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APQ Advancing Pharmaceutical Quality

ISPE Quality Management Maturity Program

GUIDE:

Process Performance and Product Quality Monitoring 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:

- CAPA system [2]
- Management Responsibilities and Management Review (MRR) [3]
- Change Management (CM) system [4]
- Process Performance and Product Quality Monitoring System (PPPQMS)

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: PPPQMS 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 PPPQMS element. Tools and examples are provided in the appendices. Additionally, a ZIP file containing the APQ Maturity Assessment Tool (for PPPQMS) and the APQ Benchmarking Tool is provided with this Guide at the time of purchase.

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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).[1] 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 excellence[2], 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

[1] 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.
[2] The terms cultural excellence and quality culture are interchangeable. For the purposes of this Guide, the term cultural excellence is used.

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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 the ICH Q10 PQS: Corrective Action and Preventive Action (CAPA) system, Management Responsibilities and Management Review (MRR), Change Management (CM) system, and Process Performance and Product Quality Monitoring System (PPPQMS)
- 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

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- 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]:

- CAPA system [2]
- MRR [3]
- CM system [4]
- PPPQMS

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 [5, 6, 7] and PQS enablers (knowledge management [8] and quality risk management).

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Figure 1.1: Overview of the APQ Program

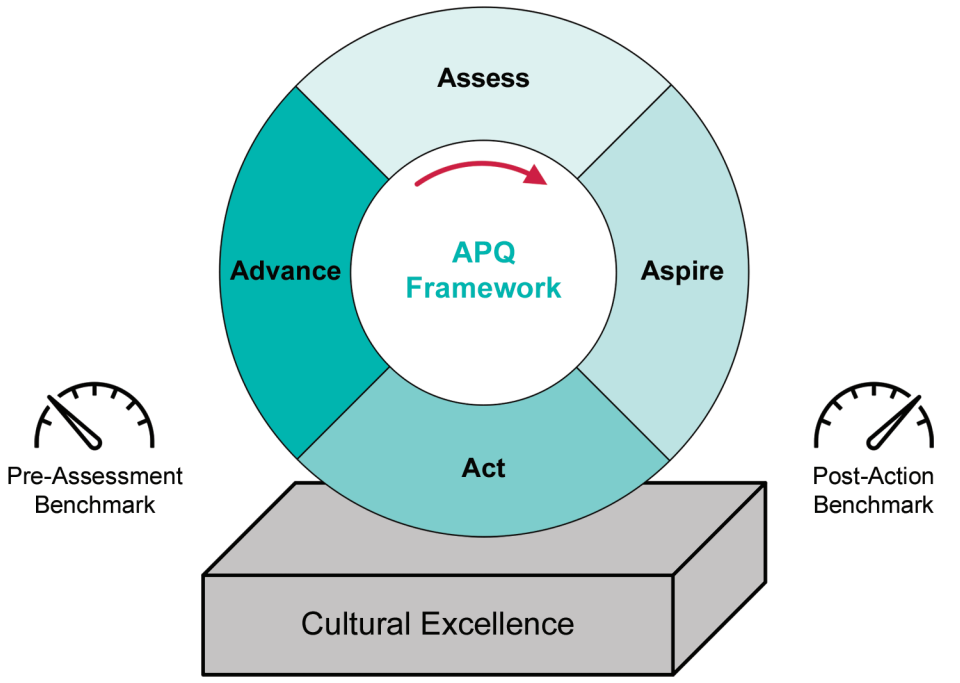
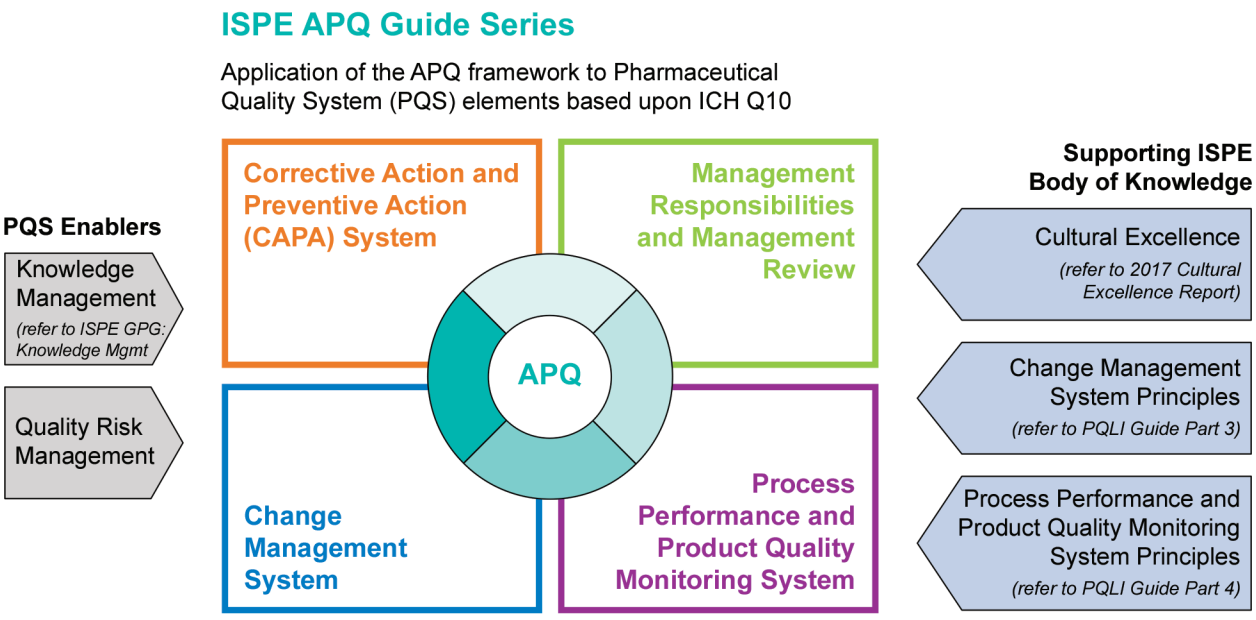


Figure 1.2: Overview of the ISPE APQ Guide Series



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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.

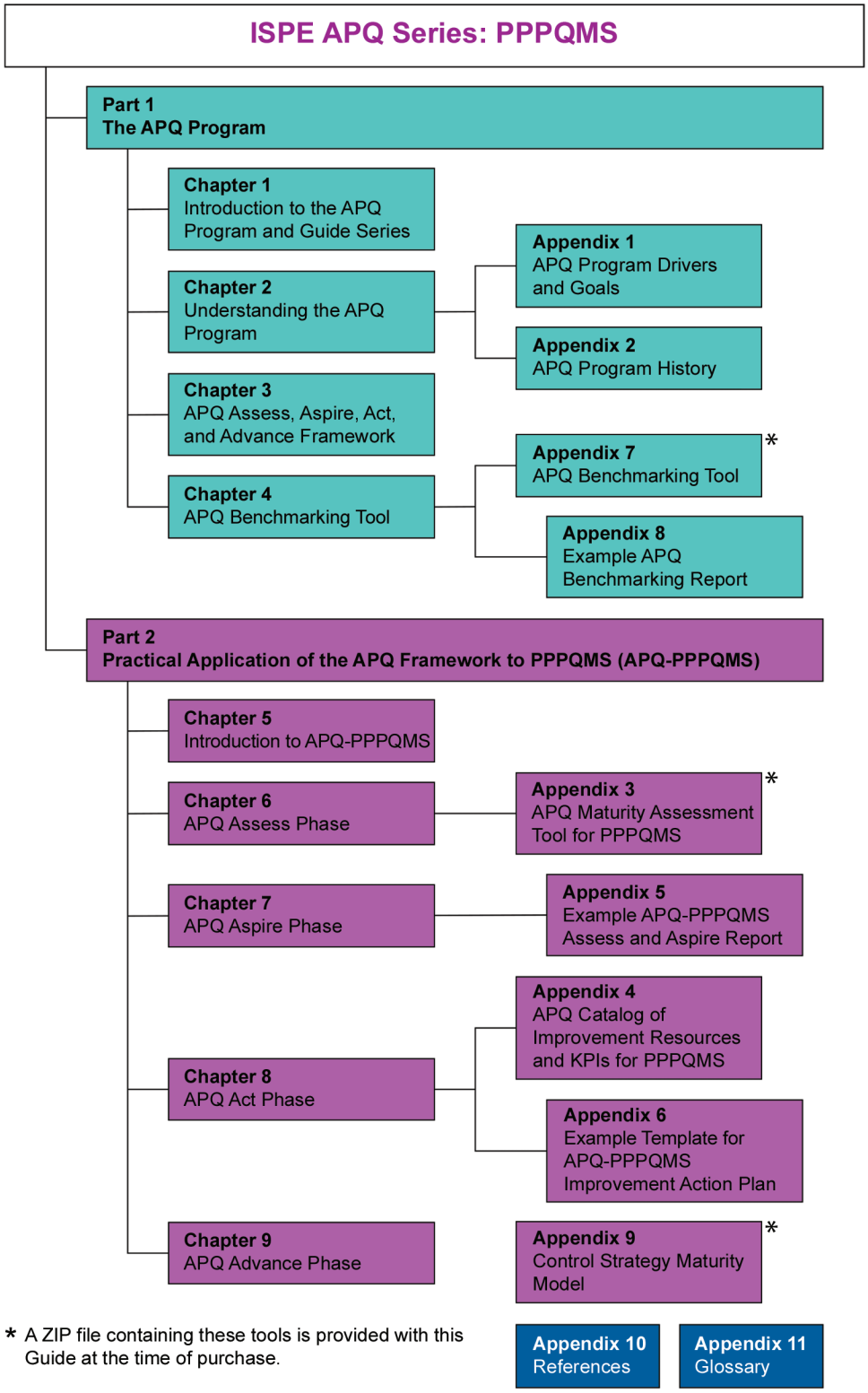
Part 2 covers the practical application of the APQ framework to PPPQMS (APQ-PPPQMS). It guides readers through the four phases of the framework, explaining in detail the comprehensive self-assessment tool for diagnosing the quality management maturity of their organization's PPPQMS. It provides guidance 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.

