

GUIDE:

Change Management System



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Preface

Advancing Pharmaceutical Quality (APQ) is a comprehensive program for assessing and improving an organization's quality management maturity. It is an industry-led approach that seeks to advance pharmaceutical quality beyond the submission of data for harmonized, reportable metrics. Organizations can leverage this program to ensure a continuous supply of quality medicines to patients.

The APQ program evolved from the ISPE Quality Metrics Initiative which represents extensive industry engagement, collaboration with academia and other associations, and knowledge sharing with regulatory agencies. The APQ program is harmonized with international regulatory initiatives that promote quality excellence.

APQ is built upon the ICH Q10 Pharmaceutical Quality System (PQS) model [1] that comprises management responsibilities and the following PQS elements:

- Process performance and product quality monitoring system
- Corrective Action and Preventive Action (CAPA) system
- Change management system
- Management review of process performance and product quality

The APQ program further enhances this ICH Q10 model with cultural excellence and operational excellence (continual improvement) principles. Due to the interconnectedness of management responsibilities and management review, these are addressed together for the purposes of the APQ program. The APQ Guide Series focuses on the application of the APQ framework to these four PQS elements that are based upon ICH Q10:¹

- CAPA system [2]
- Management Responsibilities and Management Review (MRR) [3]
- Change Management (CM) system
- Process performance and product quality monitoring system

The APQ Guide Series provides a practical set of tools and systematic approaches—the Assess, Aspire, Act, and Advance framework—for organizations to advance the maturity and effectiveness of these PQS elements.

This ISPE APQ Guide: CM System contains two parts. Part 1 covers the key principles of the APQ program and explains the Assess, Aspire, Act, and Advance framework. This prerequisite information is applicable to all four PQS elements. Part 2 covers the practical application of the APQ framework to the CM system element. Tools and examples are provided in the appendices. Additionally, a ZIP file containing the APQ Maturity Assessment Tool (for CM System) and the APQ Benchmarking Tool is provided with this Guide at the time of purchase.

¹ The APQ Guide for the process performance and product quality monitoring system is a planned future ISPE publication.

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1 Introduction to the APQ Program and Guide Series

The Advancing Pharmaceutical Quality (APQ) program seeks to advance the current state of pharmaceutical quality by providing a framework for assessing and enhancing the effectiveness of the Pharmaceutical Quality System (PQS).² The APQ program recognizes that the ability to advance quality management maturity lies within the industry itself; it has been developed by industry representatives for use by industry. A key driver for this program is to provide a range of sustainable, practical quality management improvement strategies, approaches, and tools for organizations.

The APQ program is built upon the ICH Q10 model [1] and enhances the PQS elements with the aspects of cultural excellence³, operational excellence (OPEX), and continual improvement.

As stated in ICH Q10:

“ICH Q10 demonstrates industry and regulatory authorities’ support of an effective pharmaceutical quality system to enhance the quality and availability of medicines around the world in the interest of public health. Implementation of ICH Q10 throughout the product lifecycle should facilitate innovation and continual improvement and strengthen the link between pharmaceutical development and manufacturing activities.” [1]

Pursuit of this desired state has always been central to ISPE's efforts to advancing the state of pharmaceutical quality within the industry. The APQ Guide Series represents the ongoing commitment towards that journey.

1.1 Objectives

The APQ program is intended to provide a comprehensive approach for assessing and improving an organization's quality management maturity in order to advance the state of quality within the organization. It is an industry-for-industry program that aims to identify good practices and good behaviors that support the continual improvement of quality management effectiveness within an organization.

The eight overarching goals of the APQ program are to:

- Integrate quality management maturity, cultural, and operational excellence principles, tools, and approaches
- Support and incentivize continual improvement
- Foster industry ownership of quality beyond compliance
- Promote effective and efficient use of resources
- Encourage self-improvement and supplier improvement
- Enable structured benchmarking, knowledge sharing, and learning among organizations
- Increase the reliability of supply for quality products
- Offer routes to delivering sustainable competitive advantage

² The Pharmaceutical Quality System (PQS) is also referred to as Quality Management System (QMS) by some organizations. For the purposes of this Guide, the term Pharmaceutical Quality System is used.

³ The terms cultural excellence and quality culture are interchangeable. For the purposes of this Guide, the term cultural excellence is used.

The APQ program intends to be relevant to individual organizations and to act as a forum for cooperation in the search for effective and practical solutions to the issues common to all organizations. The detailed discussion for the overarching goals is covered in Section 2.2 and Appendix 1.

The APQ program and APQ Guide Series are designed to incorporate the following aspects:

- Provide an industry-led program that includes a structured framework to assess and advance the effectiveness of pharmaceutical quality management, which organizations can leverage to ensure a continuous supply of high-quality medicines to their patients
- Built upon the principles of the ICH Q10 PQS [1] and further enhanced to include cultural excellence and OPEX tools, approaches, and behaviors which can support the effective management of quality
- Comprised of detailed self-assessments for quality management maturity along with self-improvement tools and KPIs focused on advancing organizational capabilities across the four core elements based on ICH Q10 PQS: CAPA system, Management Responsibilities and Management Review (MRR), CM system, process performance and product quality monitoring system
- Complement current international regulatory initiatives which promote quality excellence

1.2 Scope

The scope of the APQ Guide Series is aligned with the ICH Q10 PQS model [1] (as explained further in Section 2.1). Therefore, the practices described in the APQ Guides apply to all aspects of the PQS relevant to the manufacturing, packaging, testing, or holding of biological, chemical, advanced therapy medicinal products, combination medicinal drug products, and their associated active pharmaceutical ingredients. The principles described may also apply to medical devices, over the counter products, personal care, and cosmetics products and may be beneficially applied throughout the product lifecycle from research and development, technology transfer, commercialization, and discontinuation.

1.3 Benefits

The benefits of the APQ program are outlined below:

- Benefits for industry:
 - Access to an ICH Q10-based quality management maturity framework that can be utilized in full by an organization to understand the impact to the overall performance of the organization of their maturity assessment, Key Performance Indicator (KPI) application, and improvement actions
 - Supports sustained, continual improvement of an organization's PQS
 - Benchmarking against industry peer groups, i.e., by using the St.Gallen APQ Benchmarking Tool or full OPEX benchmarking program
 - Community of practitioners for sharing of best practices to accelerate progress
- Benefits for patients and consumers:
 - Increased reliability of supply of quality product

- Benefits for health agencies:
 - Better insight into industry's focus and current expectations regarding critical quality areas for advancing pharmaceutical quality
- Benefits for research:
 - Increased data availability for researching the impact of quality management maturity on pharmaceutical production site performance

1.4 About the ISPE APQ Guide Series

The ISPE APQ Guide Series provide a practical set of tools and systematic approaches—the Assess, Aspire, Act, and Advance framework—for organizations to advance the maturity and effectiveness of their PQS. Each APQ Guide focuses on the application of the framework to one of four elements that are based upon ICH Q10 [1]:⁴

- CAPA system [2]
- MRR [3]
- CM system
- Process performance and product quality monitoring system

At the core of the APQ Assess, Aspire, Act, and Advance framework is the detailed self-assessment tool to determine the current maturity level of an organization's quality system element (e.g., CAPA system). These tools integrate objective quantitative and qualitative criteria, enabling organizations to analyze the current state of quality, diagnose gaps, and identify improvement targets—**Assess and Aspire**. Using suggested continual improvement tools and KPIs, organizations can then develop an Improvement Action Plan, execute it, and evaluate it for effectiveness—**Act and Advance**.

Additionally, this Guide includes a pre-assessment and post-action benchmarking questionnaire tool that organizations can use in conjunction with the APQ framework. It offers objective evidence of performance improvement to support ongoing investment of an organization's time and resources into implementing the APQ program for each quality system element. This questionnaire was developed by the Institute of Technology Management at the University of St.Gallen (Switzerland) as part of a collaboration with ISPE.

Figure 1.1 provides a high-level overview of the APQ program which comprises the APQ Assess, Aspire, Act, and Advance framework based on a foundation of cultural excellence. Figure 1.2 shows the ISPE APQ Guide Series including the application of the APQ framework to the four ICH Q10-based PQS elements, supported by additional ISPE body of knowledge and publications associated with key principles [4, 5, 6] and PQS enablers (knowledge management [7] and quality risk management).

⁴ The APQ Guide for the process performance and product quality monitoring system is a planned future ISPE publication.



Figure 1.1: Overview of the APQ Program

ISPE Advancing Pharmaceutical Quality Program

Comprehensive industry-led approach for assessing and improving the quality management maturity of Pharmaceutical Quality System elements (based upon ICH Q10)

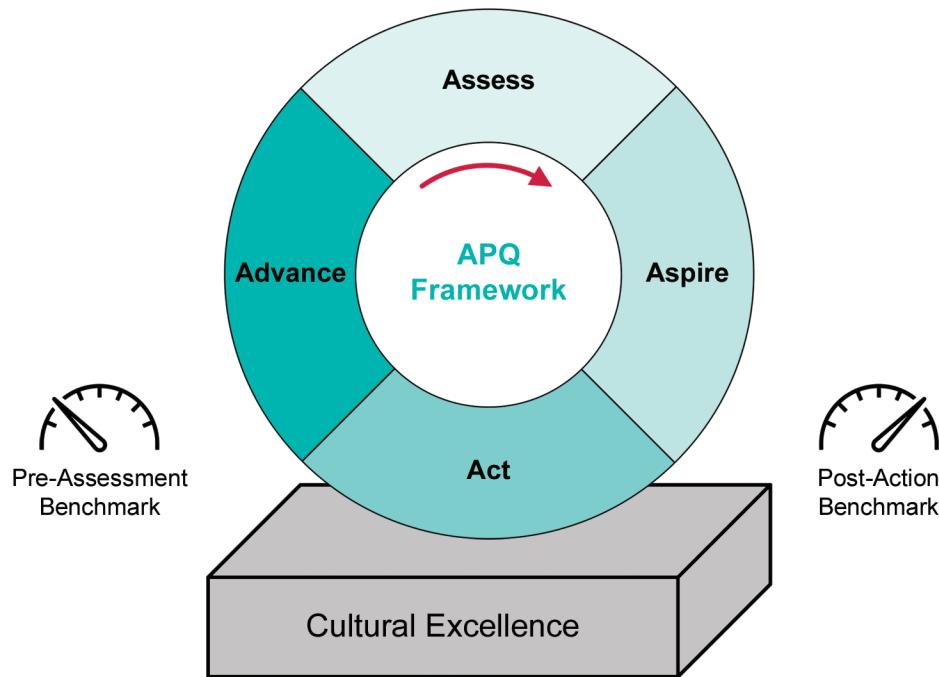
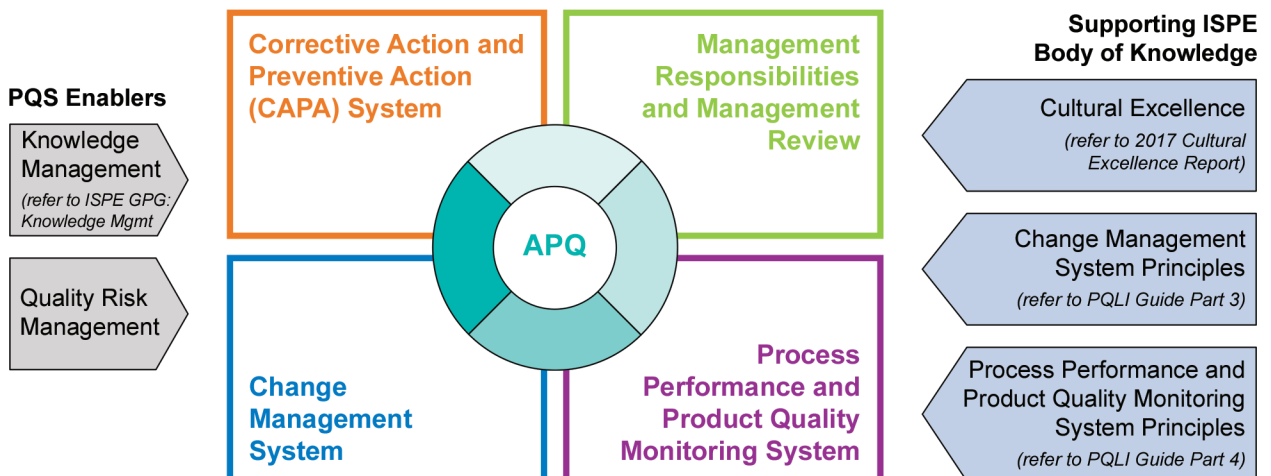


Figure 1.2: Overview of the ISPE APQ Guide Series

ISPE APQ Guide Series

Application of the APQ framework to Pharmaceutical Quality System (PQS) elements based upon ICH Q10



Note for Figure 1.2: The APQ Guide for the process performance and product quality system is a planned future ISPE publication.

