

This article provides the background and current status of ISPE's Product Quality Lifecycle Implementation (PQLI®) initiative, including the development of an ISPE PQLI Guide Series.

PQLI Roadmap: Product Design, Development, and Realization, a Science- and Risk-Based Approach to Implementation – An Overview of ISPE's First PQLI Guide

by Christopher J. Potter, John C. Berridge, and Contributing Team

Introduction

One of the key deliverables for PQLI for 2010 is the release of the first in a series of ISPE PQLI Guides. The first Guide entitled, "PQLI Roadmap: Product Design, Development, and Realization, a Science- and Risk-Based Approach to Implementation," will give an overview and top level roadmap for subsequent separate PQLI Good Practice Guides, covering various topics.

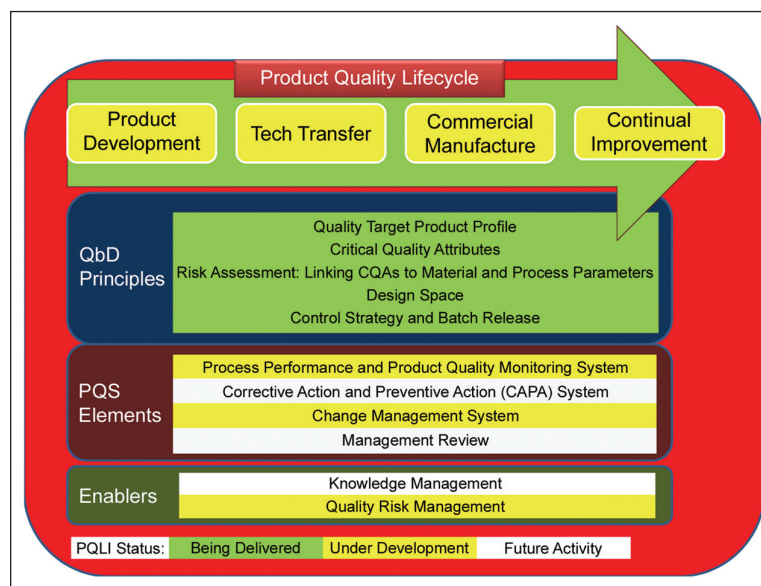
The Guides will provide the industry with "how to" options for introducing the science- and risk-based approaches from the ICH guidelines Q8(R2), Q9, and Q10 into developing and manufacturing products and processes (product realization).

The PQLI Roadmap will give an overview of the application of Quality by Design (QbD) to product realization. Subsequent PQLI Good Practice Guides will describe the relationship possibilities between Critical Quality Attributes (CQAs) and Critical Process Parameters (CPPs), options and opportunities for using design space, and development of control strategies. A case study developed by a PQLI team will be used to exemplify some of the options and this will be issued as a separate Guide. A Guide describing the application of science- and risk-based approaches to existing products also will be developed. Using the already-developed and published case study entitled, "A-Mab: A Case Study in Bioprocess Development," alterna-

tive approaches and some other considerations to development and introduction to manufacturing of a monoclonal antibody product will be discussed in a separate Guide devoted to biotechnology.

Subsequently, Guides will be produced on important topics relevant to introduction and operation of a modern pharmaceutical quality system particularly supporting products and processes developed using enhanced approaches.

Figure 1. The strategic themes, structure, and status of PQLI.



Overview of PQLI

ISPE launched its Product Quality Lifecycle Implementation (PQLI[®]) initiative in June 2007 to help industry find practical, science- and risk-based approaches to the global implementation of recent ICH guidelines. Through PQLI, ISPE is spearheading options to assist in the implementation of ICH guidelines, in particular, Q8 (R2) (pharmaceutical development),¹ Q9 (quality risk management),² Q10 (pharmaceutical quality system),³ and imminent Q11 (development and manufacture of drug substances). ISPE is working with industry and regulatory leaders worldwide to support pragmatic and practical implementation of the guidelines based on sound scientific, engineering, and business principles.