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Figure 1.3: Guide Structure



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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.

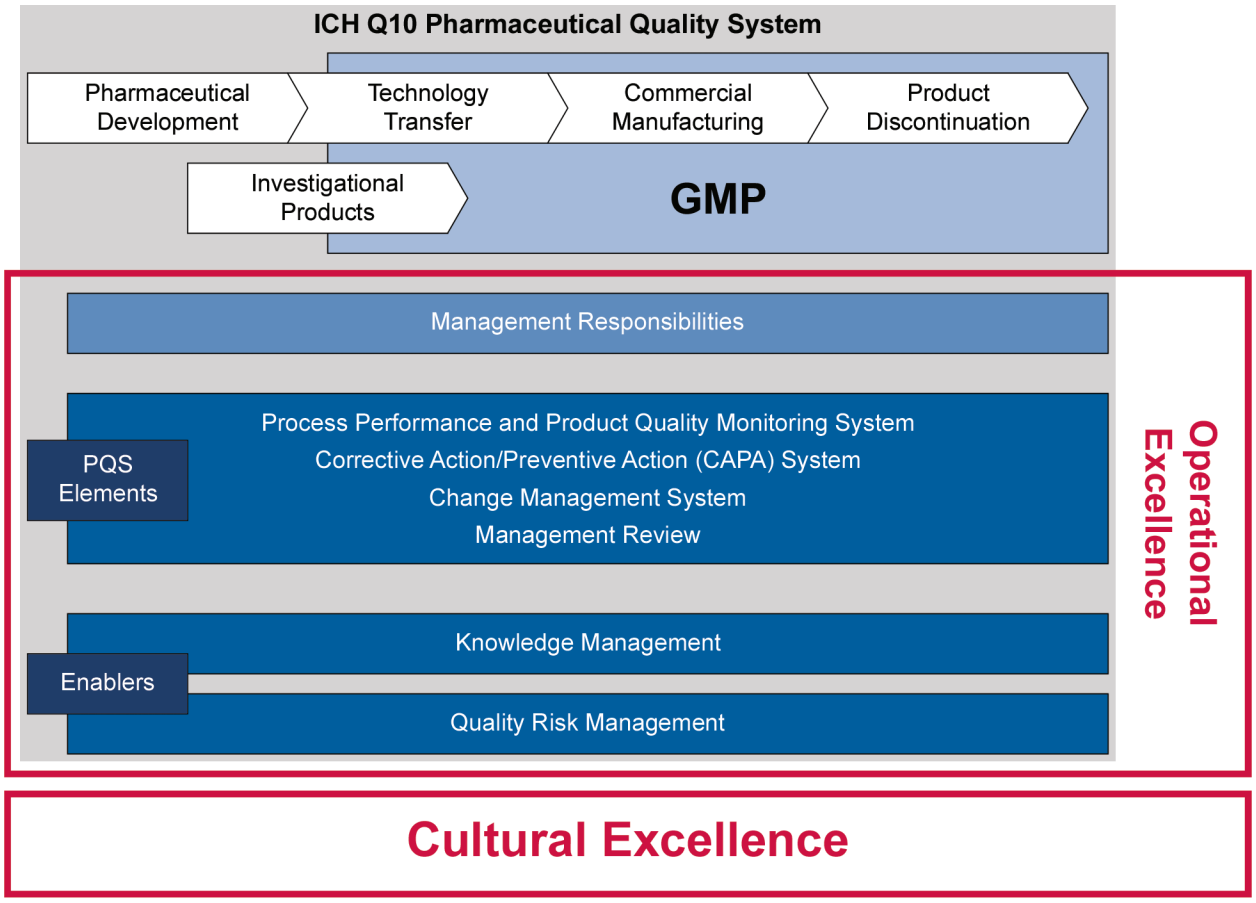
2.1 Link to the ICH Q10 PQS Model

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.

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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, CM system, and PPPQMS). 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).

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2.2 Link to Cultural Excellence and Operational Excellence

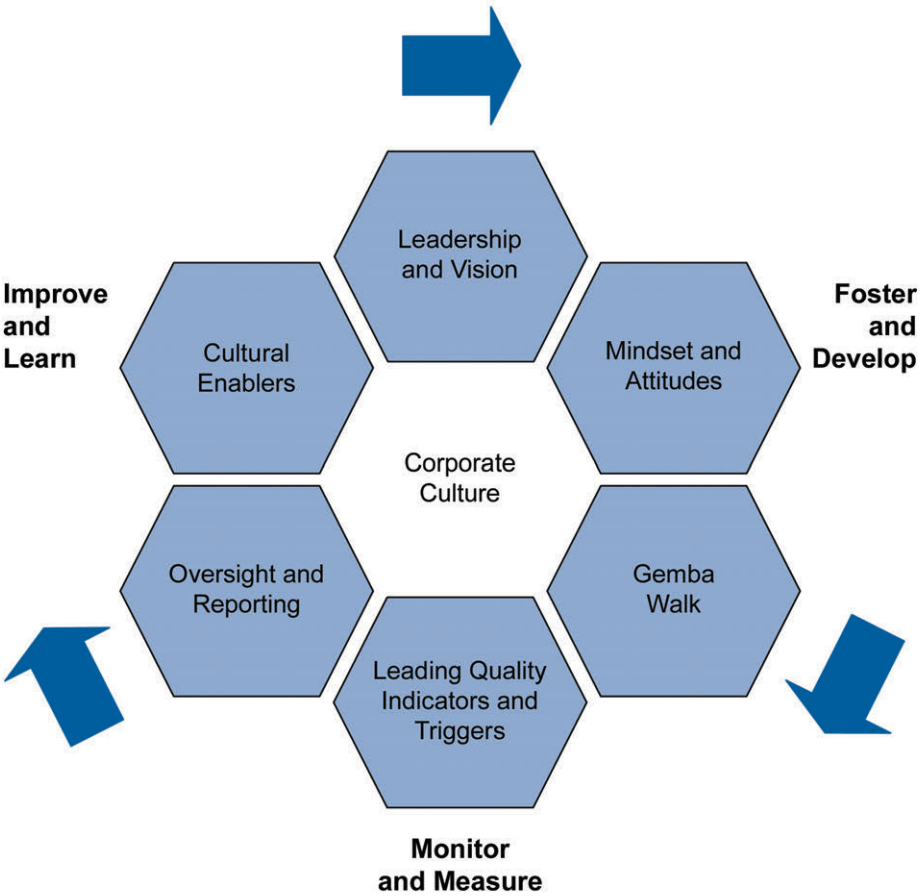
As stated earlier in this chapter, an overarching goal of the APQ program is to integrate quality, cultural, and operational excellence principles, tools, and approaches.

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 [9, 10]. (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 [5] 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 [5]



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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) [5] 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."* [11] 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* [12] 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. [13]) 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.

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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
- PPPQMS

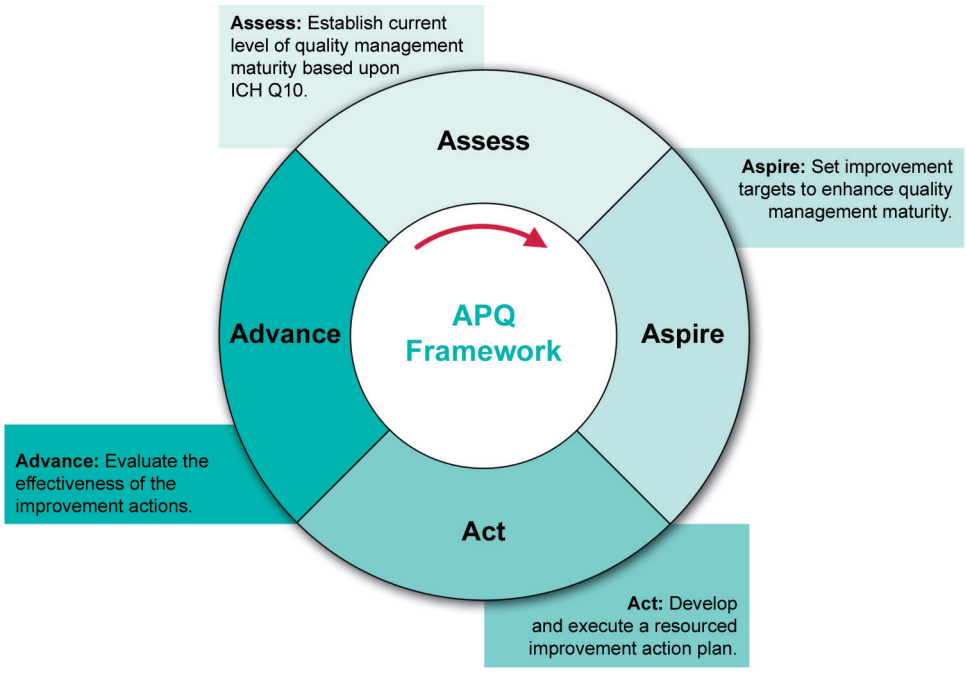
These self-assessment tools include detailed quantitative and qualitative criteria to evaluate the current state of quality, diagnose gaps, and identify improvement opportunities.