1.5 How to Use This Guide

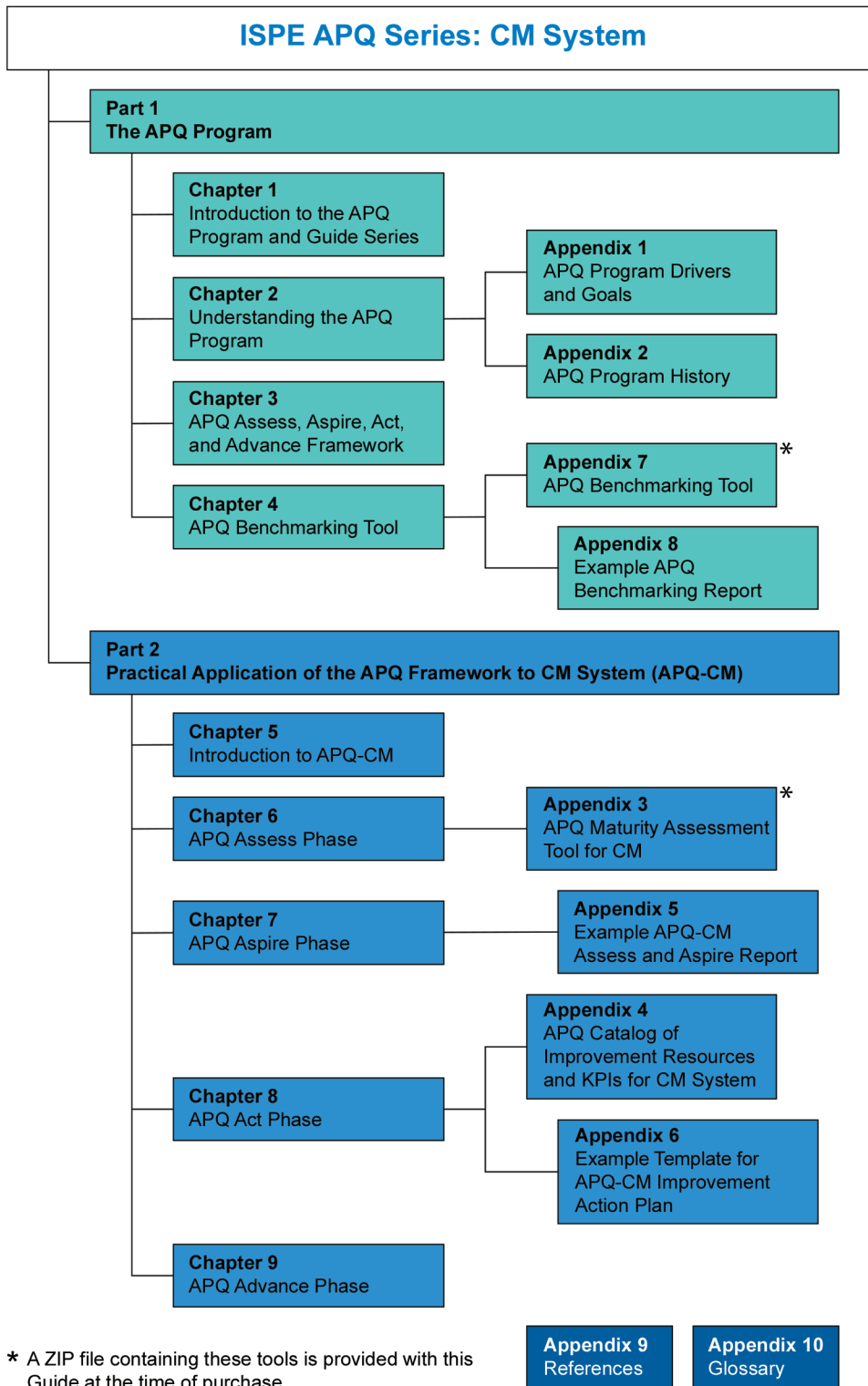
Part 1 covers the key concepts of the APQ program including the link to the ICH Q10 PQS model [1] and the link to cultural and operational excellence. It introduces the Assess, Aspire, Act, and Advance framework and explains how to perform the self-assessment. **This prerequisite information is applicable to all four PQS elements in the APQ Guide Series.** Part 1 also covers the pre-assessment and post-action benchmarking questionnaire tool.

Part 2 covers the practical application of the APQ framework to CM system (APQ-CM). It guides readers through the four phases of the framework, explaining in detail the comprehensive self-assessment tool for diagnosing the quality management maturity of their organization's CM system. It provides guidance on developing an APQ Improvement Action Plan, with recommendations for KPIs and improvement methodologies appropriate for each maturity level.

The appendices include a full explanation of the drivers and overarching goals of the APQ program, a summary of the program's history, and the tools and examples for practical application of the program.

Figure 1.3 provides the chapter organization of this Guide, showing the links between the body chapters and the appendices.

Figure 1.3: Guide Structure



2 Understanding the APQ Program

Robust and well-established quality systems subject to continual improvement are critical to superior performance outcomes. Organizations rely upon the effective implementation of PQS, from early development through to product approval, commercial launch, and routine supply. These aspects of a quality system are generally well considered and detailed in most pharmaceutical organizations; however, in organizations where quality management practices are less mature, there may be an emphasis on meeting compliance requirements and short-term business objectives rather than on achieving quality excellence and continual improvement. Activities that proceed well, according to plans, are usually well cared for; however, failure events or adverse situations leading to a quality defect or an interruption of supply are not always well-anticipated. The ability to predict, detect, and adapt to these events is the signature of a mature quality system.

These concepts are the basis upon which the APQ program has been designed. The APQ program is intended to be comprehensive without being complex. It has been developed to support organizations to **Assess, Aspire, Act, and Advance** the maturity and effectiveness of their quality management. The guiding principles of the APQ program are:

- Simple and practical
- Applicable across all sectors of the pharmaceutical industry
- Valuable and beneficial for industry
- Functional: Using “as is” company data, site definitions, and site procedures as much as possible
- Minimal additional work
- “By industry, for industry”
- Leveraging existing benchmarking, performance management, and OPEX methodologies and principles where relevant

The APQ program proposes that mature quality systems require the integration of excellence in quality with excellence in operations supported by excellence in organizational culture.

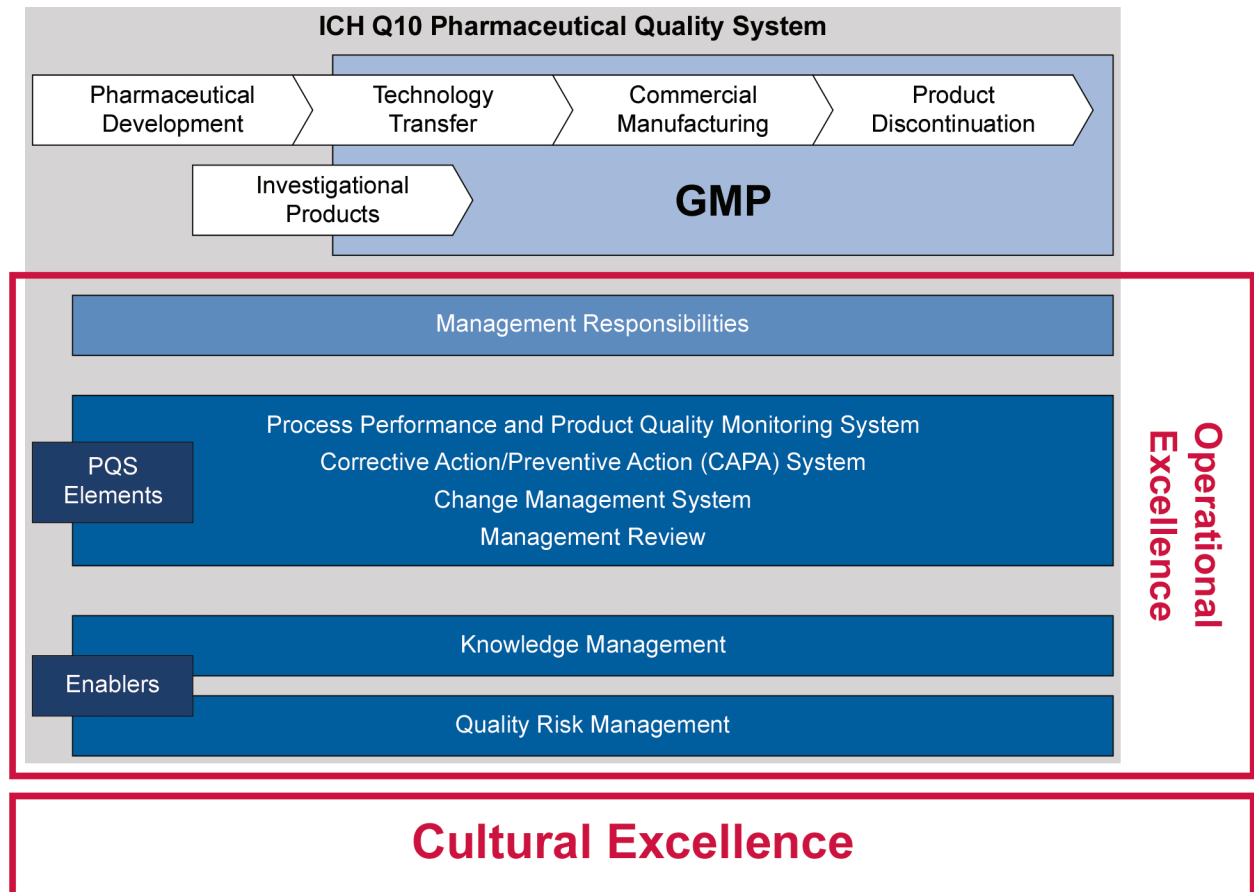
The philosophy behind the APQ program and its overarching goals is detailed in Appendix 1. It is important that readers of this Guide understand the full rationale described in this chapter and in Appendix 1 prior to the implementation of the APQ program.

For background information on how the APQ program evolved from the Quality Metrics program, see Appendix 2.

2.1 Link to the ICH Q10 PQS Model

The fundamental basis of the APQ program is the ICH Q10 PQS model [1]. Figure 2.1 shows the ICH Q10 model with APQ program enhancements (shown in red boxes) to incorporate the additional aspects of cultural excellence and OPEX.

Figure 2.1: APQ Program Link to ICH Q10 PQS Model [1]



Note: Red boxes are the APQ program enhancements to ICH Q10.

