

GUIDE:

Corrective Action and Preventive Action (CAPA) System



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Preface

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

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

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

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

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

- CAPA system
- Management responsibilities and management review
- Change management system
- Process performance and product quality monitoring system

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

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

¹ The APQ Guides for management responsibilities and management review, change management system, and process performance and product quality are planned future ISPE publications.

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- All those who participated in the development of this Guide by reviewing or pilot testing draft material.
- Thomas Friedli, PhD, Director, Institute of Technology Management; and Marten Ritz, M.Sc., Research Associate & Head of Operational Excellence; University of St.Gallen, Switzerland for their collaboration and contributions.

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Table of Contents

Part 1: The Advancing Pharmaceutical Quality (APQ) Program

1	Introduction to the APQ Program and Guide Series	7
1.1	Objectives	7
1.2	Scope.....	8
1.3	Benefits.....	8
1.4	About the ISPE APQ Guide Series	9
1.5	How to Use This Guide	11
2	Understanding the APQ Program	13
2.1	Link to the ICH Q10 PQS Model.....	13
2.2	Link to Cultural Excellence and Operational Excellence.....	15
3	APQ Assess, Aspire, Act, and Advance Framework.....	17
3.1	APQ Framework Process	18
3.2	APQ Self-Assessment Tool.....	19
3.3	Cross-Functional Team Approach.....	23
4	APQ Benchmarking.....	25
4.1	Benchmarking Questionnaire.....	25
4.2	APQ Pre-Assessment Benchmarking	27
4.3	APQ Post-Action Benchmarking	27

Part 2: Practical Application of the APQ Framework to the CAPA System (APQ-CAPA)

5	Introduction to APQ-CAPA.....	29
5.1	Key Concepts of the CAPA System	30
5.2	Seven Sub-Elements of the APQ-CAPA System	32
6	APQ Assess Phase	33
6.1	Assessing Sub-element 1 – CAPA Documentation.....	34
6.2	Assessing Sub-element 2 – Problem Identification.....	36
6.3	Assessing Sub-element 3 – Root Cause Analysis	38
6.4	Assessing Sub-element 4 – Corrective and/or Preventive Actions	40
6.5	Assessing Sub-element 5 – CAPA Effectiveness	42
6.6	Assessing Sub-element 6 – CAPA Metrics	44
6.7	Assessing Sub-element 7 – Governance, Management Oversight, and CAPA Prioritization	47
7	APQ Aspire Phase	51
7.1	Evaluation of the Assigned Maturity Ratings.....	53
7.2	Prioritization of Targeted Improvements	53
8	APQ Act Phase.....	55
9	APQ Advance Phase	57

Appendices

10 Appendix 1 – APQ Program Drivers and Goals 59

10.1 What Does Advancing Pharmaceutical Quality Mean?..... 59

10.2 APQ Program Overarching Goals..... 60

11 Appendix 2 – APQ Program History: From Quality Metrics to Advancing Pharmaceutical Quality 65

12 Appendix 3 – APQ Maturity Assessment Tool for the CAPA System 67

13 Appendix 4 – APQ Catalog of Improvement Tools and KPIs for the CAPA System..... 75

14 Appendix 5 – Example APQ-CAPA Assess and Aspire Report..... 77

15 Appendix 6 – Example Template for APQ-CAPA Improvement Action Plan 99

16 Appendix 7 – APQ Benchmarking Tool.....103

17 Appendix 8 – Example APQ Benchmarking Report.....117

18 Appendix 9 – References 127

19 Appendix 10 – Glossary 129

19.1 Acronyms and Abbreviations 129

19.2 Definitions 130

1 Introduction to the APQ Program and Guide Series

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

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

As stated in ICH Q10:

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

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

1.1 Objectives

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

The eight overarching goals of the APQ program are to:

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

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

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

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

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

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

1.2 Scope

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

1.3 Benefits

The benefits of the APQ program are outlined below:

- Benefits for industry:
 - Access to an ICHQ10-based quality management maturity framework that can be utilized in full by an organization to understand the impact to the overall performance of the organization of their maturity assessment, Key Performance Indicator (KPI) application, and improvement actions
 - Supports sustained, continual improvement of an organization's PQS
 - Benchmarking against industry peer groups, i.e., by using the St.Gallen APQ Benchmarking Tool or full OPEX benchmarking program
 - Community of practitioners for sharing of best practices to accelerate progress
- Benefits for patients and consumers:
 - Increased reliability of supply of quality product