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.

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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 PPPQMS, 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 PPPQMS).

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.

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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

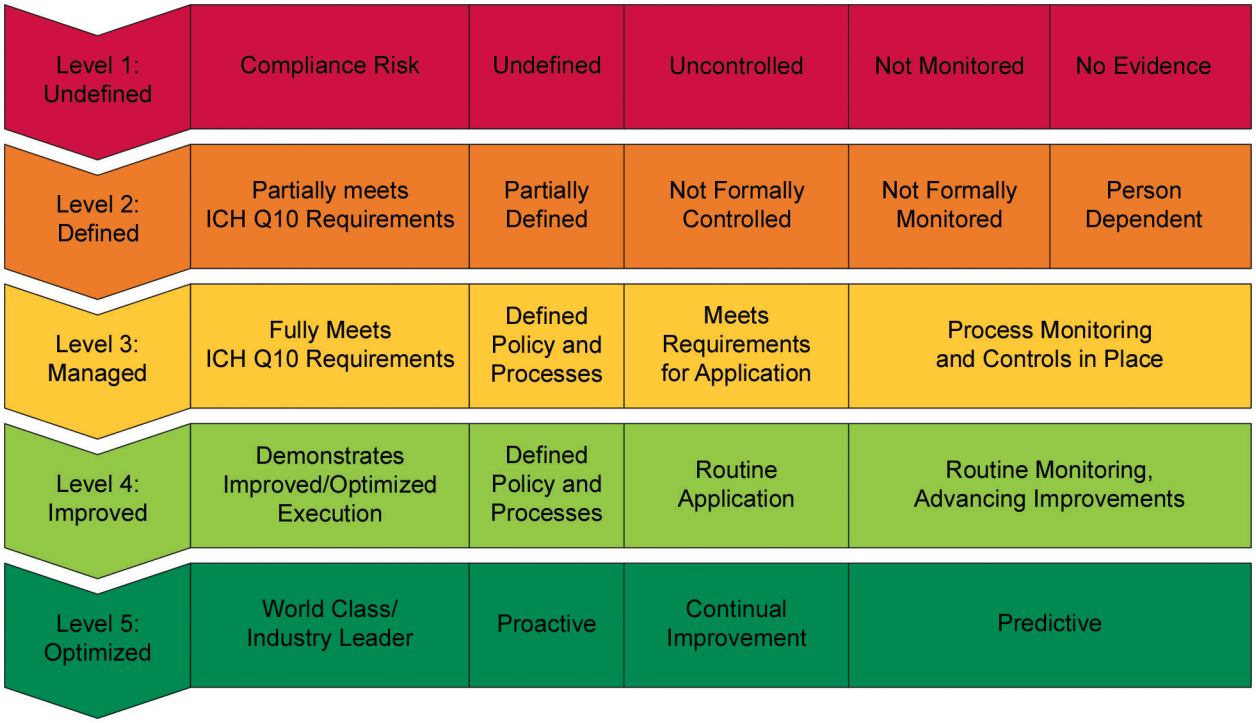
The APQ self-assessment tool incorporates quantitative scoring against a 5-Level Maturity Model, where **Level 1 Undefined** represents the lowest level of maturity and **Level 5 Optimized** represents the highest level of maturity.

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.

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Figure 3.2: APQ 5-Level Maturity Model



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.

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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.

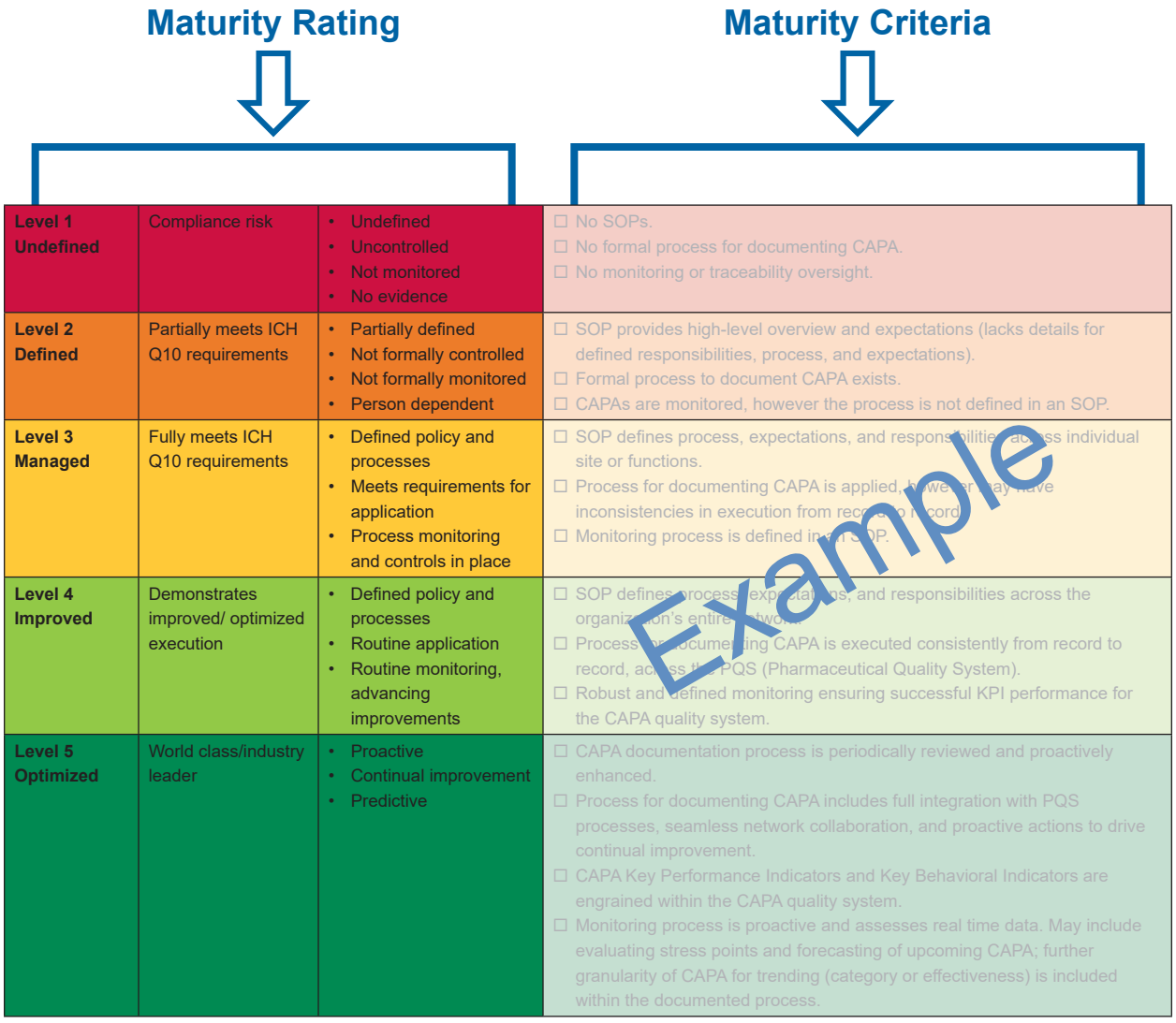
3.2.2 Quantitative and Qualitative Aspects

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.

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



Example

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.

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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 [5].

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.

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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.

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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.[3] 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).[4]

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 [11].

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)

[3] 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.

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

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- 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.

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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.

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5 Introduction to APQ-PPPQMS

Part 2 of this Guide covers the practical application of the APQ framework to an organization's Process Performance and Product Quality Monitoring System (PPPQMS). It provides guidance on how to use the APQ framework to:

- **Assess:** Evaluate the current maturity level of the PPPQMS using a Maturity Assessment Tool (Chapter 6)
- **Aspire:** Set improvement targets to enhance and improve the PPPQMS (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 PPPQMS for ease of understanding.