ICH Q10 states the following objectives for the implementation of the Q10 model:

- “Achieve product realization”
- “Establish and maintain a state of control”
- “Facilitate continual improvement” [1]

The concept of PQS effectiveness is raised early in the ICH Q10 guideline. Firstly, it emphasizes that the “use of knowledge management and quality risk management enable a company to implement ICH Q10 effectively and successfully.” The guideline then acknowledges that “while some aspects of the pharmaceutical quality system can be company-wide and others site-specific, the effectiveness of the pharmaceutical quality system is normally demonstrated at the site level.” ICH Q10 recommends that “performance indicators . . . should be identified and used to monitor the effectiveness of processes within the pharmaceutical quality system.” [1]

The APQ program has been specifically developed to provide a systematic process that can be used to objectively assess and advance PQS effectiveness at a site or functional unit level through the four elements based on ICH Q10 (CAPA system, MRR, change management system, and process performance and product quality monitoring system). The APQ program includes detailed diagnostic tools, based on a 5-Level Maturity Model, for assessing and improving the effectiveness of each PQS element. A detailed description of the APQ program and how to apply it to a PQS element is provided in the next chapter (Chapter 3).

2.2 Link to Cultural Excellence and Operational Excellence

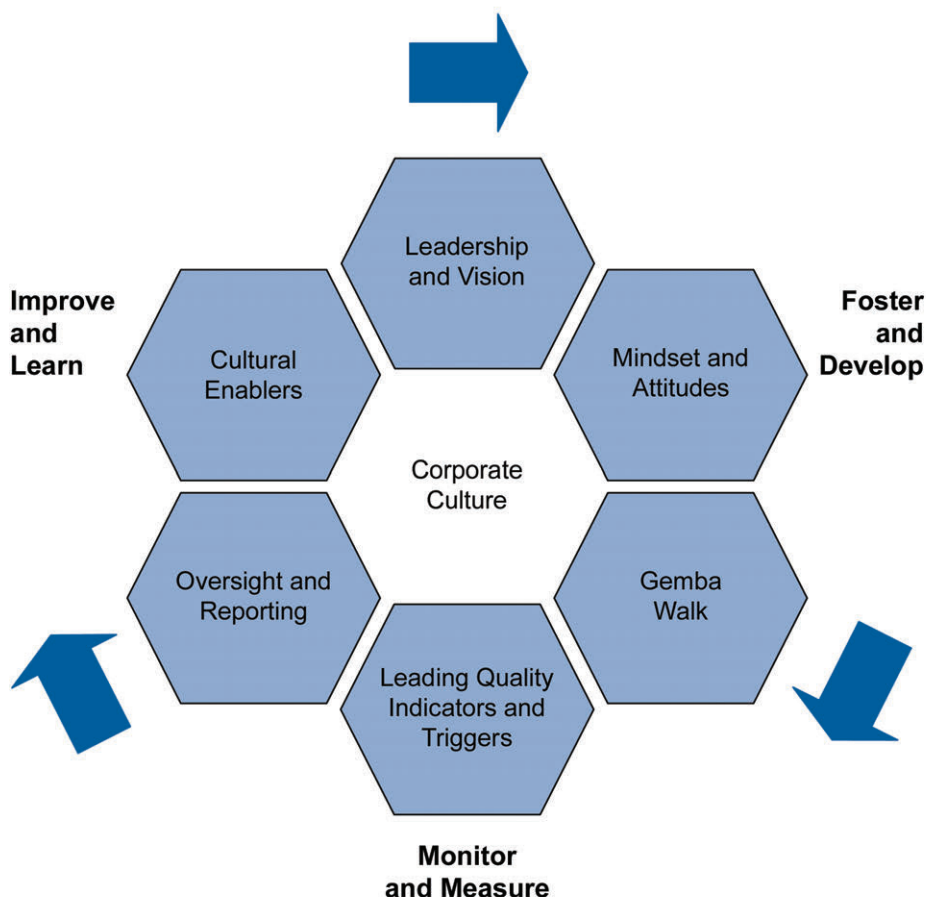
As stated earlier in this chapter, an overarching goal of the APQ program is to integrate quality, cultural, and operational excellence principles, tools, and approaches.

2.2.1 Cultural Excellence

Excellence in quality culture is essential for delivering robust and sustained quality performance, as demonstrated in the analyses from the ISPE Quality Metrics Wave 1 and Wave 2 pilot programs. [8, 9] (Background information on Quality Metrics and the relationship to APQ is covered in Appendix 2.) In Figure 2.1 (from Section 2.1), cultural excellence is depicted as the foundation stone for all other elements in the APQ program.

To address this key cultural excellence aspect, ISPE developed the six dimensions of the cultural excellence framework, as published in the 2017 ISPE Cultural Excellence Report [4] comprised of tools for assessing and improving the impact of culture on the performance outcomes for an organization. See Figure 2.2 for a diagram of the six dimensions of cultural excellence framework.

Figure 2.2: Six Dimensions of Cultural Excellence Framework [4]



There is broad alignment between the mature quality behaviors valued in the APQ assessments and the key behavioral criteria provided in the Cultural Excellence Report. For example, appropriate leadership behaviors include:

- Regular emphasis from management on quality topics and the importance of quality
- When quality issues conflict with business issues, consideration of both aspects by management before taking a decision
- Leaders regularly providing sufficient support and coaching to line workers to help them improve quality
- Leaders always modeling the desired behavior of “doing the right thing” on issues of quality

Another area of core alignment between the APQ program and the recommendations in the Cultural Excellence Report is in the design of meaningful metrics and leading quality indicators; these would include:

- Quality goals and objectives routinely established, linked, and aligned with organizational goals
- Management regularly involved in reviewing and assessing product, process, and quality system performance
- Organization’s oversight and reporting capabilities systematically applied to effectively manage external manufacturing performance within the supply chain
- Regular involvement by management of line workers in problem identification, problem solving, troubleshooting, and investigations

For those embarking on a journey to advancing pharmaceutical quality within their organization, it is recommended that the full Cultural Excellence Report (2017) [4] is read in conjunction with the ISPE APQ Guide Series.

2.2.2 Operational Excellence

Integration of the next key aspect of the APQ program relates to operational excellence (OPEX), which is defined as “a philosophy of the workplace where problem-solving, teamwork, and leadership leads to continual improvement in an organization.” [10] Continual improvement is a key goal of ICH Q10 [1] and should be considered as a critical factor for a comprehensive and sustainable OPEX initiative.

The *ISPE Good Practice Guide: Operations Management* [11] highlights that for many years the pharmaceutical industry has been successfully adopting operational approaches that come under the umbrella term “operational excellence”, including the use of improvement practices, Lean/Six Sigma techniques and tools, and the deployment and monitoring of relevant KPIs across the entire organization. The *ISPE Good Practice Guide: Operations Management* provides a useful knowledge base for promoting operational excellence within pharmaceutical operations management and is also recommended as a companion read to this Guide.

Recent research has shown, however, that quality and OPEX often exist as parallel dedicated functions in a formal pharmaceutical organizational structure, with OPEX activities managed independently of the quality unit. (Friedli, et al. [12]) Integration of these two infrastructures throughout the pharmaceutical organization is advised to more fully realize the positive impact of organization-wide improvement. The APQ Assess, Aspire, Act, and Advance framework has been carefully designed to incorporate cultural excellence behaviors and OPEX principles.

3 APQ Assess, Aspire, Act, and Advance Framework

The APQ program comprises a practical and systematic set of tools and approaches called the APQ Assess, Aspire, Act, and Advance framework that organizations can use to assess the current state of their quality management maturity at either a single site or across all sites within their organization.

The APQ Assess, Aspire, Act, and Advance framework is:

- A guided self-assessment and self-improvement process
- Comprised of four distinct but interconnected phases of Assess, Aspire, Act, and Advance
- Based on a 5-Level Maturity Model that identifies good practices and behaviors which support the advancement of quality management maturity within an organization
- Intended as an iterative, continual improvement process

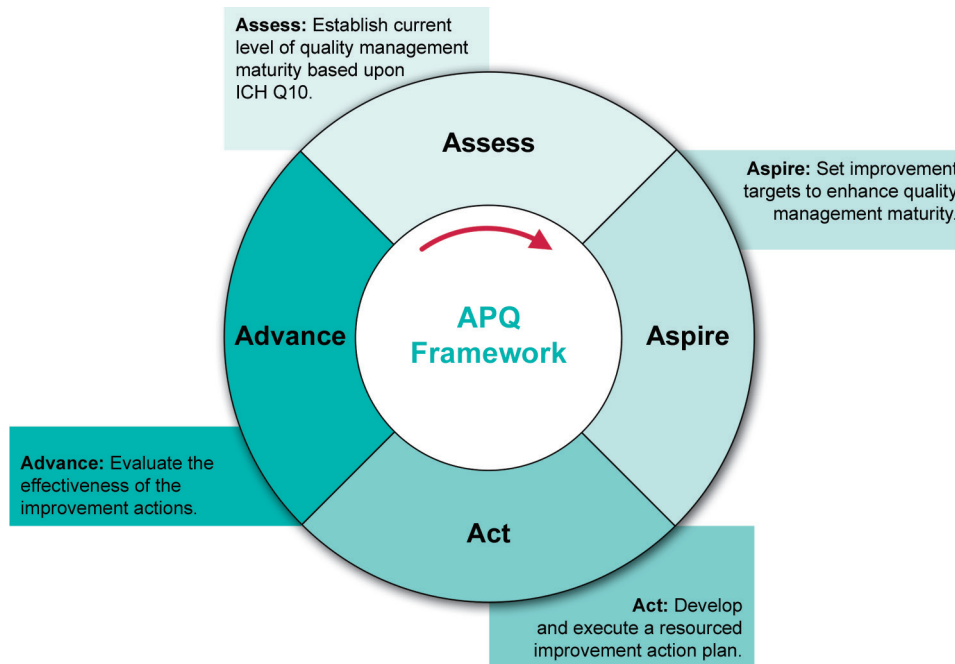
The APQ Assess, Aspire, Act, and Advance framework provides deep diagnostic tools for each of the four PQS elements based on ICH Q10 [1]:

- CAPA system
- MRR
- CM system
- Process performance and product quality monitoring system

These self-assessment tools include detailed quantitative and qualitative criteria to evaluate the current state of quality, diagnose gaps, and identify improvement opportunities.

The APQ framework for assessment and improvement is based on the classic Plan-Do-Check-Act (PDCA) improvement cycle. It involves establishing a baseline and assessing for gaps, developing a set of systematic improvement goals, acting to advance maturity against those goals, monitoring the outcomes periodically for effectiveness, and prioritizing the next improvement opportunities. Furthermore, the program is iterative, as shown by the cycle in Figure 3.1. Ideally, continual improvement of the maturity of the PQS should remain a key focus for organizations.

Figure 3.1: APQ Assess, Aspire, Act, and Advance Framework



3.1 APQ Framework Process

This section provides a high-level overview of the four phases in the APQ framework process. Part 2 of this Guide (starting with Chapter 5) covers the practical application of the APQ framework to CM system, explaining the four phases in more detail.

1. Assess Phase

In the Assess phase, an APQ self-assessment team performs a deep evaluation of the current state of maturity of the organization's PQS with respect to the PQS elements (CAPA system, MRR, CM system, and process performance and product quality monitoring system).

The evaluation may include one or more of these PQS elements, depending on the improvement focus or business need. The APQ Benchmarking Tool described in Chapter 4 can be used to inform the prioritization of the PQS elements. For each PQS element, the detailed self-assessment is divided into a number of sub-elements to enable a deeper level of enquiry.

The APQ Maturity Assessment Tool is a deep diagnostic tool that comprises quantitative and qualitative criteria against which the PQS element maturity can be evaluated. Using the assessment tool, the team evaluates the current state of maturity, establishes objective evidence of organizational capability, and assigns an appropriate maturity rating for each sub-element. This assessment forms the basis for setting objective, measurable improvement goals.

2. Aspire Phase

In the Aspire phase, the self-assessment team analyzes the results of the assessment process to review the improvement opportunities identified and to determine where and by how much the organization aspires to improve. This analysis involves confirming the overall maturity rating for the PQS element under consideration and prioritizing the specific improvement opportunities based on current performance or business needs. An APQ Assess and Aspire Report should be prepared to summarize and present the findings from the self-assessment team. The report should be presented to management, the functional leader, and the business process owner(s) to ensure the analysis is endorsed and appropriately resourced. A formal summary report should also be presented to the executive sponsors. The output of the Aspire phase forms the basis for the Improvement Action Plan developed in the next phase.