Key goals of PQLI include the provision of a technical framework starting with a series of PQLI Guides, which will include explanatory documents supported by illustrative examples and references to case studies in the public domain, explaining options for implementation of enhanced science- and risk-based approaches to product realization, and its continual improvement. PQLI recognizes that there is no one way to implement the ICH guidelines, rather there are many perfectly satisfactory ways to address the concepts that are described, and the Guides will reflect this important concept.

PQLI uses, where appropriate, output from discussions and interactions in many forums, meetings, and presentations, for example, from regulators' presentations, ISPE and other similar organizations' meetings and workshops, and EFPIA, PhRMA, Japan PMDA work.

The principles from ICH Q8 (R2), Q9, and Q10 are applicable to new products and processes emerging from the innovative industry, and additionally, it is also considered that these principles could be applied to existing products, and potentially to generic or branded-generic products.

Current Status of the Initiative

PQLI encompasses three strategic themes given in Figure 1. Topics relating to Quality by Design (QbD) principles have been developed. An overview of the direction of the PQLI Initiative will be presented in the first Guide entitled, "PQLI Roadmap: An Overview of Product Design, Development, and Realization, a Science- and Risk-Based Approach to Implementation." A case study illustrating how the key concepts can be applied to product realization will be published as a separate Guide. The series will include a Guide explaining how science- and risk-based approaches could be applied to existing products. Throughout the PQLI Guide Series, there will be references to other case studies and relevant publications, which are in the public domain. These parts of the series will be published in 2010.

PQLI is now expanding to help in the implementation and/or operation of a modern pharmaceutical quality system using the concepts outlined in Q10. The first two topics are Process Performance and Product Quality Monitoring System, and Change Management. In line with PQLI processes, these topics will be discussed and developed at the ISPE Conference co-sponsored with the FDA in Washington in June. From this

Conference, further detail will be generated as output for publication as potential additional Guides. Updates of the PQLI program will be issued in due course and progress can be followed in the PQLI section of the ISPE Web site.

PQLI Good Practice Guides

Some phrases and concepts used in ICH guidelines, such as "critical" as applied, for example, to Critical Quality Attributes and Critical Process Parameters, and Design Space as defined in Q8 (R2),¹ and Control Strategy as defined in Q10³ are judged to require further discussion and explanation to assist in their routine application and use. Consequently, the topic initially called "criticality" as applied to Critical Quality Attributes and Critical Process Parameters, and other topics, Design Space and Control Strategy, were selected by the PQLI program as the first to be given further attention and explanation. Initial thoughts related to these concepts were published for comment.^{4,5,6}

Feedback was received on the first three papers from both industry and regulators. This feedback recommended that Criticality, Design Space, and Control Strategy needed to be presented in an integrated way to show clearly how these concepts fit together to demonstrate effectively the application of QbD principles described in ICH Q8(R2), Q9, and Q10. There were other technical comments, which have resulted in our revising some of the explanations in the original papers.

Consequently, the PQLI Guide Series will include overview roadmap or "bridging" guidance relating to development of a product and its process or processes using the enhanced approach, and subsequent introduction to commercial manufacturing (product realization) with the establishment of the state of control (control strategy). The series will include a case study to illustrate this overview, and additional explanatory Guides on Critical Quality Attributes and Critical Process Parameters (CQA/ CPP), Design Space, and Control Strategy. Another Guide will include an example of Continual Improvement of Process Performance and Product Quality dealing

Unit Operation	Element of the Dissolution CQA	What to Control	How to Control
High Shear Wet Milling of Drug Substance	Dissolution	Drug Substance Particle Size	High Shear Wet Milling Time
	Dissolution Algorithm	Drug Substance Particle Size	Particle Size by Focussed Beam Reflectance Method
Dispensing of Excipients for Drug Product Process	Dissolution Algorithm	Magnesium Stearate Specific Surface Area	Analysis of Material Attribute in Excipient
Final Blend	Dissolution Algorithm	Lubrication Time,	Time
Compression	Dissolution Algorithm	Tablet Hardness	Use Compression Force as a Surrogate for Hardness

Table A. Table showing examples of elements of unit operations impacting on dissolution CQA and associated algorithm

with the application of science- and risk-based approaches to an existing product, which was based on a paper⁷ containing three case studies.