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

- APQ Maturity Assessment Tool for the PPPQMS (Appendix 3)
- APQ Catalog of Improvement Tools and KPIs for the PPPQMS (Appendix 4)
- Case studies:
  - Example APQ-PPPQMS Assess and Aspire Report (Appendix 5)
  - Example Template for APQ-PPPQMS Improvement Action Plan (Appendix 6)
- Control strategy control model (Appendix 7)

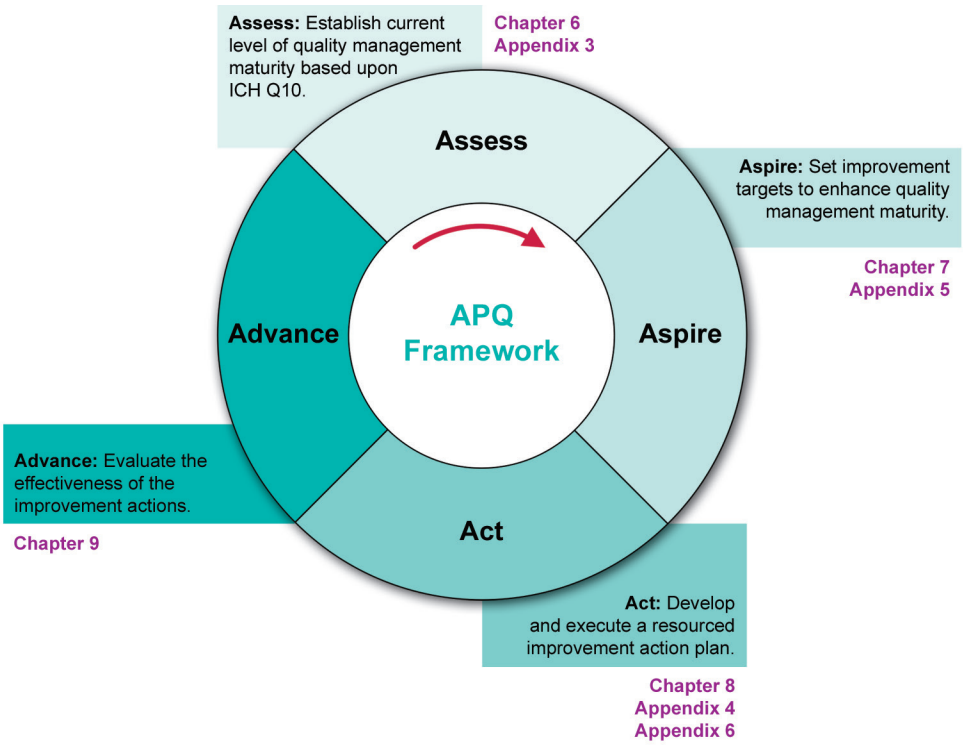
Note: The information presented in Part 2 of this Guide builds on the prerequisite explanation of the APQ framework in Chapter 3.

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

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



5.1 Key Concepts – Introduction

ICH Q10 [1] provides a comprehensive model for an effective PQS and sets out three main objectives which should be achieved through focused implementation. These are:

1. Achieve product realization
2. Establish and maintain a state of control
3. Facilitate continual improvement

The second of these objectives, establishing and maintaining a state of control, requires the development and use of *"effective monitoring and control systems for process performance and product quality, thereby providing assurance of continued suitability and capability of processes."* [1]

In addition to maintaining a state of control, these crucial monitoring and control systems play a significant role in enabling and facilitating continual improvement within an organization. These systems are also key to proactively identifying the need for product quality and process improvements or opportunities for variability reduction based on routine trend reviews. For the purposes of this Guide, these monitoring and control systems are collectively referred to as the ICH Q10 PQS element Process Performance and Product Quality Monitoring System (PPPQMS) [1]. ICH Q10 summarizes the central role that the PPPQMS plays within the overall PQS as follows:

> *"The pharmaceutical quality system should assure that the desired product quality is routinely met, suitable process performance is achieved, the set of controls are appropriate, improvement opportunities are identified and evaluated, and the body of knowledge is continually expanded."*

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ICH Q10 [1] recommends that, at a minimum, an effective organization's PPPQMS should include the following aspects:

> *"(a) Use quality risk management to establish the control strategy . . .;*
>
> *(b) Provide the tools for measurement and analysis of parameters and attributes identified in the control strategy (e.g., data management and statistical tools);*
>
> *(c) Analyse parameters and attributes identified in the control strategy to verify continued operation within a state of control;*
>
> *(d) Identify sources of variation affecting process performance and product quality for potential continual improvement activities to reduce or control variation;*
>
> *(e) Include feedback on product quality from both internal and external sources, e.g., complaints, product rejections, non-conformances, recalls, deviations, audits and regulatory inspections and findings;*
>
> *(f) Provide knowledge to enhance process understanding, enrich the design space (where established), and enable innovative approaches to process validation."*

For the APQ program, the aspects shown in Figure 5.2 are used as the six distinct sub-elements to assess the maturity of the PPPQMS using specific maturity criteria. The critical role that a number of these sub-elements play in establishing and maintaining the effectiveness of the overall PQS is discussed in Sections 5.2 to 5.5.

Figure 5.2: Aspects of an Effective PPPQMS Based on ICH Q10 [1]



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5.2 Measuring What Matters – Maintaining a State of Control

ICH Q10 [1] establishes the following expectation:

> *"Pharmaceutical companies should plan and execute a system for the monitoring of process performance and product quality to ensure a state of control is maintained. An effective monitoring system provides assurance of the continued capability of [each] process and [the associated] controls to produce a product of desired quality and to identify areas for continual improvement."*

5.2.1 What to Measure

A PPPQMS data collection plan should be established for each product and should indicate which manufacturing, quality, and laboratory data should be collected to evaluate process stability and capability. The specific parameters should be based on the approved control strategy for the product (see Section 5.3 for further details), understanding of the process, and any other relevant prior knowledge related to the facility, equipment, and PQS performance within the organization.

This plan can include parameters and attributes related to the following:

- Drug substance
- Drug product
- Materials and components
- Facility and equipment operating conditions
- In-Process Controls (IPCs)
- Finished product specifications and the associated methods
- Frequency of data collection and analysis for monitoring and control

The PPPQMS should facilitate timely feedback and/or feedforward communications and include appropriate CAPA information, in the event of a deviation from the plan, to support confirmation of maintenance of the state of control.

The US FDA Guidance for Industry: Process Validation: General Principles and Practices (2011) [14] also highlights the regulatory expectation that:

> *"An ongoing program to collect and analyze product and process data that relate to product quality must be established (§ 211.180(e)). The data collected should include relevant process trends and quality of incoming materials or components, in-process material, and finished product."*

Within the EU GMPs, the regulatory expectations for a PPPQMS are set out in the EMA Eudralex Volume 4, Chapter 1 – Pharmaceutical Quality System [15], which states:

> *"(viii) A state of control is established and maintained by developing and using effective monitoring and control systems for process performance and product quality.*
>
> *(ix) The results of product and processes monitoring are taken into account in batch release, in the investigation of deviations, and, with a view to taking preventive action to avoid potential deviations occurring in the future."*

Ultimately, the information collected should verify that the quality attributes are being appropriately controlled throughout the process.

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5.2.2 Who Should Measure

It is recommended that a statistician or person with adequate training in Statistical Process Control (SPC) techniques is involved in the development of the PPPQMS data collection plan and determines the statistical methods and procedures to be used in measuring and evaluating process stability and process capability. It is also recommended that the PPPQMS data is statistically trended and reviewed by trained personnel on a routine, ongoing basis.

The collection, analysis, and evaluation of information and data about the performance of the process should ensure timely detection of undesired process variability, identification of problems, and determination of whether action must be taken to correct, anticipate, and prevent problems so that the process remains in control.

The PPPQMS plan and the outputs from the routine data analysis and review should also be reviewed by the quality unit.

5.2.3 How to Measure

Good process design and development should account for significant sources of variability and establish appropriate detection, control, and/or mitigation strategies, as well as appropriate alert and action limits. Many tools and techniques, some statistical and others more qualitative, can be used to detect variation, characterize it, and determine the root cause.

Procedures should describe how trending and calculations are to be performed and should guard against overreaction to individual events as well as against failure to detect unintended process variability. If properly carried out, these efforts can identify variability in the process and/or signal potential process improvements. The FDA Process Validation Guidance [14] also recommends that:

> *"Scrutiny of intra-batch as well as inter-batch variation is part of a comprehensive continued process verification program under § 211.180(e)."*

In terms of new products, the design and development of the PPPQMS plan should build upon the knowledge gained during early Continued Process Verification (CPV)/Ongoing Process Verification (OPV) activities. Initially, it is recommended that monitoring and sampling of process parameters and quality attributes should continue at the level established during the process qualification activities, until sufficient data are available to generate significant variability estimates. These estimates can provide the basis for establishing revised levels and frequencies of routine sampling and monitoring for the particular product and process. As more experience with the product is gained and process understanding increases, monitoring can be adjusted to a statistically appropriate and representative level more suited to routine monitoring.

It is important to note that process variation can also be detected by the timely assessment of defect complaints, Out-of-Specification (OOS) findings, process deviation reports, process yield variations, batch records, incoming raw material records, and adverse event reports. This PQS data should be included in the PPPQMS plan for the product. Maintenance of the facility, utilities, and equipment is another important aspect in ensuring that a process remains in control. The equipment and facility qualification data should be assessed periodically to determine if maintenance and calibration frequencies should be adjusted based on feedback from these activities.

Front-line operators and quality staff should be encouraged to provide feedback on process performance and surface issues and concerns. Forums should be established where cross-functional teams, including front-line personnel, can come together to evaluate data, discuss possible trends or undesirable process variation, and coordinate any correction or process improvement actions.