3. Act Phase

In the Act phase, an APQ improvement team develops and executes an Improvement Action Plan for the prioritized gaps and improvements that were determined in the Assess and Aspire phases by the APQ self-assessment team. The APQ Improvement Action Plan should meet the SMART criteria—Specific, Measurable, Attainable, Relevant, and Time-bound.

To support the production of the Improvement Action Plan in the Act phase, the APQ Catalog of Improvement Tools and KPIs is a resource that action owners can leverage. It provides a listing of recommended good practices and useful KPIs specific to the PQS element undergoing the APQ framework process.

4. Advance Phase

In the Advance phase, an evaluation of the Improvement Action Plan effectiveness criteria is performed to demonstrate the achievement of the improvement goals. If the results are shown to be fully effective, reproducible, and sustainable, then the improvement team may recommend the next PQS element to be prioritized for improvement, thus commencing the next cycle of the APQ framework as an iterative process for continual improvement.

After confirmation of effectiveness has been completed in the Advance phase, a post-action benchmark may be triggered at an appropriate time point to demonstrate the impact of the improvements on the relevant company performance outcomes and KPIs.

3.2 APQ Self-Assessment Tool

3.2.1 *The 5-Level Maturity Model for Quality Management Maturity*

The APQ self-assessment tool incorporates quantitative scoring against a 5-Level Maturity Model, where **Level 1 Undefined** represents the lowest level of maturity and **Level 5 Optimized** represents the highest level of maturity.

The qualitative criteria contained within each maturity level are specific to each of the individual PQS elements, e.g., the APQ self-assessment tool for the CAPA system contains specific qualitative criteria that are distinct from the criteria for assessing maturity of the change management system.

Figure 3.2 provides descriptions for each of the five levels in the maturity model. These five levels are applicable to all PQS elements.

Figure 3.2: APQ 5-Level Maturity Model

Level 1: Undefined	Compliance Risk	Undefined	Uncontrolled	Not Monitored	No Evidence
Level 2: Defined	Partially meets ICH Q10 Requirements	Partially Defined	Not Formally Controlled	Not Formally Monitored	Person Dependent
Level 3: Managed	Fully Meets ICH Q10 Requirements	Defined Policy and Processes	Meets Requirements for Application	Process Monitoring and Controls in Place	
Level 4: Improved	Demonstrates Improved/Optimized Execution	Defined Policy and Processes	Routine Application	Routine Monitoring, Advancing Improvements	
Level 5: Optimized	World Class/ Industry Leader	Proactive	Continual Improvement	Predictive	

To determine which maturity rating should be assigned, the APQ self-assessment tool incorporates specific qualitative criteria to each of the five levels in the maturity model. The cross-functional assessment team should review evidence of maturity against the qualitative criteria and then assign the appropriate maturity rating for that PQS element.

The typical attributes of the five levels in the APQ 5-Level Maturity Model are described below:

Level 1 Undefined

An assigned maturity assessment rating of 1 indicates that the element under review is poorly or not defined, reactive, and operates on an ad hoc basis or not done at all. There are no formal controls in place and no monitoring or oversight of results/outcomes is undertaken. There is no consideration given to supply chain risk. This level of maturity represents a compliance risk.

Level 2 Defined

An assigned maturity assessment rating of 2 indicates that the element under review has been partially defined but is not formally controlled or managed by a well-defined business process. The level of understanding is limited, and the process is applied inconsistently. The operation of the process is reactive. This level of maturity is likely to arise where processes are person dependent and rely on an individual or small number of individuals to function. There is little consideration given to supply chain risk with potential for supply chain disruption. This level of maturity may be considered to partially meet ICH Q10 requirements.

Level 3 Managed

An assigned maturity assessment rating of 3 indicates that the element under review has defined policies and procedures. While this level of maturity is considered to meet the minimum ICH Q10 requirements, it may be inefficient. For example, it may have a relatively high number of CAPAs, some repetition or recurrence of events, high levels of pharmaceutical process troubleshooting, and a costly supply chain supported by high stock levels with potential for supply disruption. Improvement projects identified from CAPA processes are more likely to be focused on corrective actions. Risks to the supply chain are identified with reactive actions to resolve disruptions. Continual improvement projects are largely reactive with some traces of proactive activity. This level of maturity represents the application of the minimum acceptable standard.

Level 4 Improved

An assigned maturity assessment rating of 4 indicates that the element under review demonstrates improved execution and enhanced performance. There are well-defined policies and procedures that are routinely and effectively applied. The management review and oversight processes are routinely deployed, and improvements are identified and acted upon. The process operates on both a reactive (corrective) and proactive (preventive) basis. Risks to the supply chain are identified, understood, and proactively managed. This level of maturity fully meets ICH Q10 requirements.

Level 5 Optimized

An assigned maturity assessment rating of 5 indicates best in class. The element under review is optimized and continual improvement processes are routinely embedded in the workflow. The process is proactive, agile, and can respond quickly to the business needs. It reacts effectively with minimal resources to emerging issues and routinely operates on a proactive, preventive, and predictive basis. Oversight and review processes are optimized to drive accountability and ownership, and there is a formal responsive process for escalation. The supply chain is effective and agile with risks identified and minimized, and efficiency is optimized to its highest level. This level of maturity is best in class and is optimized to deliver maximum benefit to the business.

3.2.2 Quantitative and Qualitative Aspects

Detailed and specific qualitative criteria associated with the five maturity levels are included in the tool to guide the assessment team in accurately evaluating the current state of capabilities, competencies, and associated behaviors and to reflect those findings in the assigned maturity ratings.

Figure 3.3 illustrates the relationship between the quantitative (Maturity Rating) and qualitative (Maturity Criteria) aspects for the APQ self-assessment tool.

Figure 3.3: APQ Self-Assessment Tool – Relationship between the Maturity Rating and Maturity Criteria

Maturity Rating

Maturity Criteria

Level 1 Undefined	Compliance risk	• Undefined • Uncontrolled • Not monitored • No evidence	☐ No SOPs. ☐ No formal process for documenting CAPA. ☐ No monitoring or traceability oversight.
Level 2 Defined	Partially meets ICH Q10 requirements	• Partially defined • Not formally controlled • Not formally monitored • Person dependent	☐ SOP provides high-level overview and expectations (lacks details for defined responsibilities, process, and expectations). ☐ Formal process to document CAPA exists. ☐ CAPAs are monitored, however the process is not defined in an SOP.
Level 3 Managed	Fully meets ICH Q10 requirements	• Defined policy and processes • Meets requirements for application • Process monitoring and controls in place	☐ SOP defines process, expectations, and responsibilities across individual site or functions. ☐ Process for documenting CAPA is applied, however may have inconsistencies in execution from record to record. ☐ Monitoring process is defined in an SOP.
Level 4 Improved	Demonstrates improved/ optimized execution	• Defined policy and processes • Routine application • Routine monitoring, advancing improvements	☐ SOP defines process, expectations, and responsibilities across the organization's entire network. ☐ Process for documenting CAPA is executed consistently from record to record, across the PQS (Pharmaceutical Quality System). ☐ Robust and defined monitoring ensuring successful KPI performance for the CAPA quality system.
Level 5 Optimized	World class/industry leader	• Proactive • Continual improvement • Predictive	☐ CAPA documentation process is periodically reviewed and proactively enhanced. ☐ Process for documenting CAPA includes full integration with PQS processes, seamless network collaboration, and proactive actions to drive continual improvement. ☐ CAPA Key Performance Indicators and Key Behavioral Indicators are engrained within the CAPA quality system. ☐ Monitoring process is proactive and assesses real time data. May include evaluating stress points and forecasting of upcoming CAPA; further granularity of CAPA for trending (category or effectiveness) is included within the documented process.

The APQ self-assessment tool provides space to contemporaneously record observations, evidence, and outcomes that may be later leveraged to develop the formal assessment report. This APQ Assess and Aspire Report, prepared in the organization's preferred format, details the findings of the assessment and the recommendations for next steps. The report should be presented to management, the functional leader, and the business process owner(s). A formal summary report should also be submitted to the executive sponsors. Each Guide in the APQ Guide Series Practical Module includes an example APQ Assess and Aspire Report.

3.3 Cross-Functional Team Approach

3.3.1 Self-Assessment Team (*Assess and Aspire*)

An APQ self-assessment team should be formed to perform the Assess and Aspire phases of the APQ framework process. The APQ program is not intended as an audit process but as an overall self-improvement process undertaken in the development of an organization. Effective self-assessment emerges from a culture of honest dialogue and critical thinking. It is best approached as a learning opportunity for a cross-functional self-assessment team made up of technical experts drawn from relevant fields such as:

- Quality Assurance
- OPEX
- Learning and development professionals
- Process owners and/or process users from independent sites in the organization

A small cross-functional team that has strong executive sponsorship is essential to ensuring an effective assessment is conducted. Potential improvements that are identified may be more difficult to implement if executive sponsorship is not secured at the outset.

This self-assessment team should actively engage with both the business process owner(s) and functional leadership of the element under assessment. This is essential to ensuring that the improvement recommendations and prioritization are agreed by all stakeholders. If this is not the case, a meeting between the sponsors, the self-assessment team, and the functional/process owner may be necessary to negotiate the next steps. The self-assessment team should have excellent interpersonal and communication skills and be committed to completing the tasks on time with a consistent approach to all criteria.

The cross-functional team approach should help to neutralize the challenges of team bias and ensure that there is an appropriate knowledge of detail within the team necessary to perform a thorough assessment. During the assessment, evidence of the following factors should be reviewed by the team to document the baseline “as found” practices, and serve as a basis for prioritizing the improvement and the post-action comparison:

- Process inputs (e.g., SOPs, process documentation/workflows, and training records)
- Execution-related documents (e.g., completed or in-process records, and related documentation)
- Demonstrated process outcomes (e.g., results, efficacy analysis, and trend analysis)
- Demonstrated behaviors such as leader standard work

It is strongly recommended that the cross-functional assessment team practice the Gemba method of “Go, Look, Ask, Coach” as part of the inquiry and assessment process. This approach ensures a full understanding of the current situation, identification of potential improvement opportunities and issues, and opportunity to provide constructive feedback to the department or function under review. The location of the Gemba walks should include observing front line activities including engagement with a cross-section of process users (e.g., attendance at CAPA meetings run by the CAPA system owner) and participation in the relevant oversight and review meetings conducted by the process and/or functional owners. For additional recommendations on how to conduct an effective Gemba activity refer to the ISPE Cultural Excellence Report [4].

Ideally, the assessment activities should be carried out by an independent self-assessment team not directly responsible for the activities under review. This team is also responsible for preparing the Aspire Report which identifies and prioritizes the improvement opportunities.

3.3.2 Improvement Team (Act and Advance)

In the Act phase, the design of the Improvement Action Plan should include engagement with key stakeholders, process owners, and process users. When the Improvement Action Plan is fully developed, ownership of the APQ framework process transitions from the self-assessment team to an APQ improvement team.

This APQ improvement team is responsible for the execution and evaluation of the APQ Improvement Action Plan during the Act and Advance phases. This team should be led by the functional owner and/or business owner of the PQS system element under review. The team should consist of the necessary cross-functional resources applicable to the improvement area(s). Oversight of the progress of this team's improvement actions should be the responsibility of the site leadership team, actively supported and sponsored by the global leadership.