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

1.4 About the ISPE APQ Guide Series

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

- CAPA system
- Management responsibilities and management review
- Change management system
- Process performance and product quality monitoring system

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

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

Figure 1.1 provides a high-level overview of the APQ program which comprises the APQ Assess, Aspire, Act, and Advance framework based on a foundation of cultural excellence. Figure 1.2 shows the ISPE APQ Guide Series including the application of the APQ framework to the four ICH Q10-based PQS elements, supported by additional ISPE body of knowledge and publications associated with key principles [2, 3, 4] and PQS enablers (knowledge management⁵ and quality risk management).

⁴ The APQ Guides for management responsibilities and management review, change management system, and process performance and product quality are planned future ISPE publications.

⁵ *ISPE Good Practice Guide: Knowledge Management* is a planned future publication.

Figure 1.1: Overview of the APQ Program

ISPE Advancing Pharmaceutical Quality Program

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

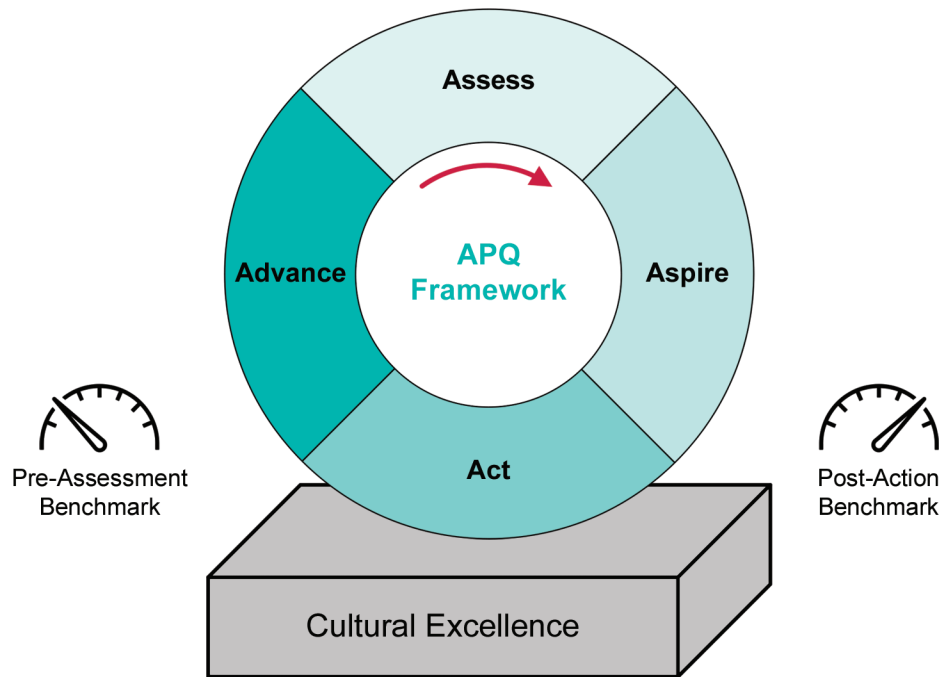
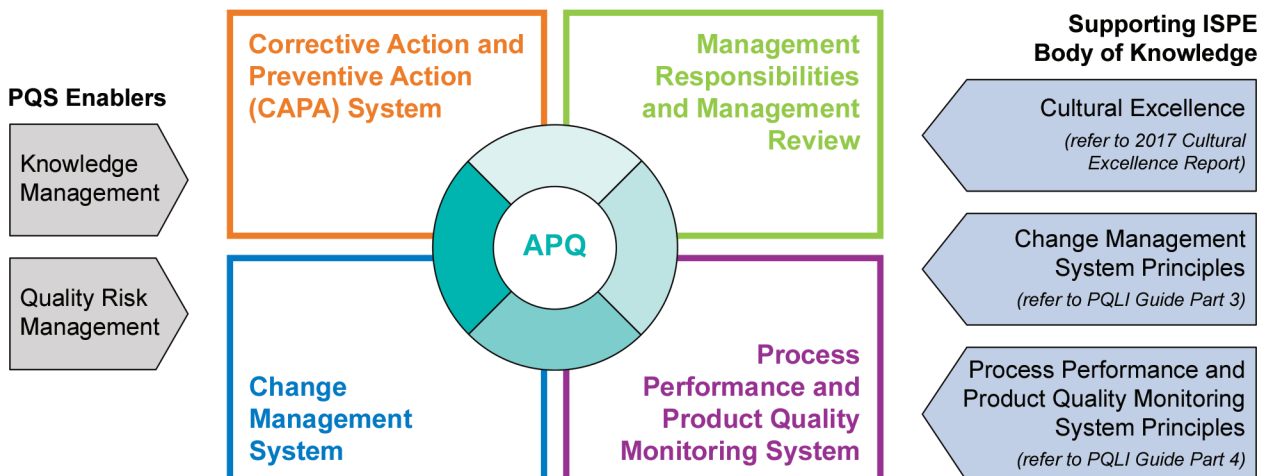