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5.3 Establishing and Implementing a Control Strategy

The control strategy serves as the basis for establishing an effective process performance and product quality monitoring strategy for any product. The control strategy goes beyond the controls which may be registered in the product dossier to describe how to manufacture, monitor, control, and release a product that consistently meets the required product Critical Quality Attributes (CQAs) within the approved limits or operating ranges, and therefore provides the baseline for the design of the PPPQMS.

Defining the control strategy is a multi-disciplinary exercise performed for each product and should be based on science, knowledge, and robust quality risk management principles. Establishing this control strategy is considered foundational for the planning and execution of an effective PPPQMS, i.e., defining the data to collect, including what, when, and how, as well as how to best analyze and report this data to ensure product quality, enhance process understanding, and facilitate continual improvement.

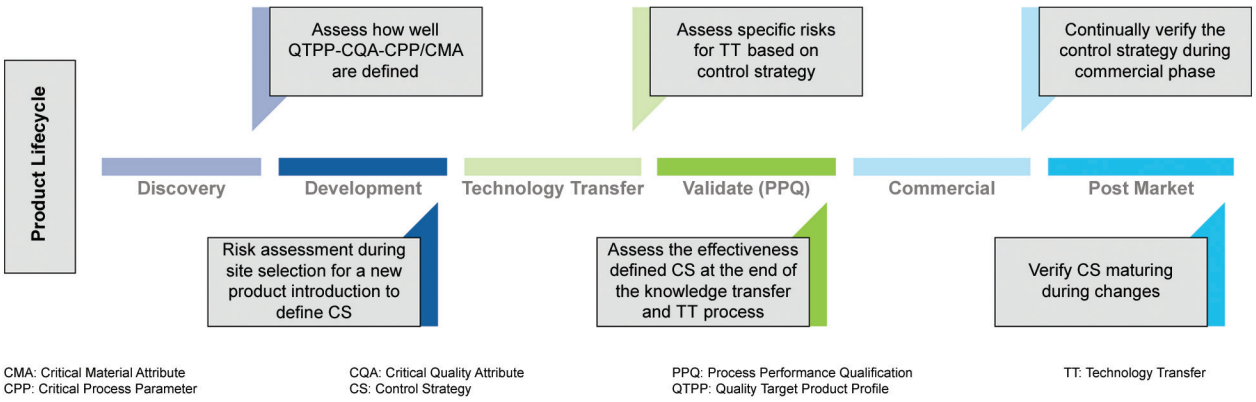
It is important to recognize that a control strategy defines a more comprehensive set of considerations than the product specifications alone.

The control strategy is defined in ICH Q10 [1] as follows:

> *"A planned set of controls, derived from current product and process understanding, that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control."*

To design an effective PPPQMS, it is crucial to understand how the control strategy is established and applied throughout the different product lifecycle stages. Figure 5.3 depicts the evolution of the control strategy across the product lifecycle.

Figure 5.3: Evolution of the Control Strategy across the Product Lifecycle
Modified and used with permission from AstraZeneca, www.astrazeneca.com.



Considerations for the control strategy are as follows:

- The control strategy should be initially developed during the pharmaceutical development stage based on process knowledge, understanding, and risk, and confirmed during the technology transfer and scale-up required for commercial manufacturing before product launch.

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- The control strategy is then evaluated to determine if it is capable of reproducible commercial manufacture and providing demonstrable control during the Process Performance Qualification (PPQ) (FDA Process Validation Guidance, 2011 [14]) or Process Validation (PV) (EU GMP Annex 15, 2015 [16]) phase of the product lifecycle. This phase also clearly describes, in sufficient detail, any corrective actions or changes that should be made to proposed controls before commercial production commences.

- Ongoing effectiveness of the control strategy should then be monitored and improved as part of the PPPQMS during the commercial manufacturing phase of the lifecycle, typically as part of the CPV [14] or OPV [16] lifecycle activities.

- Monitoring and sampling of process parameters and CQAs should continue at the level established during the process qualification stage until sufficient data is available to generate significant variability estimates. These estimates may provide the basis for establishing the levels and frequency of routine sampling and monitoring for the particular product and process. Process variability should be periodically assessed and monitoring adjusted accordingly.

- Changes to the control strategy should be reviewed and considered in subsequent commercial technology transfers to new manufacturing sites to ensure alignment with the current state of control and account for any improvements made at the previous commercial site.

During commercial manufacturing, the primary focus of the control strategy is to consistently produce a compliant, high-quality product that can be released to the market and is not adversely impacted over time by either manufacturing variability or variations in the supply chain. The manufacturing equipment, utilities, and facility must also be controlled from a GMP perspective to mitigate risks such as product contamination. These controls are typically not product specific. When the control strategy is extended to include controls related to the commercial process equipment, facility, and other GMP controls, it may be referred to as the manufacturing control strategy. It defines the controls and associated monitoring for the overall manufacturing process and the expected limits or operating ranges that will ensure CQAs are maintained within the approved acceptance limits.

The control strategy is not only important as the baseline for the PPPQMS, but it should also capture the current level of process understanding and inform the continual improvement activities as the product matures.

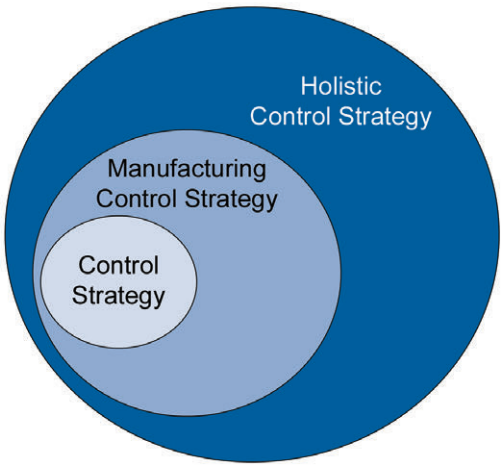
For organizations focused on advancing the maturity of their PQS beyond one which meets the expectations of ICH Q10, from Managed (Level 3 in the APQ 5-Level Maturity Model) to Improved (Level 4) or Optimized (Level 5), the entire supply network is likely to be interconnected and additional data and control information may be included in the PPPQMS. Market demand requirements may be integrated into supplier management, real-time manufacturing controls, and product release and distribution data, as well as sources of information related to patient and customer feedback that may be available for inclusion in the evaluation of process performance and product quality. Such an end-to-end process perspective ensures that these more mature organizations are well positioned to meet the necessary product quality expectations, respond with agility to changes in the market, and minimize the risk of supply disruption issues while also improving overall business performance.

The ability to advance to a more mature, holistic approach is often supported by increased digitalization of the manufacturing and business processes, which is further discussed in Section 5.4. Within this advanced approach, the PPPQMS becomes optimally effective and efficient by creating and using real-time (or near real-time) information and accurate data to support knowledge-led, risk-based decision-making. Not all organizations will be in a position or need to aspire to this level of integration of its business processes.

Figure 5.4 shows the progression of control strategy maturity to support an optimally effective and efficient PPPQMS.

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Figure 5.4: Advancing Control Strategy Maturity to Support an Optimally Effective and Efficient PPPQMS



For further details related to other ISPE initiatives providing additional technical support to organizations wishing to advance the maturity of their control strategy approaches, see Appendix 9.

5.4 The Relationship between Digital Maturity and Pharmaceutical Quality System Maturity

The easy of availability, access, and accuracy of the key process and product data is a fundamental requirement for an effective PPPQMS. Over the past decade, traditional paper-based PQS have been increasingly transitioning toward automation, a process often referred to as digital transformation, from paper-based systems towards more digital and services-based architectures (e.g., Software as a Service (SaaS), Infrastructure as a Service (IaaS) or cloud-based technologies). This digital transformation is typically performed in two distinct steps:

1. **Digitization** of the paper-based quality and process data

2. **Digitalization** of the overarching business processes that store, access, and take actions based upon the digitized quality and process data.

The definitions and differences between digitization and digitalization are provided below. Although the terms may be misused, understanding the distinctions is an important first step on the digital maturity journey. The principles expressed here on digitization, digitalization, and the impact on quality maturity can be equally applied to the other PQS elements in this APQ Guide series.

5.4.1 Understanding the Scope of Digitization

Digitization is the process of converting information into a digital format. [17] The result is the representation of an object, image, or document sometimes referred to as “paper on glass”. An example of this type of digital transformation is the transfer of paper-based Standard Operating Procedures (SOPs) into an electronic document management system, rendered and made available for viewing as PDF documents (static data).

5.4.2 Understanding the Scope of Digitalization

Digitalization is the use of digital technologies to change a business model or implement a digital business [18]. An example of this type of the transformation is transforming SOPs rendered in PDF format into a dynamic, workflow-based electronic document management system, containing executable business process descriptions of the SOP content (dynamic data) which can enable activities such as key word content searches, automated distribution, and approval processes.