4 APQ Benchmarking

The APQ program incorporates a pre-assessment and post-action benchmarking questionnaire tool developed by the St.Gallen OPEX Benchmarking team specifically for use with the APQ program.⁵ It provides standardized support to initially baseline the level of quality performance and allows organizations to prioritize which of the four ICH Q10 elements to embark upon first with the APQ framework. Used in conjunction with the APQ self-assessment and self-improvement tools, the pre- and post-benchmarking activities offer objective evidence of performance improvement to support ongoing investment of time and resources. The effectiveness and impact of the improvements from the APQ program can be evaluated and quantified, and priorities for next improvement opportunities can be derived.

4.1 Benchmarking Questionnaire

The St.Gallen APQ benchmarking questionnaire (provided in Appendix 7) can be used by organizations for either:

- Internal self-evaluation (no peer comparison possible), or
- External benchmarking against a tailored industry peer group (selected from the St.Gallen OPEX database of hundreds of pharmaceutical production sites).⁶

The benefits of opting to engage in the external benchmarking process include:

- Support from the St.Gallen team in terms of accurate data collection and completion, as part of data validation procedures applied to all datasets entering the benchmarking process
- A personalized APQ Benchmarking Report (example provided in Appendix 8) as an output of the process – this report will allow organizations to:
 - Understand individual strengths and weaknesses
 - Gain meaningful comparisons of its position as compared to a tailored peer group of comparable organizations/sites (based on the contextual factors queried in the questionnaire)

This APQ benchmarking questionnaire is a subset of the scientifically derived legacy St.Gallen OPEX benchmarking performance indicators and selected enablers that have been proven as meaningful surrogates for overall system stability and performance [10].

The APQ Benchmarking Tool is simple to use and user friendly, but still comprehensive enough to deliver a solid and balanced overview of operational performance and quality management maturity. The benchmarking tool includes:

- 13 KPIs in four dimensions (maintenance, quality, delivery, and people)
- 18 maturity questions in three categories (organization enablers, social and employee enablers, and technical and tool enablers)
- Contextual factors (such as site type and size, production technology platforms and size, and days of inventory on hand)

⁵ ISPE is in a partnership with the Institute of Technology Management at the University of St.Gallen (Switzerland) to collaborate on tools designed to advance the state of pharmaceutical quality.

⁶ For information about participating in the external benchmarking study, contact the St.Gallen OPEX Benchmarking team at benchmarking@unisp.ch. St.Gallen may collect a fee for the benchmarking service.

- High-level ICH Q10 maturity evaluation that contains questions scored on a Likert scale:
 - 71 maturity questions evaluating management responsibilities, knowledge management, CAPA system, quality risk management, process performance and product quality monitoring system, change management system, and management review
 - 8 dedicated maturity questions on Environment, Health, and Safety to complement the overall picture of maturity

This tool is intended to assist in the determination of where initial improvement efforts can be best invested.

Additionally, the St.Gallen team offers participating APQ sites that are engaged in broader business performance improvement programs an opportunity to seek synergies and upgrade the APQ Benchmarking to a full St.Gallen OPEX & QC Lab Benchmarking, which provides a more granular and comprehensive set of benchmarking results and insights.

The metrics and enablers included in the APQ Benchmarking Tool are summarized in Table 4.1.

Table 4.1: High-Level Performance Evaluation using the St.Gallen APQ Benchmarking Tool

St.Gallen APQ Benchmarking Tool			
Maintenance	Quality	Delivery	People
1. Share of Unplanned Maintenance 2. Maintenance FTE / Total FTE	3. Rejected Batches 4. Recurring Deviation 5. Quality FTE / Total FTE 6. IOOS rate (Lab) 7. Deviation Closure Time	8. Service Level – Delivery (OTIF) 9. Service Level – Supplier (OTIF) 10. Customer Complaint Rate 11. Adherence to standard lead time	12. Safety level 13. Sick leave
Enabler		Contextual Factors	
• Organization enablers • Social and employee enablers • Technical and tool enablers		• Site type and size • Production technology platforms and size • Days on Hand (DOH)	
ICH Q10 Maturity Assessment			
• Management Responsibilities • Knowledge Management • CAPA System • Quality Risk Management		• Process Performance and Product Quality Monitoring System • Change Management System • Management Review	

Refer to Appendix 7 for the APQ Benchmarking Tool and to Appendix 8 for an example APQ Benchmarking Report.

4.2 APQ Pre-Assessment Benchmarking

At the outset of the APQ framework process, it is useful to establish a baseline of current performance by formally documenting selected KPIs and organizational enablers. The goal of the pre-assessment benchmark is to set a quantitative baseline and to identify potential improvement opportunities. The APQ Benchmarking Tool can also inform the prioritization of which PQS element an organization should focus its resources to apply the deeper diagnostic APQ self-assessment tool as part of the first Assess phase. Ultimately, the results from this pre-assessment benchmark can act as an important comparator or baseline against which future advancement results can be evaluated using the post-action benchmark.

4.3 APQ Post-Action Benchmarking

At an appropriate duration after implementation of the APQ framework process (generally within an 18- to 24-month timeframe), it is recommended that post-action benchmarking is performed using the APQ Benchmarking Tool. This post-action benchmarking is intended to evaluate the impact of the improvements on the overall company performance.

The results of the post-action benchmark can be compared to the pre-assessment baseline to provide evidence of value to the business and return on investment.

As part of the iterative continual improvement process, if the overall performance goals have not yet been met, a return to the Aspire phase may be needed to identify further improvement activities or to review the effectiveness criteria. If the overall performance goals are confirmed, the next improvement opportunity may be prioritized to commence another cycle of the APQ Assess, Aspire, Act, and Advance process on any one of the four PQS elements as required.

5 Introduction to APQ-CM

Part 2 of this Guide covers the practical application of the APQ framework to an organization's Change Management (CM) system. Given the central role of the CM system to the ongoing effectiveness of the PQS, this Guide offers practical strategies on how to use the APQ framework to:

- **Assess:** Evaluate the current maturity level of the CM system using a Maturity Assessment Tool (Chapter 6)
- **Aspire:** Set improvement targets to enhance and improve the CM system (Chapter 7)
- **Act:** Develop and execute a targeted Improvement Action Plan (Chapter 8)
- **Advance:** Evaluate the effectiveness of the improvement actions (Chapter 9)

In Chapters 6 to 9, **APQ Framework Universal Topics** are noted. These sections represent information that is universally applicable to all four PQS elements, though content may be provided in the context of the CM system for ease of understanding.

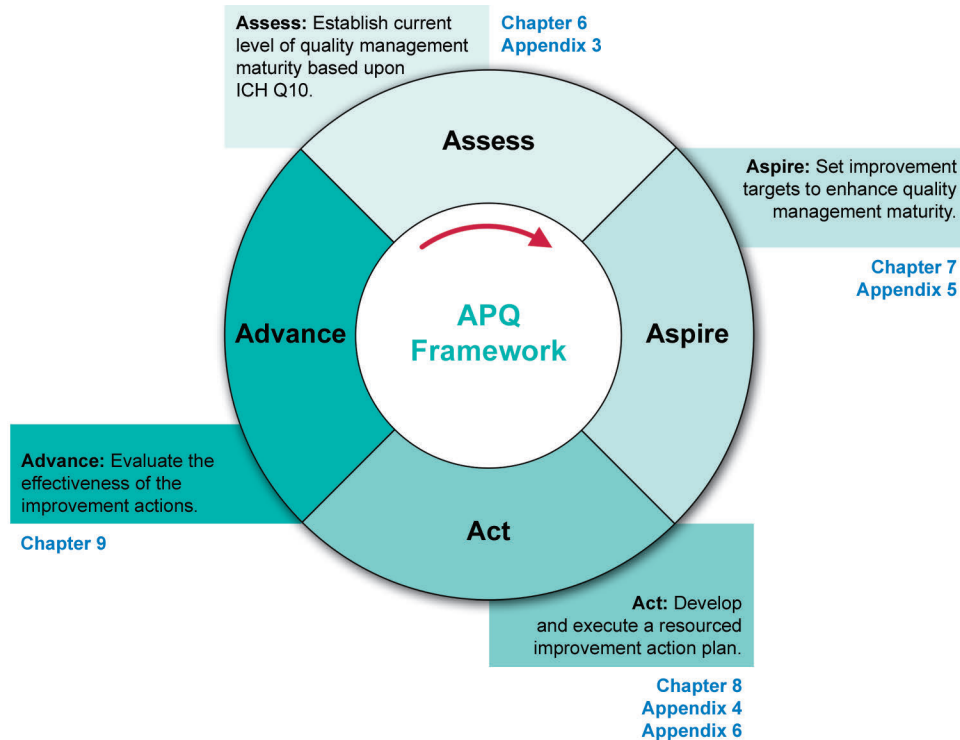
The following resources are provided in the APQ-CM Appendices:

- APQ Maturity Assessment Tool for the CM system (Appendix 3)
- APQ Catalog of Improvement Tools and KPIs for the CM system (Appendix 4)
- Case studies:
 - Example APQ-CM Assess and Aspire Report (Appendix 5)
 - Example Template for APQ-CM Improvement Action Plan (Appendix 6)

Note: The information presented in Part 2 of this Guide builds on the prerequisite explanation of the APQ framework in Chapter 3.

Figure 5.1 provides a roadmap of the application of the APQ framework to the CM system, with chapter references for each phase of the framework.

Figure 5.1: Practical Application of the APQ Framework to the CM System – Roadmap



5.1 Key Concepts of the Change Management System

ICH Q10 [1] defines CM as:

“A systematic approach to proposing, evaluating, approving, implementing and reviewing changes.”

CM is one of the fundamental components of any PQS. The effective management of change throughout the product lifecycle enables quality improvement and is critical to patient safety, supply reliability, as well as operational effectiveness and efficiency.

Changes may be driven reactively by corrective actions and proactively by continual improvement initiatives and innovation. Changes can be driven through knowledge gained from management review of process performance and product quality monitoring data. The PQS must have a robust CM system that uses knowledge management and quality risk management principles to facilitate quality improvement and to ensure a continued state of control. There are many diverse drivers, sources, and triggers for change that emerge across the pharmaceutical product lifecycle. These can include, for example:

- Evolving regulatory requirements
- Inspection findings
- Equipment and facility upgrades
- Changing customer or third-party requirements
- Supplier changes

- Process optimization to reduce variability and improve system efficiency
- Performance reviews of the CM system and other PQS metrics such as deviation and CAPA trends
- Technology transfers internally or to the external network
- Scientific or technological advances

Each organization should therefore ensure that its CM system is capable of planning, evaluating, and executing change in an agile and timely manner. Figure 5.2 outlines some of the potential drivers of change that can arise across the product lifecycle.

Figure 5.2: Potential Change Triggers



5.1.1 Central Role of Change Management within the Pharmaceutical Quality System

ICH Q10 [1] emphasizes that a key role of the CM system is to ensure that “*continual improvement is undertaken in a timely and effective manner.*” Most importantly, the CM system “*should provide a high degree of assurance there are no unintended consequences of the change.*” The ICH Q10 guideline recommends that “*all changes should be evaluated by a company’s change management system*” and lists four critical aspects which should be taken into account in the evaluation and implementation of proposed changes:

“(a) Quality risk management should be utilised to evaluate proposed changes. The level of effort and formality of the evaluation should be commensurate with the level of risk;

(b) Proposed changes should be evaluated relative to the marketing authorisation . . . and/or current product and process understanding. There should be an assessment to determine whether a change to the regulatory filing is required under regional requirements. . . .;

(c) Proposed changes should be evaluated by expert teams contributing the appropriate expertise and knowledge from relevant areas . . . , to ensure the change is technically justified. Prospective evaluation criteria for a proposed change should be set;

(d) After implementation, an evaluation of the change should be undertaken to confirm the change objectives were achieved and that there was no deleterious impact on product quality.”

In addition to these minimum CM system requirements, mature programs will include further important attributes relating to:

- Performance management reviews of the CM system
- Application of a range of change effectiveness evaluation approaches which are applied post- implementation to confirm that outcomes are sustained
- Ongoing competency development of personnel involved in the planning, execution and evaluation of changes.