Figure 1.2: Overview of the ISPE APQ Guide Series

ISPE APQ Guide Series

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



Note for Figure 1.2: The APQ Guides for management responsibilities and management review, change management system, and process performance and product quality monitoring system are planned future ISPE publications.

1.5 How to Use This Guide

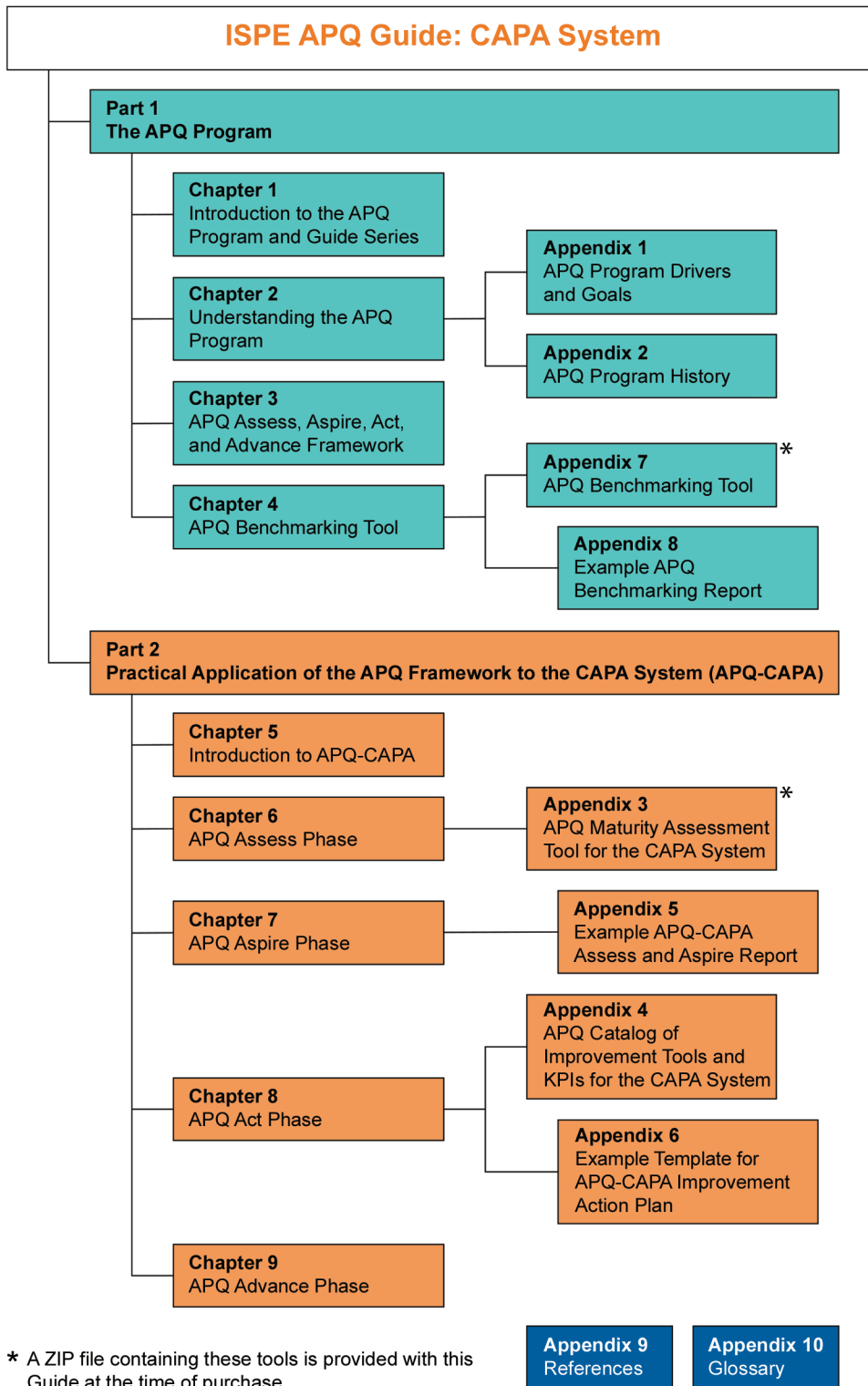
Part 1 covers the key concepts of the APQ program including the link to the ICH Q10 PQS model [1] and the link to cultural and operational excellence. It introduces the Assess, Aspire, Act, and Advance framework and explains how to perform the self-assessment. **This prerequisite information is applicable 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 the CAPA system element (APQ-CAPA). 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 CAPA system. It provides guidance on developing an APQ Improvement Action Plan, with recommendations for KPIs and improvement methodologies appropriate for each maturity level.