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5.4.3 Digital Maturity: Transformation Towards Pharma 4.0™

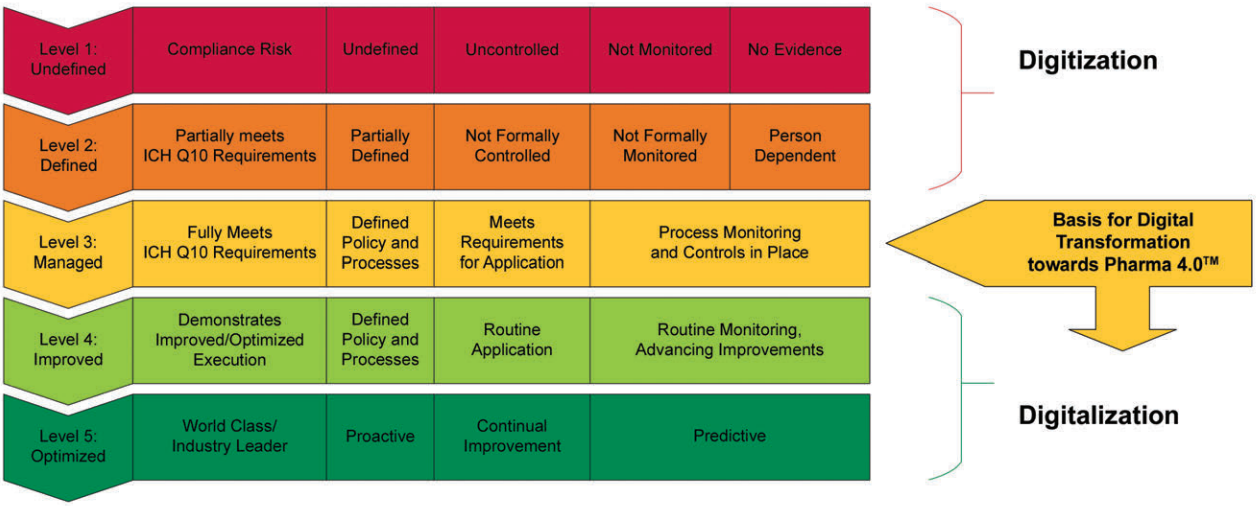
Any digital transformational program requires the organization to first establish a clear vision, strategy, and business case for the transformation. This strategy should set out the organizational capabilities and workforce competencies required to support a successful implementation. Within the pharmaceutical industry, it is important that a robust, mature ICH Q10-based PQS is in place to enable the transformation.

The APQ PPPQMS maturity assessment tool can assist in understanding the **current** state of maturity of the data collection, monitoring, and control systems in place, while identifying and aspiring towards the step-wise improvements required to advance to a **future** state of digital maturity.

Figure 5.5 shows that lower levels of organizational maturity may include some level of digitization. Progress towards Level 2 Defined towards Level 3 Managed typically involves the organization routinely utilizing a range of non-integrated digitized content management systems to capture and analyze data. However, it is difficult to progress to Level 4 Improved without a more holistic, interconnected, end-to-end digitalization approach, and this capability becomes essential to aspiring to a fully integrated Level 5 Optimized organization.

Advancing to APQ PPPQMS maturity Levels 4 and 5 will only be successful if a digital transformation strategy and implementation plan is applied. However, it is critical to understand that the prerequisite for a well-planned digitalization strategy is a stable and effective, well-managed PQS.

Figure 5.5: APQ 5-Level Maturity Model – Mapped to Digital Maturity Capability



The tools and resources provided in this Guide can assist organizations to establish the minimum APQ maturity Level 3 Managed, which provides the foundation for a comprehensive data and knowledge driven digital transformation strategy.

For more information on digital transformation opportunities for the pharmaceutical industry, refer to the ISPE Pharma 4.0™ initiative website [19].

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5.5 Using the PPPQMS to Enhance Process Understanding, Manage What We Know, and Inform What We Do

As the body of knowledge about our products and processes expands, the next challenge for those responsible for the operation and oversight of the PPPQMS is how to harness what we "now" know to enhance our process understanding and inform what we do "next". Conducting periodic reviews of the data and knowledge related to product quality are a common GMP compliance practice within organizations, occurring at least annually as part of the CPV/OPV program and product quality reviews. Beyond these minimum requirements, many organizations have also created product or quality stewardship roles to collate, curate, and share product knowledge and process understanding across the organization. For detailed information on these stewardship roles and responsibilities, see Chapter 4 in the *ISPE Guide Series: Product Quality Lifecycle Implementation (PQLI®) from Concept to Continual Improvement, Part 4 – Process Performance and Product Quality Monitoring System* [7].

ICH Q8 Pharmaceutical Development [20] explains that this process understanding can be gained through a range of approaches, from the application of formal experimental design to the use of Process Analytical Technology (PAT) and the utilization of prior knowledge. It states:

> *"Appropriate use of quality risk management principles can be helpful in prioritising the additional pharmaceutical development studies to collect such knowledge."*

ICH Q8 [20] also cautions that:

> *"[T]he level of knowledge gained, and not the volume of data, provides the basis for science-based submissions and their regulatory evaluation."*

The opportunity to avail of regulatory flexibility by demonstrating enhanced process understanding and product knowledge is also supported in ICH Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management [21], which states:

> *"Increased knowledge and effective implementation of the tools and enablers described in this guideline should enhance industry's ability to manage many CMC [Chemistry, Manufacturing, and Controls] changes effectively under the company's Pharmaceutical Quality System (PQS) with less need for extensive regulatory oversight prior to implementation."*

Capturing knowledge in a way that ensures it is freely available and can be readily applied is essential to enhancing product robustness and to building an organization's overall capability. Application of knowledge in this manner requires the right information is available to the right people at the right time and for the right decisions to be made at the right levels within the operation. This is the essence of effective knowledge management, which is a key enabler to an effective PQS.

The *ISPE Good Practice Guide: Knowledge Management in the Pharmaceutical Industry* [8] points to a useful definition:

> *"The application of a structured process to help information and knowledge flow to the right people at the right time so they can act more efficiently and effectively to find, understand, share, and use knowledge to create value."* (American Productivity & Quality Center, [22])

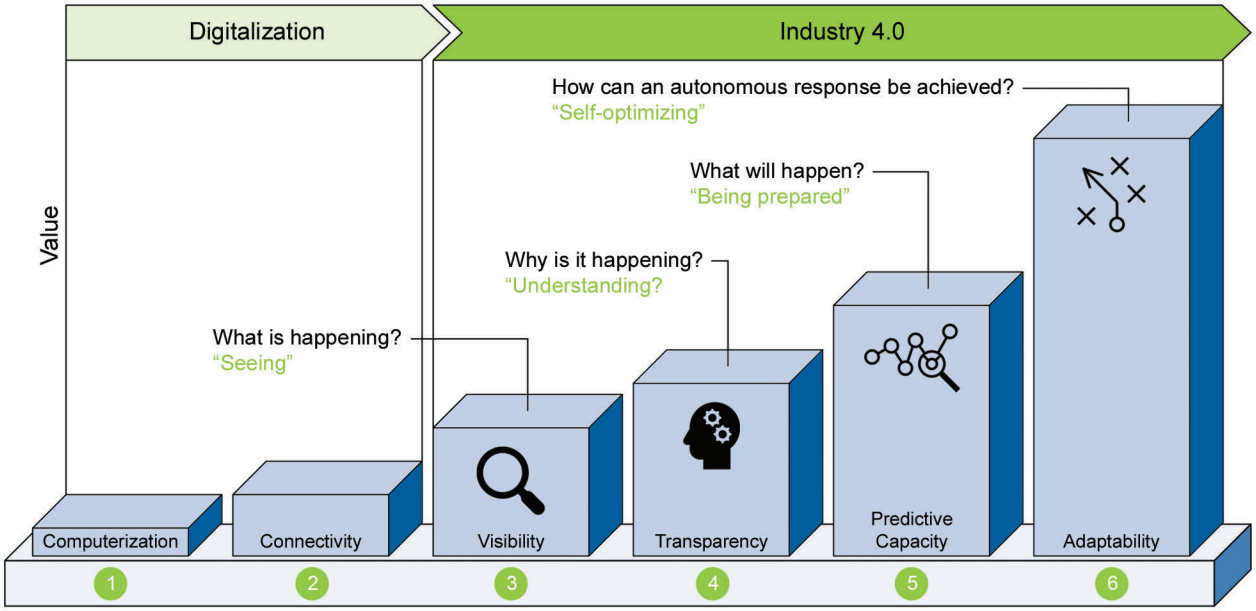
This definition is more commonly used by knowledge management practitioners because it embraces the two main aspects of knowledge management: the needs of the knowledge user for access to the right knowledge at the right time and the opportunity for effective managing knowledge to create value for the organization.

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This concept of using what we know to create and enhance business value is also reflected in the Acatech – National Academy of Science and Engineering digital maturity model [23] shown in Figure 5.6. Having the visibility to **see** what is happening is a prerequisite to enabling transparent access for users in order to facilitate their **understanding** of **why** something is happening. This in turn is foundational to being **prepared** and predicting what will happen next as a means to enabling higher order capabilities which may even include Artificial Intelligence (AI) or Machine Learning (ML) driven **autonomous responses** to a given situation.

Figure 5.6: Acatech Digital Maturity Model
Used with permission from Acatech [23].



New digital solutions, which help organizations manage data, information, and knowledge, are fundamentally reshaping the way people and organizations collaborate [8].