Content of the PQLI Guide Series

The PQLI Guide Series is a comprehensive discussion of the concepts underpinning enhanced product and process understanding and how to use this enhanced understanding to the benefit of the company throughout the lifecycle of the product. The series considers the totality of a drug product realization, including some aspects of development of the API, the selection of excipients, the choice of the manufacturing process, identification of the CQAs and CPPs, technology transfer and implementation into commercial manufacturing, and much more. Through practical examples, extended and focused discussion, and a comprehensive case study, the vital principles outlined in the ICH guidelines are translated into practical opportunities and application.

The following gives more detail of the content to be covered in the PQLI Roadmap and subsequent PQLI Guides:

The lifecycle of a pharmaceutical product is defined in Q8 (R2) as:

All phases in the life of a product from the initial development through marketing until the product's discontinuation.

A schematic of how this could be achieved using QbD principles is given in Figure 2 and the PQLI Guide Series uses

this as a high-level guide and explains in detail examples of the science- and risk-based steps. While this figure was developed by EFPIA⁸ to apply to drug products, the same principles are equally applicable to the development of the active ingredient.

Q8 (R2) gives guidance on the flow from developing and defining Quality Target Product Profile to Continual Improvement. Figure 2 gives the impression that product/process development and continual improvement are linear processes. However, in practice, development and continual improvement processes may consist of several parallel activities and are typically iterative and the iterative nature is represented in Figure 3 for a drug product. In addition, Figure 3 shows the relationship between formulation and process development of a drug product, and the application of quality risk management as described in ICH Q9. More detailed explanation of the iterative nature of formulation and process development is discussed in the PQLI Guide Series.

In summary from Figure 2, a Quality Target Product Profile (QTPP) is proposed, which is a defined¹ as “a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product.” During development of a new product, the QTPP could evolve and be refined as the project development process progresses. For example, when developing a simple tablet, the strength(s) to be submitted and included in a QTPP may not be finalized