ISO 9001 [13]¹, the internationally recognized standard for QMS requirements, states:

“The adoption of a quality management system is a strategic decision for an organization that can help to improve its overall performance and provide a sound basis for sustainable development initiatives.”

“The organization shall continually improve the suitability, adequacy and effectiveness of the quality management system.

The organization shall consider the results of analysis and evaluation, and the outputs from management review, to determine if there are needs or opportunities that shall be addressed as part of continual improvement.”

Similar to the APQ framework, ISO 9001 [13] employs the Plan-Do-Check-Act (PDCA) cycle to systematically manage these improvements and emphasizes the importance of applying risk-based thinking, stating:

“Risk-based thinking enables an organization to determine the factors that could cause its processes and its quality management system to deviate from the planned results, to put in place preventive controls to minimize negative effects and to make maximum use of opportunities as they arise.”

This focus on risk-based continual improvement lies at the heart of an effective CM system and is one of the three main objectives of the ICH Q10 Guideline [1]:

“Facilitate Continual Improvement: *To identify and implement appropriate product quality improvements, process improvements, variability reduction, innovations and pharmaceutical quality system enhancements, thereby increasing the ability to fulfill quality needs consistently. Quality risk management can be useful for identifying and prioritising areas for continual improvement.”*

ICH Q10 specifically states:

*“In order to evaluate, approve and implement these changes properly, a company should have an **effective** [emphases added] change management system.”*

This requires the CM system to adopt a robust and integrated approach to the science and risk-based assessment, planning, and execution of change, in support of the original ICH Quality Vision (2003) [16]:

“Develop a harmonised pharmaceutical quality system applicable across the life cycle of the product emphasizing an integrated approach to quality risk management and science.”

¹ ISO [14] also provides useful advice for implementing efficient and effective quality management systems within small businesses in its handbook, titled ISO 9001:2015 for Small Enterprises – What to do? Advice from ISO/TC 176 [15].

In recent years, there has been an increased focus on the management of change across the pharmaceutical product lifecycle with the development of the ICH Q12 Guideline on Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management (2019) [17]. The concept paper for ICH Q12 from 2014 [17] acknowledged that challenges in realizing the ICH Quality Vision still remained. This highlighted a pressing need to improve the execution and communication of the science and risk-based assessments that enable change, with a particular focus required on the commercial manufacturing phase of the lifecycle. A more comprehensive set of principles of CM is provided in ICH Q12, Appendix 2 [17], which are consistent with the basic requirements already outlined in ICH Q10 [1]. These principles are provided in Table 5.1 and are helpful to review as they are consistent with the criteria presented in this Guide.

Table 5.1: ICH Q12 Principles of Change Management [17]

1.	Captures stimuli for change, including those that can improve product performance or process robustness;
2.	Ensures full understanding of the scope of the change and its implications for all aspects of the process and control strategy including the impact on ECs and aspects that are not ECs in affected marketing authorisations;
3.	Leverages existing process performance and product quality knowledge;
4.	Requires science-based risk management and risk categorisation of the intended change; considers the potential impact if the intended change is not implemented;
5.	Determines data (existing and/or to be newly generated) needed to support the change and accordingly develops study protocols describing the methods, prospective acceptance criteria as well as additional post-implementation process performance and/or product quality monitoring as necessary;
6.	Ensures that an appropriate regulatory submission is filed when required;
7.	Uses a defined change control process to approve or reject the intended change and involve appropriate stakeholders, including but not restricted to Manufacturing, Quality, and Regulatory Affairs personnel;
8.	Ensures implementation of the change is based on: a. Review that the change as implemented remains aligned with the relevant study protocols, PLCM [Product Lifecycle Management] document, or PACMP [Post-Approval Change Management Protocol]; b. Assessment of data generated to demonstrate that the change objective and acceptance criteria were met;
9.	Ensures that risk-mitigating steps are developed in the case of deviations from acceptance criteria, or identification of unanticipated risks;
10.	Verifies, post-implementation, that relevant changes have been effective in achieving the desired outcome with no unintended consequences for product quality; If deviations associated with post-approval changes are detected, ensures that the issue is managed via the company's deviation management process and appropriate corrective and/or preventive actions are identified and undertaken via the company's corrective and preventive action (CAPA) system;
11.	Post-implementation: a. Captures new product/process knowledge gained during implementation of the change; b. Where applicable, ensures that regulatory filings are updated, and an assessment is made as to whether updates to the PLCM document are needed; c. Where applicable, ensures that the change is included and assessed as part of the Product Quality Review (PQR);
12.	The change management system should be available for review during audit/inspection.

The imperative for the effective management of change in the post-approval phase of the lifecycle was also highlighted in the FDA Drug Shortages: Root Causes and Potential Solutions Report [18]:

“Following first approval, continual technical improvement and updating is needed because facilities age, routine operations require updates to maintain a state of control, technology evolves, suppliers change, and scientific expectations may also change. A failure to implement such updates and improvements can lead to quality problems that result in drug shortages.”

Proactive management of change to avoid these quality problems requires the purposeful integration of the dual enablers of the PQS, namely quality risk management and knowledge management. In addition, product and process knowledge obtained through effective monitoring presents opportunities for continual improvement. Sections 5.1.3 and 5.1.4 discuss these key concepts as they relate to the effective management of change within an organization.

5.1.2 Support and Incentivization for Continual Improvement

One of the eight overarching goals of the APQ program (see Appendix 1) is to support and incentivize continual improvement as a means to achieving long-term value within a pharmaceutical organization. However, the APQ program also acknowledges that this requires considerable skill and effort to ensure effective and consistent application of these principles.

The APQ program embraces a culture of continual improvement and seeks to provide practical strategies to facilitate a shift away from a traditional view that maintaining a post-approval “state of control” equates to maintaining the *status quo*. Effective management of change is inherent to any continual improvement program and requires tools and approaches for change planning, data analysis and review, effective decision making, change execution, and change evaluation. This Guide seeks to support the development of these skills and approaches.

The Pharmaceutical Inspection Co-operation Scheme (PIC/S) guidance document, Recommendation on How to Evaluate and Demonstrate the Effectiveness of a Pharmaceutical Quality System in relation to Risk-based Change Management (PI-054-1) [19], also acknowledges:

“A risk-based change management system . . . should lead to the timely management of risks to product quality and patient safety, as well as better quality and manufacturing performance, continual improvement and innovation.”

Published in July 2021, this PIC/S guidance document provides practical guidance on PQS effectiveness and CM for GMP health authority inspectors noting that:

“Mature risk-based change management within an effective PQS is considered foundational to enable greater regulatory flexibility in reporting of post-approval changes.”

Risk-based CM within an effective PQS is essential to support continual improvement and is a key aspect of post-approval lifecycle management. With this in mind, the PIC/S [20] Expert Circle on Quality Risk Management has trained GMP inspectors from PIC/S participating health authorities on what a good risk-based CM system can look like within the PQS as well as how to assess the overall level of effectiveness of the PQS and quality risk management implementation. Details of their expectations can be found in the PIC/S Aide Memoire on Assessment of Quality Risk Management Implementation (PI-038-2) [21]. This inspector training initiative could play a significant role in post-approval lifecycle management which depends on consistent application of risk-based thinking by both industry and health authorities, working together within the context of more flexible regulatory oversight. Robust risk-based decision making and the role of quality risk management as an enabler to an effective PQS is further discussed in Section 5.1.3.

One further example of regulatory guidance related to CM and quality improvement can be found in EU EMA Eudralex Volume 4, Chapter 1 – Pharmaceutical Quality System [22], which states:

“Continual improvement is facilitated through the implementation of quality improvements appropriate to the current level of process and product knowledge.”

“Arrangements [should be] in place for the prospective evaluation of planned changes and their approval prior to implementation taking into account regulatory notification and approval where required”

“After implementation of any change, an evaluation [should be] undertaken to confirm the quality objectives were achieved and that there was no unintended or deleterious impact on product quality.”

The **APQ Assess, Aspire, Act and Advance Framework** has been specifically developed to provide such a formal quality improvement process where:

- **Assess** allows a baseline to be established and opportunities for potential improvement to be identified
- **Aspire** involves selecting and prioritizing the improvements to act upon aligned with the organizational mission
- **Act** requires an integrated, fully resourced action plan is developed, which considers potential technological solutions, to deliver targeted improvement outcomes
- **Advance** evaluates and confirms the required outcomes have been achieved, lessons learned are shared, and the revised practices are integrated into key business processes to sustain the improvements into the future.

Application of the holistic APQ framework to the CM system provides a structured approach to critically evaluate the robustness of current practices and offers best practice improvement suggestions to build strength into future practice.

5.1.3 Integration of Quality Risk Management in the Effective Management of Change

Effective management of change requires that risk-based approaches are embedded across every stage of the change process, including but not limited to:

- Evaluation of the initial change stimuli
- Establishment of the ability of the proposal or design to deliver improved product performance or process robustness
- Risk categorization
- Consideration of the potential implementation impacts (including the impacts of not implementing it)
- Development of the risk-based acceptance criteria and the risk mitigations in the event of deviations arising or identification of unanticipated risks

From a patient safety perspective, it is even more important to continue to evaluate the post-implementation outcomes through a risk perspective to confirm that the change has been effective and that there are no unintended consequences to product quality. This may require enhanced monitoring in the initial phases post-implementation. If deviations are detected via the organization's deviation management process, timely and appropriate corrective and/or preventive actions must be put in place and tracked through the CAPA system; the lessons learned should be captured and shared as part of the PQS continual improvement process.

A useful framework for evaluating risks throughout the CM process is provided in the *ISPE Guide: PQLI® from Concept to Continual Improvement, Part 3 – Change Management System as a Key Element of a Pharmaceutical Quality System* [5]. Figure 5.3 shows the relationship and connection points between the CM system and the quality risk management system. Table 5.2 covers the application of quality risk management at each of the four stages of the CM system model, as provided in the PQLI Change Management Guide.

Figure 5.3: Relationship between Change Management System Model and ICH Q9 Quality Risk Management Model [5]

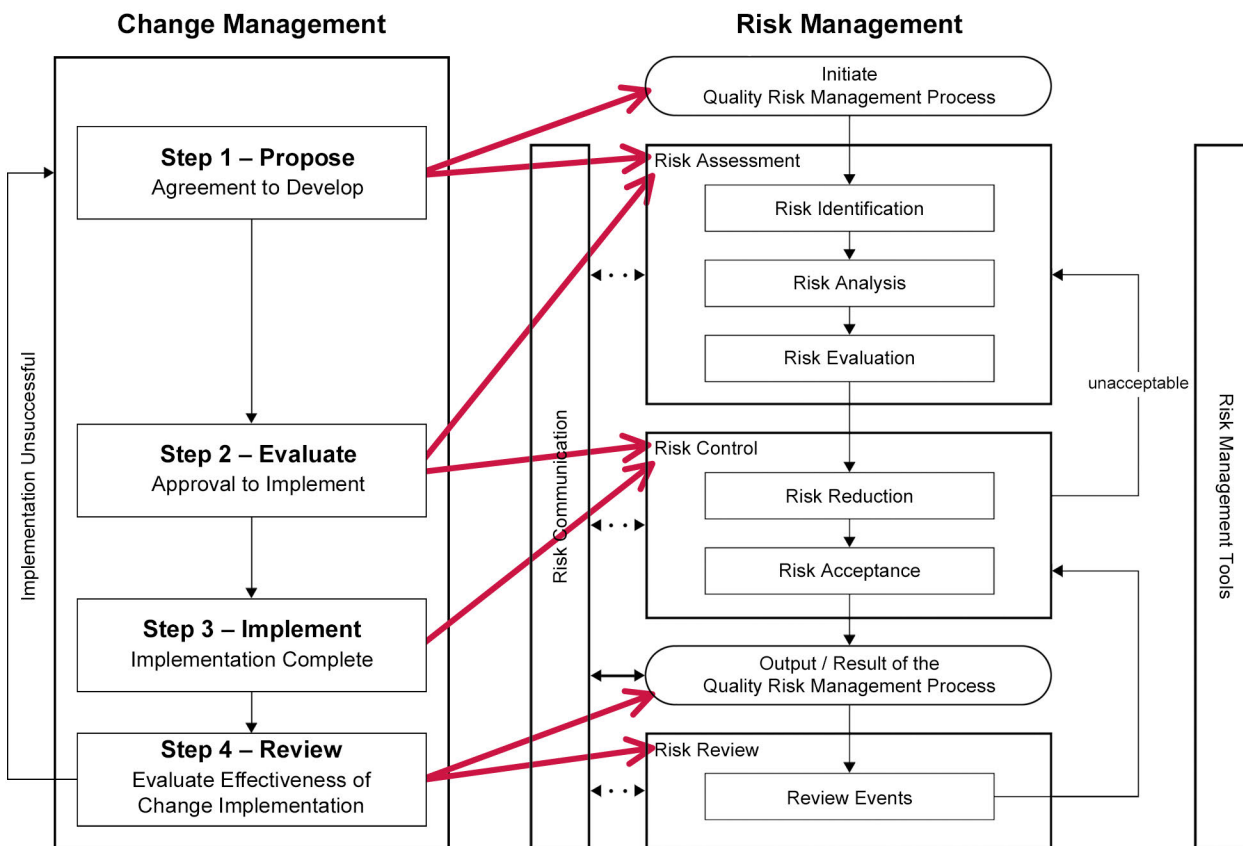


Table 5.2: Integration of ICH Q9 Quality Risk Management Model and the CM System [5]