However, it is important to remember that successful digital transformation is still mainly about people, not technologies, and organizations need to be aware of their strengths and limitations in building out these capabilities. The *ISPE Good Practice Guide: Knowledge Management in the Pharmaceutical Industry* [8] cautions that:

> *"technology infatuation is a risk to be kept in check in order to successfully implement digital solutions."*

To create real value, there needs to be a new culture that recognizes the potential for data to inform our ability to make robust risk-based decisions and take the necessary actions to protect the patient and add real value to the business.

The power to predict a possible deviation in a costly and complex biotechnology production process and automatically act **in advance**—in a timely and controlled manner—based on key process parameters before the deviation occurs could minimize the risk of losing the batch and the potential consequences to the supply chain, in the interest of the patient waiting for a critical medicine.

For more details on the application of effective knowledge management strategies within the pharmaceutical industry to harness process understanding and product knowledge, refer to the *ISPE Good Practice Guide: Knowledge Management in the Pharmaceutical Industry* [8] including Appendix 3 which provides an ISPE Knowledge Management Maturity Table as a companion tool to the overall APQ program. In addition, readers may find helpful examples for gaining and managing process understanding in the *ISPE Guide Series: Product Quality Lifecycle Implementation (PQLI®) from Concept to Continual Improvement, Part 1 – Product Realization using Quality by Design (QbD)* [24].

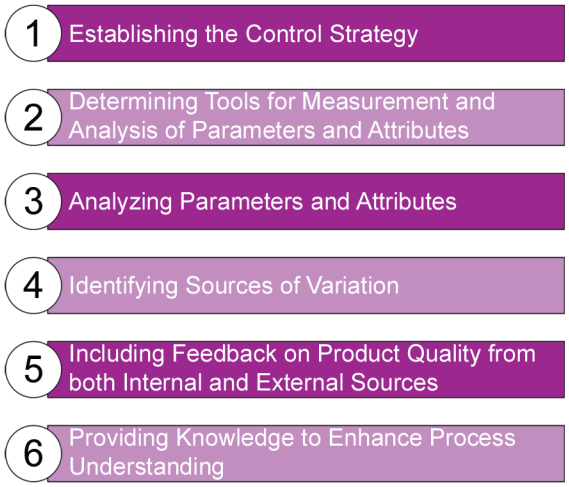
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5.6 Six Sub-Elements of the APQ-PPPQMS System

For the APQ program, the PPPQMS is categorized into six distinct sub-elements as based on ICH Q10 [1] and shown in Figure 5.7.

Figure 5.7: APQ-PPPQMS Sub-Elements



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

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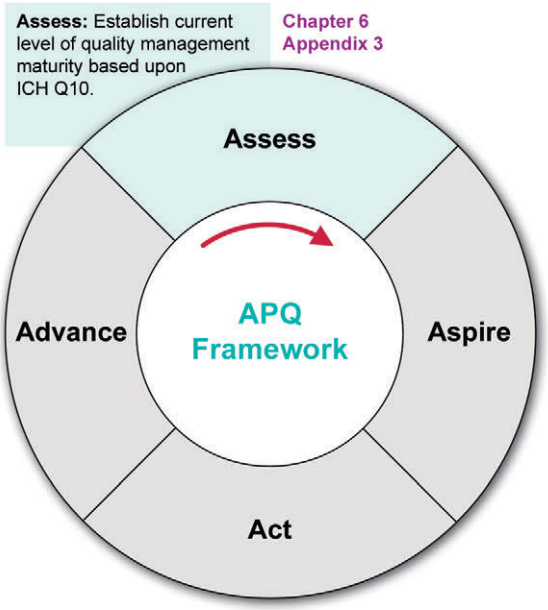
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6 APQ Assess Phase

In the APQ **Assess** phase (see Figure 6.1), the cross-functional assessment team performs the deep evaluation of the current maturity state of the organization's PQS with respect to PPPQMS. Using the APQ Maturity Assessment Tool, the team evaluates the current state of maturity, establishing objective evidence of organizational capability, and assigns an appropriate maturity rating for each PPPQMS sub-element. This chapter covers the self-assessment tool in depth, explaining the rationale for the criteria. The full APQ Maturity Assessment Tool for PPPQMS is provided in Appendix 3.

Note: The information presented in this chapter builds on the description of the APQ framework in Chapter 3.

Figure 6.1: APQ-PPPQMS Guide – Assess Phase



APQ FRAMEWORK UNIVERSAL TOPIC

The APQ Assess phase is a guided process using objective quantitative and qualitative criteria to assess business process capabilities and performance, leadership and workforce competencies, and associated behaviors of the selected PQS element. The self-assessment process enables a proactive and honest review of current practices and outcomes in order to determine the current level of quality management maturity.

For each sub-element assessed using the APQ Maturity Assessment Tool, the self-assessment team should observe, review, and provide demonstrated evidence of current policy and practice against specific criteria set out across the 5-Level Maturity Model. This includes seeking evidence of quality system aspects such as relevant procedures, checklists, and forms as well as observing the behaviors of those routinely responsible for executing the tasks under review.

Most criteria requirements should be met in full, as determined by the self-assessment team, in order to assign a particular maturity rating to that quality system sub-element. These ratings can then be actioned individually or grouped as a weighted rating for the quality system element under review. Each organization can determine their own preference on whether they wish to assign an overall quality management maturity rating to each quality system element or simply continue to prioritize improvements based on the sub-element ratings.

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6.1 Assessing Sub-element 1 – Establishing the Control Strategy

The control strategy serves as the foundation for establishing an effective PPPQMS for any product, as noted in the detailed key concepts discussion in Section 5.3. ICH Q10 [1] also notes that a key function of the control strategy is to facilitate timely feedback and feedforward communications to ensure that appropriate CAPAs can be implemented where adjustments are required.

In organizations with lower levels of maturity (Levels 1 and 2), while the control strategy may be present, it is often poorly defined and poorly understood by the commercial operations teams. This, coupled with an overreliance on the registered product specifications and end-product testing, can lead to ad hoc trending of release specifications to support investigations without robust routine monitoring. At lower levels of maturity, while process understanding can be expanded as commercial manufacturing experience is gained, this increase in process understanding and product knowledge can tend to be person specific and only retained informally within a small number of operations personnel.

As the maturity moves upwards towards a Level 3 Managed process, it is more common to find a well-documented control strategy based on more clearly defined Critical Process Parameters (CPPs) and CQAs (including in-process CQAs) for the finished product with "standard" material specifications based on pharmacopeia specifications using a minimal science and risk-based Quality by Design (QbD) approach. In such cases, CPPs are typically identified and understood for all CQAs, and effective controls do exist for the CPPs. The main interactions between CPPs and/or material attributes may be understood, and where these are significant, ranges are typically defined.

At Level 4 Improved, a well-established control strategy is based on the following attributes using an extensive science and risk-based QbD approach:

- Critical Material Attributes (CMAs): raw material CQAs or excipient CQAs
- CPPs
- In-process CQAs
- CQAs of the finished product

In such organizations, CQAs, CPPs, and CMAs have been identified based on first principles, enhanced understanding, and Design of Experiment (DoE) approaches to define ranges and acceptance criteria for all raw materials, intermediates, and primary packaging. Such organizations have the ability to target the control of the process within the control strategy to achieve an optimized CQA range. The frequency of CPV/OPV monitoring is constantly evaluated based on routine review of the performance of the process and product quality, and more advanced statistical control methodologies are applied to proactively monitor the performance of the CQAs, CPPs, and CMAs. The control strategy is based on knowledge of the main manufacturing process including the raw materials and excipients. As the maturity of Level 4 organizations advance, some elements of a more holistic control strategy may be formalized.

In Level 5 Optimized organizations, the control strategy is extended towards a more end-to-end process perspective of the entire supply network. In such cases, CPPs will have been identified based on enhanced process understanding, with sustainability of control as a key criterion. The established control strategy is based on knowledge and holistically covers all elements of the manufacturing environment with a high level of process understanding, data analysis, data linkage, and data management. Inputs from across the entire supply network are used to inform and continually improve the control strategy. These inputs may include external business aspects such as sustainability, supply security, and patient feedback, which are routinely used to improve performance. Where the ability exists, predictive controls may be used to operate the process within the control strategy to achieve an optimized CQA range. The frequency of monitoring CPV/OPV and other aspects of this holistic control strategy are constantly evaluated based on the performance of the process and product quality. Advanced statistical controls are applied to monitor and improve the control of the process and product.

The detailed evaluation criteria for the establishing the control strategy sub-element are provided in Table 6.1.