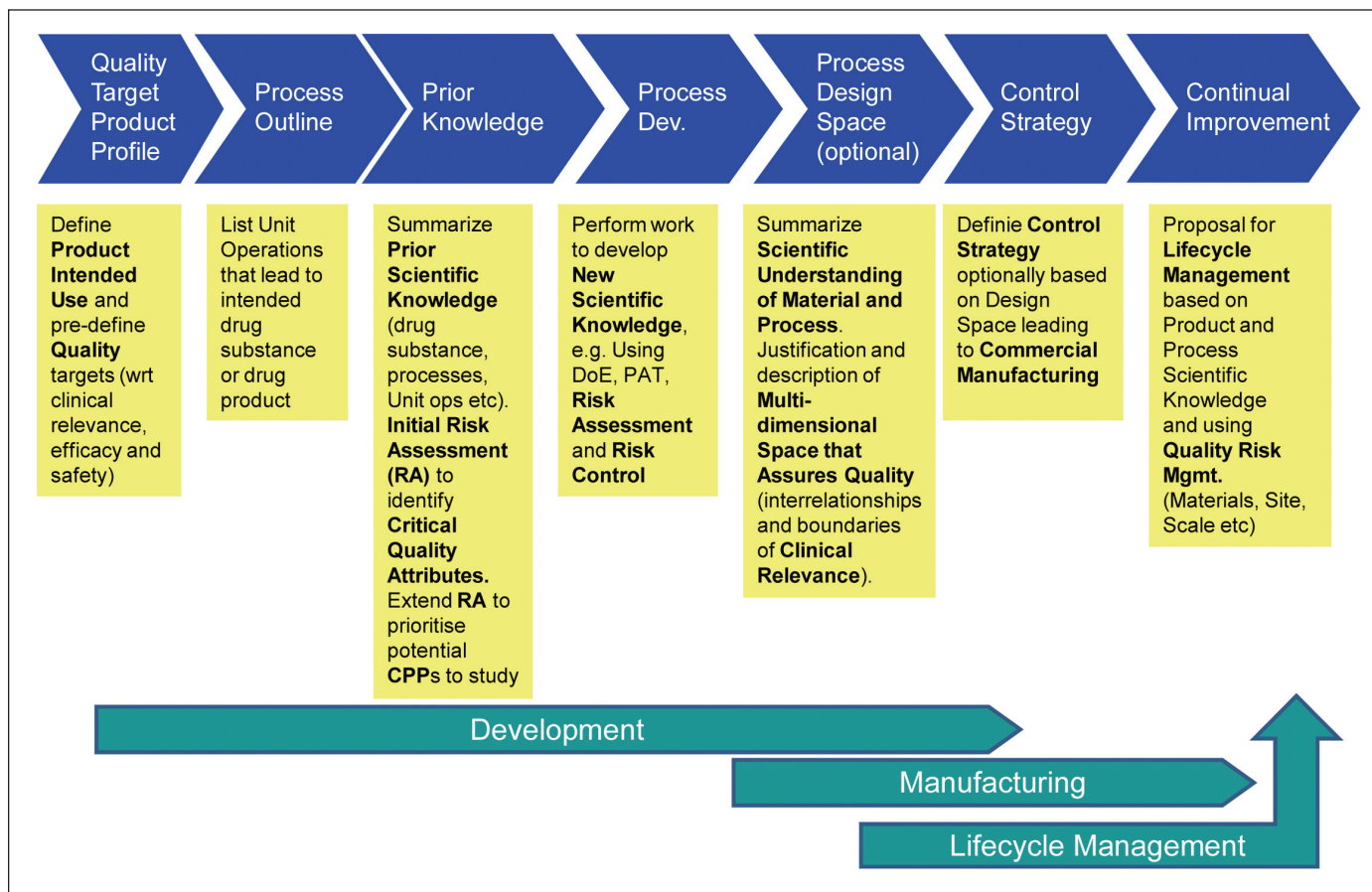


Figure 2. Application of QbD through a product's lifecycle (from EFPIA model).

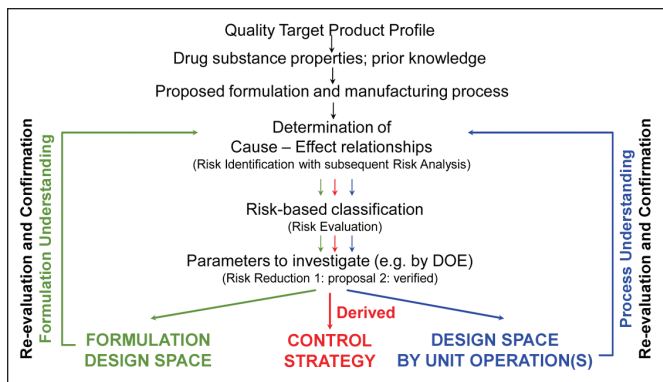


Figure 3. Iterative approach.

until after completion of Phase 3 clinical studies. A QTPP could be considered a qualitative and quantitative description of the design goal. The Guide Series shows how the QTPP enables a putative product and manufacturing process to be proposed, perhaps with several options, which may require experimental data to enable decisions to be made between options. Company strategy, prior knowledge, and experience of a process or availability of equipment and facilities also could influence the choice of manufacturing process. The case study exemplifies how these factors were brought together in the selection of a manufacturing process for an oral solid dosage form.

The PQLI Guide Series gives examples and explanation of application of quality risk management steps to product and process design. The case study explains the risk management steps as applied to drug product formulation and process development as outlined in Figure 2, giving examples of risk assessment (identification, analysis, and evaluation) leading to risk control (reduction and acceptance), which essentially are the studies designed to understand interactions with the intention of reducing risk.

The Guides on CQA/CPPs and case study will describe how prior knowledge can be used for example in a cause and effect analysis (risk identification and analysis) to prioritize (risk evaluation) as a continuum of quality attributes based on a “harm to the patient” or “severity” risk ranking to determine which are potential Critical Quality Attributes (CQAs) - Figure 4. These three risk steps constitute risk assessment.

