considerations for inclusion in the change management system in relation to the stage in the lifecycle, these include:

- The potential impact of the change using quality risk management tools
- The potential impact on marketing authorizations
- Evaluation of the proposed change by subject experts
- That the change objectives were achieved

The CGMP requirements must be met regardless of the stage of the lifecycle or whether the product and processes have been developed using minimal or enhanced, QbD approaches. CGMP requirements usually include:

- A Standard Operating Procedure (SOP) which describes the approach to evaluation, approval, and implementation of the proposed change and confirmation that the change is effective and did not have negative consequences
- Clear accountabilities for all change management activities
- Prioritization of urgent and important changes (e.g., a corrective or preventive action)

In regard to change management, the Quality Unit (QU) should:

- Ensure that a change management system is established
- Approve or reject proposed changes
- Audit the impact of changes post implementation
- Review effectiveness of the change management system and recommend improvements, where necessary

AVA Documents
Document Sharing Hub
Full document details: ISPE Guide Series PQLI Part 3 - Change Management System as a Key Element of a Pharmaceutical Quality System 2012