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

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

Figure 1.3: Guide Structure



2 Understanding the APQ Program

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

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

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

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

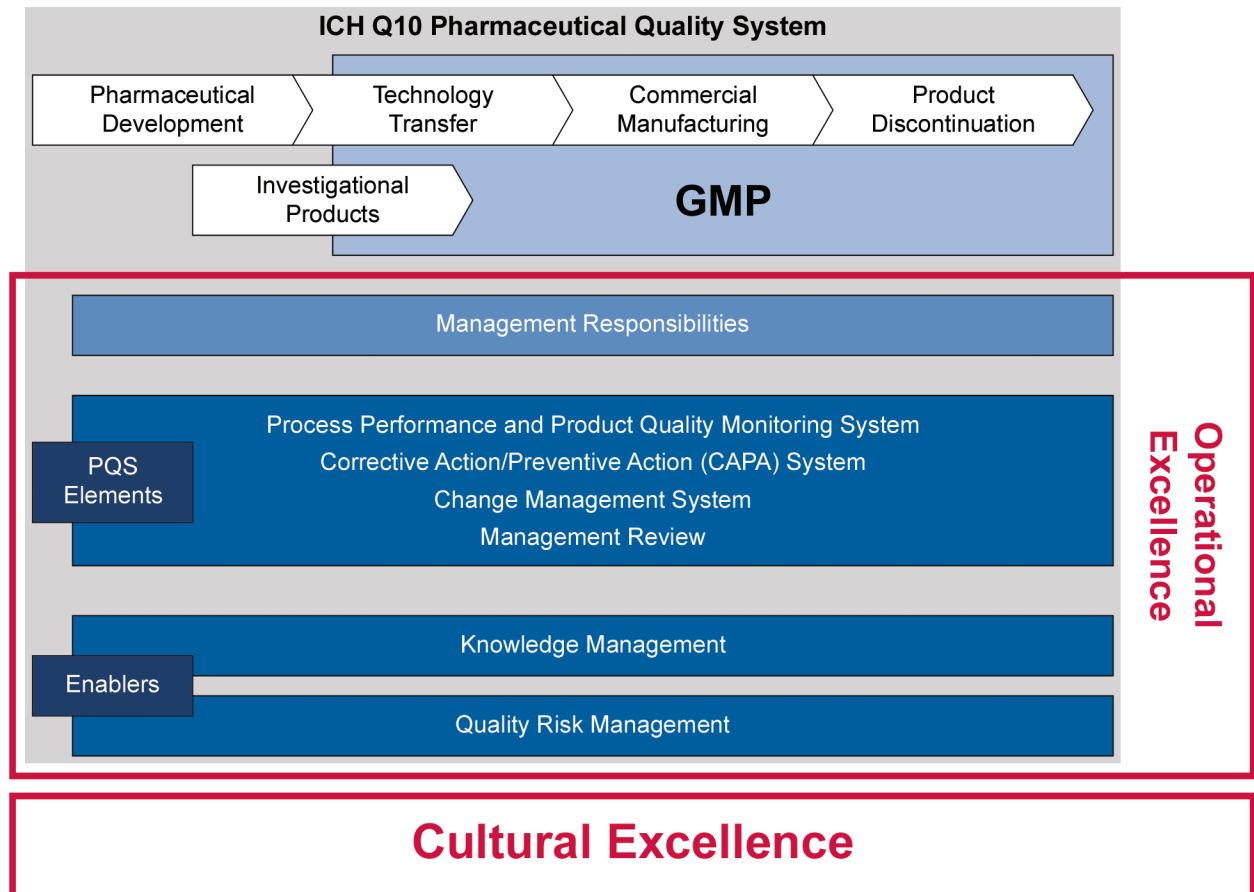
The philosophy behind the APQ program and its overarching goals is detailed in Appendix 1. It is important that readers of this Guide understand the full rationale described in this chapter and in Appendix 1 prior to the implementation of the APQ program.