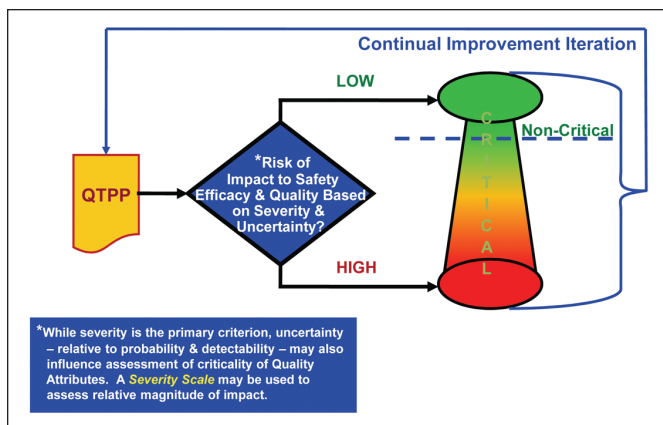


Figure 4. Quality attribute continuum of criticality.

Potential product CQAs could be modified as development progresses. For example, at the start of development of a controlled release product, quantitative in vitro drug release acceptance criteria, and selection of an appropriate dissolution medium are frequently not known. These are often developed in parallel with development of the formulation. The PQLI Guide Series will exemplify how qualitative or semi-quantitative acceptance criteria for CQAs could change as development progresses.

Prior knowledge also may be employed, for example, using Failure Mode, Effects, and Criticality Analysis (FMECA) to assess the combination of “severity,” “probability,” and “detectability” to prioritize the evaluation of the potential Critical Process Parameters (CPPs) and Material Attributes (MAs) whose variability may impact potential product CQAs (risk assessment). The PQLI Guide Series will give examples of how to derive a list of potential CPPs and MAs to study, showing how this list will have a continuum risk level. Furthermore, examples will be given of how factors to study are taken from this list and included in statistically-designed studies showing examples of how ranges of factors to study could be chosen. In risk management terms, execution of studies is considered risk reduction and review of the results of these studies could lead to risk acceptance or recycling through the risk process again by repeating risk assessment steps and designing further studies. Examples of use of risk iteratively to select and prioritize factors to study in a systematic manner, usually in statistically-designed experiments are given.

How the understanding from these studies is used to establish control strategy options is explained and exemplified, particularly showing the links between CPPs and MAs, potentially from more than one unit operation to a CQA as shown in Table A. Examples of multi-variant design of experiments are given, leading to understanding of variability. How this understanding is represented in an algorithm and used to propose flexible processing is discussed. Additionally, use of this understanding to support real time release testing applying process analytical technology tools is exemplified.

Given control strategy options, selection of a control strategy for implementation into manufacturing is discussed.

Optionally, enhanced understanding could be presented as a design space and examples of design space are given with expanded discussion of how to derive a design space, options to represent a design space, role across the product lifecycle, and considerations of scale as a factor influencing design space.

Following introduction of commercial manufacture of the product, opportunities for appropriate improvements to process performance and/or product quality could be identified from, for example, development studies, the process performance and product quality monitoring system or the Corrective Action and Preventative Action (CAPA) system, and changes made using the change management system. This continual improvement process is iterative throughout the lifecycle of the product. The PQLI Guide Series discusses introduction of a product into manufacturing and introduces considerations for a company quality system, particularly

when a science- and risk-based approach has been used for development and transfer to manufacturing. It also introduces and discusses opportunities for continual improvement of process performance and product quality.

Continual Improvement of Process Performance and Product Quality is further described in Section 3 of ICH Q10. Section 3 is split into two parts, 1. Lifecycle Stage Goals, which is a summary of the product lifecycle stages and 2. Pharmaceutical Quality System Elements (PQSE), which has more detail of the PQS to support manufacturing operations. There are four sub parts to the PQSE and they are the following:

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

Control strategy is discussed as part of the Process Performance and Product Quality Monitoring System section.

Technical and business processes that companies could consider to effect continual improvement of process performance and product quality, whether the product was originally developed using science applicable at that time or a science- and risk-based approach, are given in the *Journal of Pharmaceutical Innovation* paper, "Application of Science- and Risk-based Approaches (ICH Q8, Q9, and Q10) to Existing Products"⁷ and will be included as a separate Guide in the PQLI Guide Series.