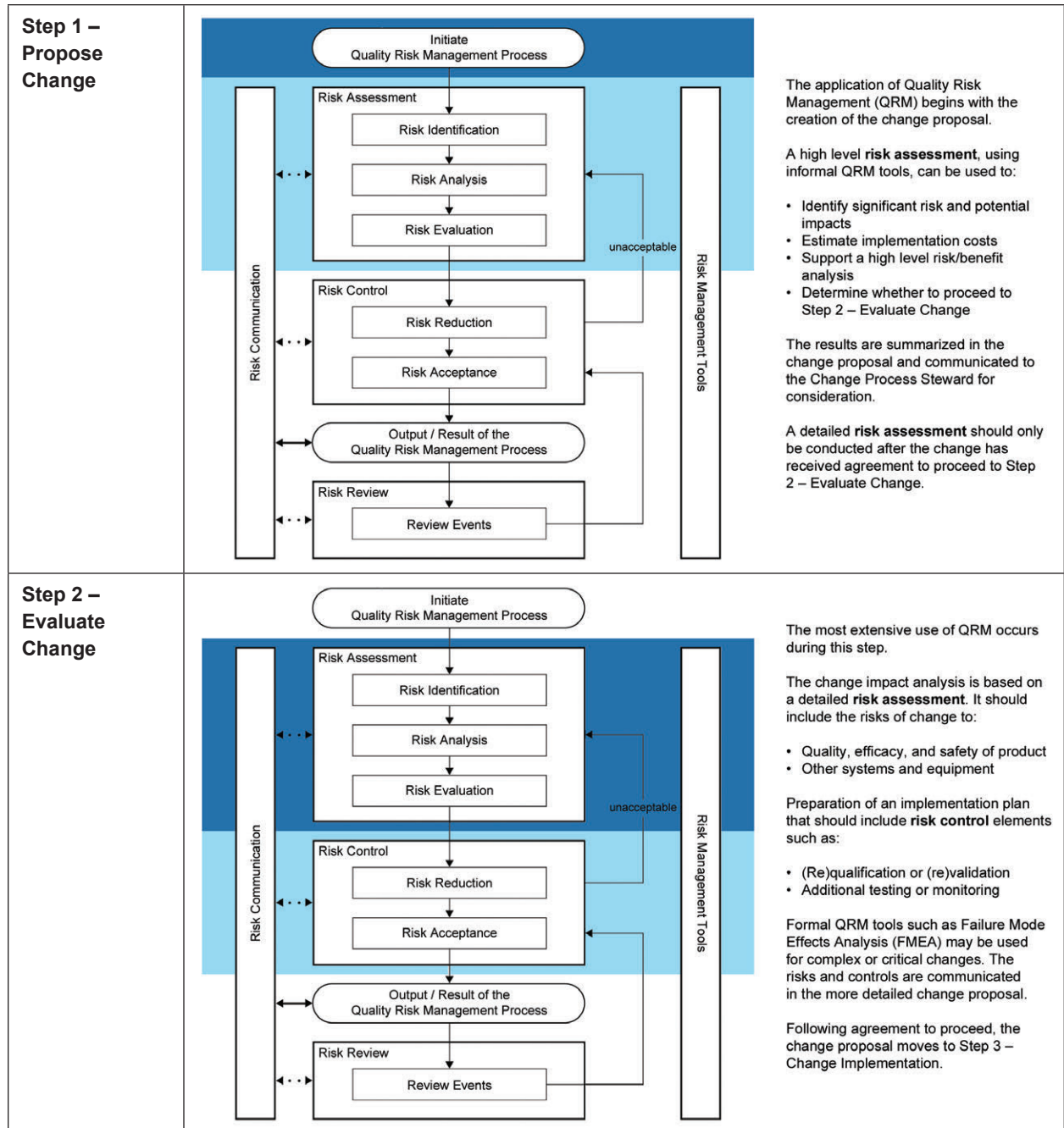
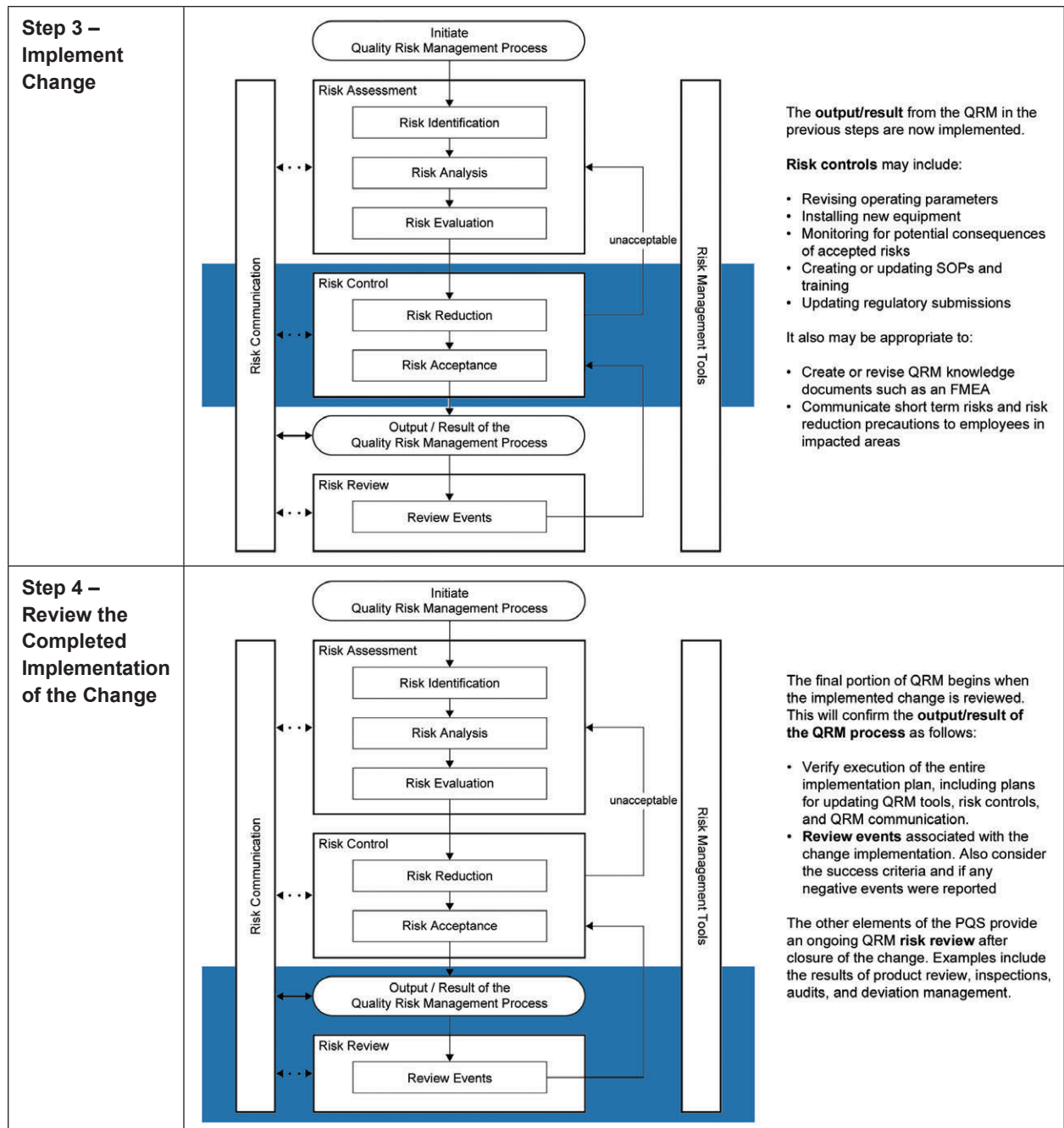


Table 5.2: Integration of ICH Q9 Quality Risk Management Model and the CM System [5] (continued)



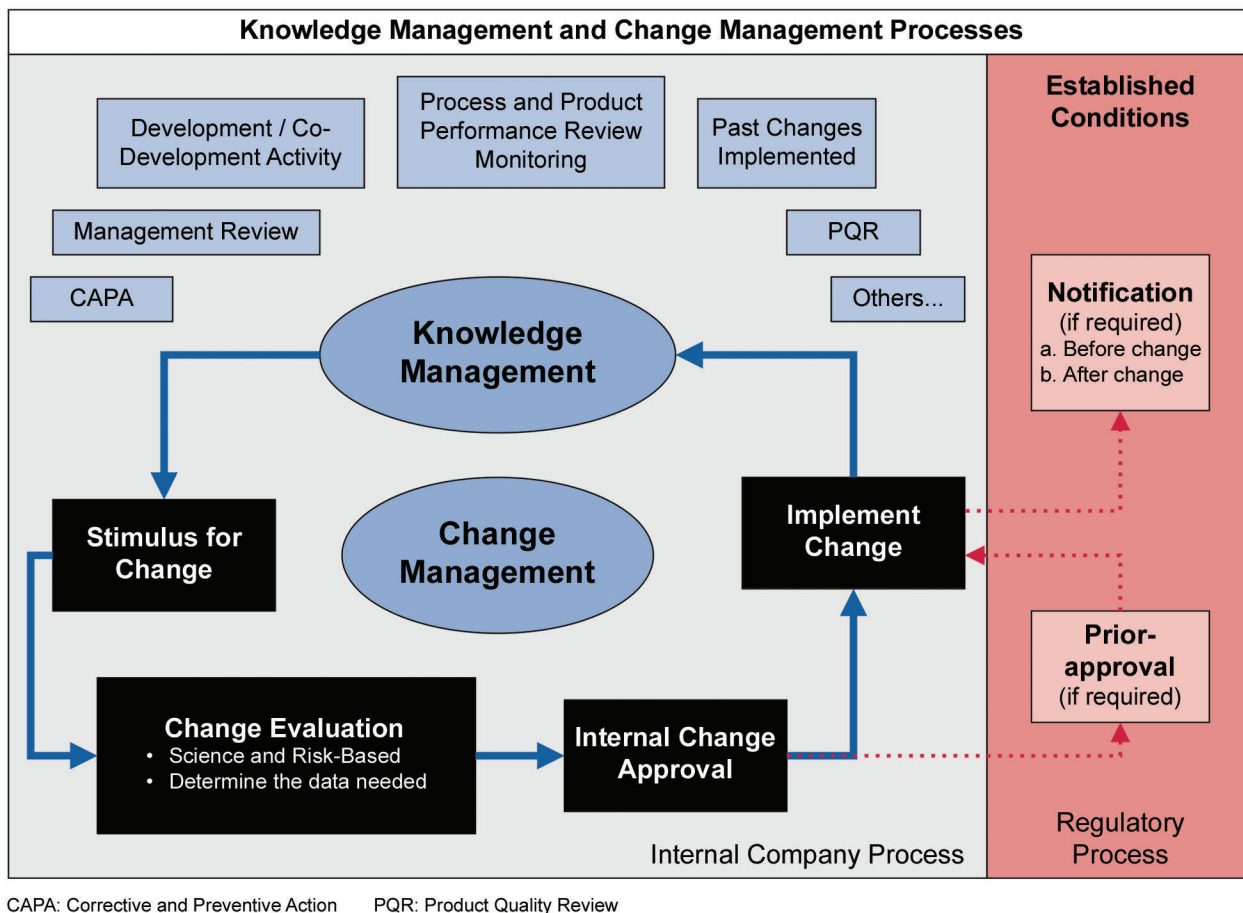
5.1.4 Integration of Knowledge Management in the Effective Management of Change

The ICH Q12 Guideline [17] states:

“An effective change management system includes active knowledge management, in which information from multiple sources is integrated to identify stimuli for changes needed to improve product and/or process robustness.”