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Table 6.1: Assessment Criteria Establishing the Control Strategy

PPPQMS Sub-element 1: Establishing the Control Strategy **What to monitor and control**			
Level 1 **Undefined**	Compliance risk	• Undefined • Uncontrolled • Not monitored • No evidence	☐ No formal documented control strategy exists, and controls are based on registered specifications. ☐ The control strategy is not well-defined during the development phase of the product lifecycle and is only based on end-product testing of quality attributes, IPCs, and process parameter setpoints and ranges. ☐ Process parameters are widely used and specified, but CPPs have not been identified yet. ☐ Quality attributes such as specifications are used, but CQAs have not been defined yet. ☐ Trending of release specifications is only done ad hoc (not routinely performed). ☐ Process understanding is limited but based on commercial manufacturing experience. ☐ Process parameters are not routinely monitored or controlled.
Level 2 **Defined**	Partially meets ICH Q10 requirements	• Partially defined • Not formally controlled • Not formally monitored • Person dependent	☐ Some elements of the control strategy are defined. Some process parameters are recognized to be more important than others. ☐ CQAs may not be defined using QbD approaches, but the term is used for release attributes. ☐ The executed control strategy elements are based on experience, and their acceptance criteria are taken from the master batch records. ☐ The identified control strategy elements are not improved based on feedback from CPV/OPV. ☐ The defined control strategy elements have established control limits. ☐ Process understanding is mainly based on commercial manufacturing experience.
Level 3 **Managed**	Fully meets ICH Q10 requirements	• Defined policy and processes • Meets requirements for application • Process monitoring and controls in place	☐ The control strategy is based on CPPs, CQAs (including in-process CQAs), and standard material specifications (pharmacopeia specifications) using a minimal science and risk-based QbD approach. ☐ CPPs are identified and understood for all CQAs. ☐ All CQAs are identified, and effective controls exist for them. ☐ All elements of the control strategy are established in manufacturing. The manufacturing control strategy is established, documented, and maintained. ☐ Interactions between CPPs and/or CMAs/in-process CQAs are understood and ranges defined where these are significant. ☐ Statistical control is applied to monitor the performance of the CPPs and CQAs, included in the CPV/OPV program, forms part of the control strategy. ☐ Some holistic elements of the control strategy are recognized independently, e.g., to minimize the risk of drug product shortage.
Level 4 **Improved**	Demonstrates improved/ optimized execution	• Defined policy and processes • Routine application • Routine monitoring, advancing improvements	☐ The control strategy is based on CMAs (raw material CQAs or excipient CQAs), CPPs, in-process CQAs, or CQAs of the finished product, using an extensive science and risk-based QbD approach. ☐ CPPs have been identified based on enhanced understanding (e.g., DoE has been applied to define ranges and acceptance criteria for CQAs, CPPs, and CMAs for all raw materials, intermediates, primary packaging) ☐ The process is targeted within the control strategy to achieve an optimized CQA range, where this ability exists. ☐ The frequency of CPV/OPV monitoring is constantly evaluated based on the performance of the process and product quality. ☐ Statistical control are applied to monitor the performance of the CPPs, CMAs/CQAs. ☐ The established manufacturing control strategy is based on knowledge and holistically covers all elements of the manufacturing environment with focus on the main manufacturing process including raw material and excipients. ☐ Some holistic elements of the control strategy are formalized and the relevance to the manufacturing control strategy recognized.

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PPPQMS Sub-element 1: Establishing the Control Strategy *(continued)*			
What to monitor and control			
Level 5 Optimized	World class/industry leader	• Proactive • Continual improvement • Predictive	☐ The holistic control strategy is established including the manufacturing control strategy as an integral part. External aspects, e.g., sustainability, supply, and patient feedback, are used to improve performance. ☐ CPPs have been identified based on enhanced understanding and their sustainability. Other parameters which are relevant for the holistic control strategy have been identified and fully understood. ☐ Predictive controls are used to operate the process within the control strategy to achieve an optimized CQA range, where this ability exists. ☐ The frequency of monitoring CPV/OPV and other aspects of the holistic control strategy are constantly evaluated based on the performance of the process and product quality. ☐ Mature linkages between signals from CPV/OPV including statistical controls are applied to monitor and improve the controls of the process and product. ☐ The established manufacturing control strategy is based on knowledge and holistically covering all elements of the manufacturing environment. ☐ There is a high level of process/analytical data understanding (i.e., data connectivity), data linkage, and data management. ☐ Robustness also covers business aspects (supply, cost, sustainability resilience). ☐ Input from the entire supply network is used to inform and improve the manufacturing control strategy. ☐ There is a high level of connectivity and automation between the systems controlling the process.

6.2 Assessing Sub-element 2 – Determining Tools for Measurement and Analysis of Parameters and Attributes

The next aspect of an effective PPPQMS is to establish statistical techniques and tools for the routine measurement and analysis of the parameters and attributes identified in the control strategy. These parameters and attributes could include those related to the drug substance and drug product materials and components, facility and equipment operating conditions, IPCs, finished product specifications, and stability monitoring programs active throughout the shelf life of the product. In addition to developing the measurement and analysis tools, the frequency and methods for monitoring should be clearly defined.

In lower maturity organizations (Levels 1 and 2), it is often the case that only data related to the attributes identified within the manufacturing batch reports are recorded. Such organizations do not employ real-time data collection or visualization techniques and consequently have limited ability to review the degree to which performance gaps might arise. Arising from the implementation of a basic or limited control strategy, process parameters are not routinely measured or appropriately assessed. Data analysis is rarely utilized during routine manufacture and the use of SPC tools is poorly understood. At best, batch report data may be graphed during the Annual Product Quality Review (APQR) or Product Quality Review (PQR) process.

At Level 2 Defined, some data analysis tools may be in place, but they are often not standardized nor consistently utilized. Limits may be established for release specifications and IPCs, but the degree to which performance gaps are monitored or escalated is largely ad hoc and reactive. In such organizations, APQR/PQR may include minimal trending but this practice does not extend to identification of improvement opportunities.

At Level 3 Managed, typical standardized statistical methods and trending tools are in place for data analysis. These may be tracked simply with spreadsheets or using independent/non-integrated electronic systems. For such organizations, a risk-based approach is used to determine the measurement, monitoring, and SPC approach, which is documented within the control plan. A real-time data collection may be in place for some products at a site level. Routine management review processes are in place to identify and act on performance gaps or OOS results, such as evaluation of process capability (e.g., capability and performance indicators C_{pk} and P_{pk}), which are measured for critical products.

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At Level 4 Improved, a robust monitoring and control plan is in place, standardized SPC-based statistics tools are regularly used, CQAs/CPPs/CMAs are defined and measured, and statistical analysis is provided for all products. These trends and analysis reports are routinely assessed by Product/Process owners and improvement teams, often supported by specialist data scientist resources, for opportunities to strengthen the control strategy. In such organizations, real-time data is collected across most of the site, and the use of live dashboards enables early detection of any performance gaps. Signal detection and/or process capability measurement is in place for all products, and this is used as a feedback mechanism for potential prediction models. PAT is used for monitoring and controlling purposes, and a mature system for justifying the application is in place.

In Level 5 Optimized organizations, there is a high level of connectivity and automation between systems collecting process data. These organizations extensively employ real-time data to monitor and respond to any potential performance gaps. Knowledge management tools are applied to maintain and manage the product, process, and tacit knowledge. Measurement systems evolve in response to continual improvement opportunities. For mature products, real-time SPC may be utilized with predictive models used to auto-correct based upon real-time feedback mechanisms. For new product introductions where the focus is on speed to launch, platform experience will be leveraged to support measurement and analysis approaches. Performance metrics, such as process capability (Cpk) and process performance (P_{pk}), are measured for all products and used as a feedback mechanism for potential process improvements. In such organizations, external source data may be included in algorithms for product quality assessment and error proofing. Proficiency in the use of the standardized measurement and analysis tools is considered a core competency and included as part of core training.

The detailed evaluation criteria for the determining tools for measurement and analysis of parameters and attributes sub-element are provided in Table 6.2.

Table 6.2: Assessment Criteria for Determining Tools for Measurement and Analysis of Parameters and Attributes

PPPQMS Sub-element 2: Determining Tools for Measurement and Analysis of Parameters and Attributes **How to measure and assess the state of control**			
Level 1 Undefined	Compliance risk	• Undefined • Uncontrolled • Not monitored • No evidence	☐ No tools for measurement and analysis of parameters and attributes have been determined during the development phase of the product lifecycle. ☐ Only data related to the attributes identified within the manufacturing batch records is recorded. ☐ Data analysis is rarely utilized during routine manufacturing process. ☐ Batch reports data is graphed during the APQR/PQR. ☐ Real-time data collection and visualization is not employed. ☐ Review of the degree to which performance gaps are made clear is not performed. ☐ SPC is rarely utilized nor understood. ☐ Process parameters are not routinely measured or appropriately assessed.
Level 2 Defined	Partially meets ICH Q10 requirements	• Partially defined • Not formally controlled • Not formally monitored • Person dependent	☐ Some process parameters have been identified, but limits are based on release specifications and IPCs. ☐ Some tools are in place but not standardized; there may be trending of products. ☐ Real-time data collection on one or two lines is rarely employed. ☐ Review of the degree to which performance gaps are made clear is rarely performed. ☐ SPC is not consistently utilized. ☐ APQR/PQRs include minimal trending/analytics and do not include improvement options.
Level 3 Managed	Fully meets ICH Q10 requirements	• Defined policy and processes • Meets requirements for application • Process monitoring and controls in place	☐ Standardized tools are in place and may be tracked on spreadsheets or electronically; standard trends and statistics apply. ☐ Risk-based approach is used to determine SPC approach, which is documented within the control plan. ☐ Real-time data collection is employed across some of the site. ☐ Review of the degree to which performance gaps are made clear is performed. ☐ SPC is regularly utilized. ☐ Process capability is measured for all products. ☐ PAT is used mainly for monitoring purposes.

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