Activity by PQLI is planned to extend the learning and understanding relating to implementation and operation of important elements of a company's pharmaceutical quality system, for example, at the forthcoming ISPE Conference in Washington on 9 and 10 June, co-sponsored by the FDA. PQLI output from this activity may be the basis of further PQLI Good Practice Guides.

The PQLI Guide Series provides detail and considerations on "how to" implement Q8 (R2) and Q9 under a pharmaceutical quality system for achieving product realization. These suggestions must not be considered the only way to apply science- and risk-based approaches, nor should they be considered as regulatory guidance. As an example, companies have options to develop product and process understanding in many different manners and use this understanding to propose control strategies without describing a design space, as indicated in Appendix 1 of Q8 (R2).

Benefits of Using a QbD Approach

Benefits to companies of moving toward the enhanced approach are suggested in the PQLI Roadmap and examples are given, where possible.

Some examples of benefits that have already been achieved by companies applying the science- and risk-based approach to existing products are given in the case studies in reference 7.

Get Involved with Upcoming PQLI Events

You can learn and contribute with industry colleagues and regulators by attending the following ISPE meetings, seminars, and workshops:

- 20 to 22 March 2010
Milan Congress: Science and Risk Assessment for Business Success
- 22 to 23 April 2010
Japan Affiliate Annual Meeting 2010, including PQLI with A-Mab
- 7 to 10 June 2010
Washington Conference: Applying Risk-Based Approaches, featuring an FDA co-sponsored two day interactive program on Pharmaceutical Quality Systems, and a separate two day program on application of QbD to product realization
The A-Mab case study will promote discussion on the latest thinking in the application of QbD to biotechnology. A small molecule case study developed by a PQLI team, which is a core component of a forthcoming PQLI Good Practice Guide will explain some approaches to apply QbD for product realization
- 20 to 23 September 2010
Brussels Conference, featuring discussion of A-Mab and explanation of the ISPE small molecule case study

If you want to be more involved in PQLI or to contribute to any of the current or future PQLI activities, please send an email to pqli@ispe.org.

References

1. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Pharmaceutical Development, Q8 (R2), August 2009.
2. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Quality Risk Management, Q9 Step 4, 9 November 2005.
3. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Q10, Pharmaceutical Quality System, Step 4, 4 June 2008.
4. Nosal, R. and Schultz, T., PQLI Definition of Criticality, *J Pharm Innov*, (2008) 3:69-78.
5. Lepore, J. and Spavins, J., PQLI Design Space, *J Pharm Innov*, (2008) 3:79-87.
6. Davis, B., Lundsberg, L. and Cook, G., PQLI Control Strategy Model and Concepts, *J Pharm Innov*, (2008) 3:95-104.

7. Potter, C. J., PQLI Application of Science- and Risk-Based Approaches (ICH Q8, Q9, and Q10) to Existing Products, *J Pharm Innov*, (2009) 1:4-23.
8. European Federation of Pharmaceutical Industries and Associations, [www.efpia.org/Publications/Science and Technical Affairs](http://www.efpia.org/Publications/Science%20and%20Technical%20Affairs).

About the Authors

Christopher J. Potter is the PQLI Technical Project Manager for ISPE.

John C. Berridge is the European Regulatory Affairs Advisor for ISPE.

Contributing Team

Eric Ahuja, Merck
Mette Bryder, Lundbeck
Susan Busse, Lilly
Graham Cook, Pfizer,
Bruce Davis, Consultant
Ranjit Deshmukh, Pfizer
John Donaubaauer, Abbott
John Groskoph, Pfizer
Dora Kourti, GSK
Mette Kraemmer Hansen, NovoNordisk
John Lepore, Merck
Line Lundsberg Nielsen, NNE Pharmaplan
Roger Nosal, Pfizer
Chris Sinko, BMS
Paul Stott, AstraZeneca
Stephen Tyler, Abbott
Tim Watson, Pfizer 