The central relationship between knowledge management, CM, and the regulatory process is illustrated in the ICH Q12 Guideline as shown in Figure 5.4.

Figure 5.4: Connection Between Knowledge Management and Change Management Process (ICH Q12 [17])



The ICH Q12 [17] framework seeks to ensure that organizations have a full understanding of the scope of the change and its implications for all aspects of the control strategy by leveraging existing process performance and product quality knowledge. It also requires that science-based risk management and risk categorization of the intended change is undertaken, which includes consideration of the potential impact if the intended change is not implemented.

This core concept of integration of knowledge management with a strong quality risk management program is positioned as a key success factor for enhancing the effectiveness of the PQS, as detailed in the *ISPE Good Practice Guide: Knowledge Management in the Pharmaceutical Industry* [7]. That Good Practice Guide also provides practical approaches to advancing the maturity of knowledge management to ensure that product and process understanding and scientific, data-led approaches underpin risk-based decision making.

“These dual enablers need to function together so that the evolving knowledge base is readily available as a key input into the quality risk-based decisions that drive actions to maintain a state of control and facilitate continual improvement.” [7]

The Good Practice Guide provides a useful visual representation of how risk and knowledge are inversely proportional, as shown in Figure 5.5:

“Increased knowledge leads to decreased uncertainty, and therefore decreased risk . . . Over time, as knowledge increases, risk decreases.” [7]

Figure 5.5: The Risk-Knowledge Infinity Cycle: Decreasing Risk through Increasing Knowledge [7]
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The ability to demonstrate scientific knowledge and process understanding about attributes impacted by a proposed change is foundational to producing an appropriate risk assessment of the proposed change. More complex changes will require enhanced product and process understanding. The ability of an organization to manage the collation, curation, access, and use of their knowledge is quickly becoming a critical business capability.

It is important to note that when planning, evaluating, and executing changes, simply having access to organizational knowledge and relevant databases is not enough. It also requires the availability of skilled resources and personnel with appropriate expertise to accurately assess the risks as well as qualified data scientists to interpret the data and provide knowledge and insights to support effective risk-based decision making. Integration of these dual enablers of knowledge management and risk management is a critical attribute of more mature, best-in-class PQS. For those seeking to advance pharmaceutical quality within their organization, the *ISPE Good Practice Guide: Knowledge Management in the Pharmaceutical Industry* [7] is a useful resource when read in conjunction with this APQ Guide Series.

5.1.5 Management of Post-Approval Change

One further critical consideration related to post-approval changes implemented during the commercial phase of the product lifecycle is the careful evaluation of potential impacts on associated regulatory filings, existing product authorizations, and the requirement for regulatory pre-approval. These impacts have been central to some of the disincentives for timely improvements to manufacturing operations. The FDA Drug Shortages: Root Causes and Potential Solutions Report [18] acknowledges that *“global approvals for changes can often take years because of varying requirements and timelines across different regulatory authorities,”* a key consideration which ICH Q12 [17] set out to address.

When evaluating the impact of proposed changes to commercial manufacturing, the *ISPE Guide: PQLI® from Concept to Continual Improvement, Part 3 – Change Management System as a Key Element of a Pharmaceutical Quality System* [5] provides the following aspects that should be taken into consideration:

- *“The impact on other commercial and development products that are manufactured, packed, or tested in the same facility*
- *The impact on any approved regulatory filings . . . for the products which are the subject of the change, and for other products that are located in the same facility*
- *Any differences in the status or extent of regulatory filings, e.g., different countries may have different requirements for the manufacturing description or files may not yet have been approved*
- *The impact on other facilities that manufacture, pack, or test products that are the subject of the change*

- *The impact on upstream activities, e.g., component and raw material supplies*
- *The impact on downstream activities, e.g., packing, distribution”*

The ICH Q12 Guideline (2019) [17] was developed with the intent of harmonizing post-approval CM by enabling companies and regulators to manage Chemistry, Manufacturing, and Controls (CMC) changes in a more transparent and efficient manner across the product lifecycle. This is driven by the need to facilitate regulatory oversight on the basis of risk while optimizing resources for assessment and inspection. It places greater responsibility on organizations themselves to maintain and update their dossier to ensure conformance, using harmonized approaches and simplified interpretations of expectations across the ICH regions. An even greater emphasis is placed on the effectiveness and maturity of both the internal CM system and the quality risk management process for those organizations seeking this regulatory flexibility.

ICH Q12 [17] states:

“The extent of this operational and regulatory flexibility and its adequate implementation is subject to the regulatory framework in place, as well as product and process understanding (ICH Q8(R2) and Q11), application of quality risk management principles (ICH Q9), and an effective pharmaceutical quality system (ICH Q10).”

The opportunity to attain this regulatory flexibility is unlikely to become a reality until more agreement is reached on global regulatory reliance practices between agencies. Nevertheless, the ICH Q12 Guideline [17] and Q12 Annexes [23] offer valuable resources for any organization planning to advance the maturity of their risk-based CM processes. The ICH Q12 approach positions the product control strategy as the central component of the regulatory commitment in the dossier and proposes a range of regulatory tools for prospective CM, such as the Post-Approval Change Management Protocol (PACMP) and the Product Lifecycle Management (PLCM) document, as well as structured approaches for handling frequent CMC post-approval changes and the stability data necessary to support the evaluation of CMC changes.

The attributes identified within this Guide offer one pathway to enhance the maturity of the CM system to meet the regulatory expectations for risk-based post-approval CM.

5.2 Performance Management of the Change Management System

Good governance practices and robust periodic performance reviews are central to the regulatory expectations for an effective PQS. As noted in ICH Q10 [1]:

“Management should assess the conclusions of periodic reviews of process performance and product quality and of the pharmaceutical quality system.”

ICH Q10 expectations also include a structured process for the systematic review of KPIs:

“Performance indicators that measure progress against quality objectives should be established, monitored, communicated regularly and acted upon as appropriate.”

While the capability to measure progress, monitor for trends, and report regularly is typically clear, it is the ability to act appropriately in a timely manner that distinguishes those more mature organizations. Specifically with respect to the CM system, ICH Q12 [17] provides additional guidance on expectations for management review both in terms of performance management of individual changes and of the CM system itself, which include:

- *“Assessment of data generated to demonstrate that the change objective and acceptance criteria were met.”*
- Post-implementation verification that *“relevant changes have been effective in achieving the desired outcome with no unintended consequences for product quality.”*

- Reviewing the results of that post-implementation verification *“as a measure of change management effectiveness (e.g., to identify improvements to the change management system).”*
- *“Monitoring the timeliness of the change management system to assure that changes are implemented in a timely manner commensurate with the criticality/urgency identified for the change. When implementation is delayed, an assessment and mitigation of any risks associated with the delay should be made.”*
- *“Monitoring the performance of the change management system, such as assessing the frequency of intended changes that are not approved for implementation by the quality unit.”*

This Guide includes recommendations on how to apply a number of more innovative metrics and leading indicators to the CM system to enable rigorous management review and to drive proactive action. These include tracking:

- Aging changes
- % of effective changes
- % of late effectiveness checks
- Milestone right first time
- % of open change records per phase (i.e., CM system phases of plan, evaluate, execute, and check)
- Trend of emergency (unplanned) changes
- Ratio of changes that are initiated reactively versus proactively

Further details can be found in the APQ Catalog of Improvement Tools and KPIs for the CM system (Appendix 4).

5.3 Personnel Competency Development: Knowledge, Skills, and Behaviors for Effective Change Management

In addition to robust processes and agile practices, an organization's PQS can only be truly effective if the people who use it have the requisite knowledge, skills, and behaviors to fulfill their specific responsibilities every day. With respect to the effective management of change, there is a wide range of key personnel that play an active role in the planning, evaluation, execution, and checking of individual changes. Their ability to perform consistently is directly linked to the company's approach to organizational capability development and individual competency development.

Key capabilities and competencies for effective CM include:

- Interpersonal communications skills
- Cross-functional teamwork and collaboration skills
- Knowledge seeking and knowledge sharing behaviors
- Fundamental data analysis capabilities to assess the need for change
- Proactive risk management mindset and core risk assessment and risk management skills
- Project management skills commensurate with the level and complexity of change being managed

Note: Quality records should supplement project management tools, not be the project management tool.

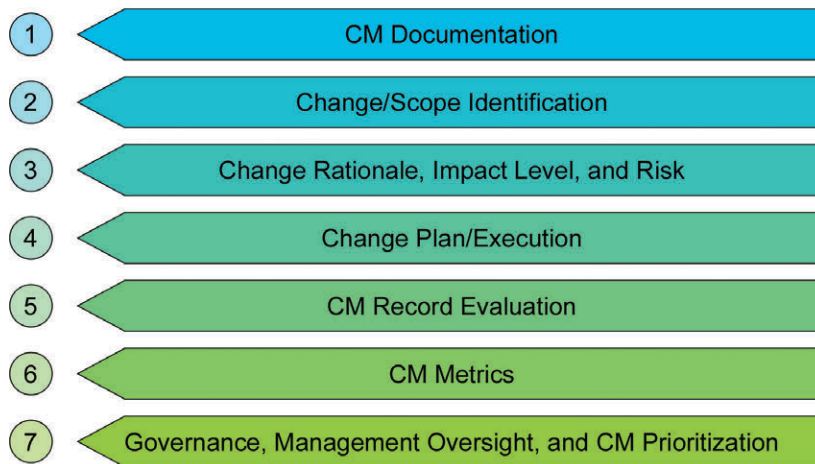
- Technical report writing skills to ensure that anyone picking up a CM record can understand the key aspects of the change
- Depending on the driver/trigger for change, other core competencies may include structured problem solving, root cause analysis and Lean/Six Sigma improvement approaches

This Guide highlights several skills and attributes necessary within a mature CM system to deliver tangible value to the organization beyond the management of compliance requirements.

5.4 Seven Sub-Elements of the APQ-CM System

For the APQ program, the CM system is categorized into seven distinct sub-elements as shown in Figure 5.6. These sub-elements were determined using feedback from a wide range of inputs from regulatory bodies, academia, and industry (through engagements, focus groups, and pilot studies).

Figure 5.6: APQ-CM Sub-Elements



Detailed qualitative evaluation criteria for these seven sub-elements are provided in the APQ-CM Maturity Assessment Tool, discussed in detail in the next chapter (Chapter 6) and provided in Appendix 3.