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

2.1 Link to the ICH Q10 PQS Model

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

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



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

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

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

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

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

2.2 Link to Cultural Excellence and Operational Excellence

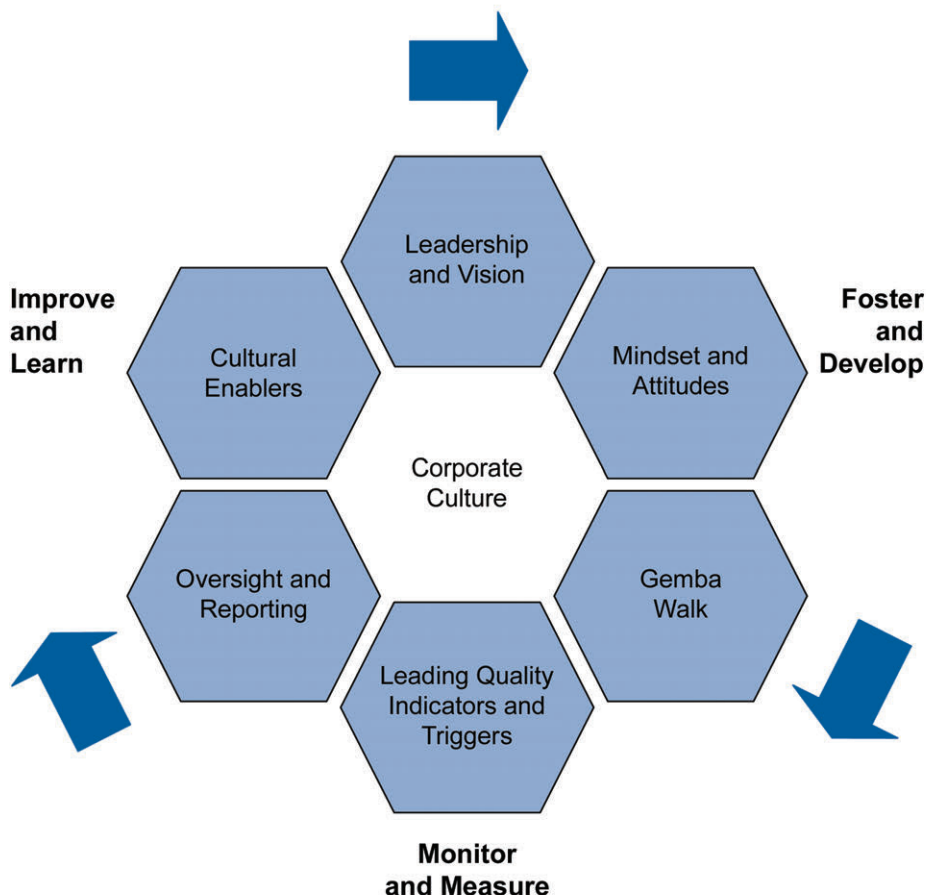
As stated earlier in this chapter, an overarching goal of the APQ program is to integrate quality, cultural, and operational excellence principles, tools, and approaches.

2.2.1 Cultural Excellence

Excellence in quality culture is essential for delivering robust and sustained quality performance, as demonstrated in the analyses from the ISPE Quality Metrics Wave 1 and Wave 2 pilot programs. [5, 6] (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 [2] 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 [2]



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) [2] 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.” [7] 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* [8] 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. [9]) Integration of these two infrastructures throughout the pharmaceutical organization is advised to more fully realize the positive impact of organization-wide improvement. The APQ Assess, Aspire, Act, and Advance framework has been carefully designed to incorporate cultural excellence behaviors and OPEX principles.

3 APQ Assess, Aspire, Act, and Advance Framework

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

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

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

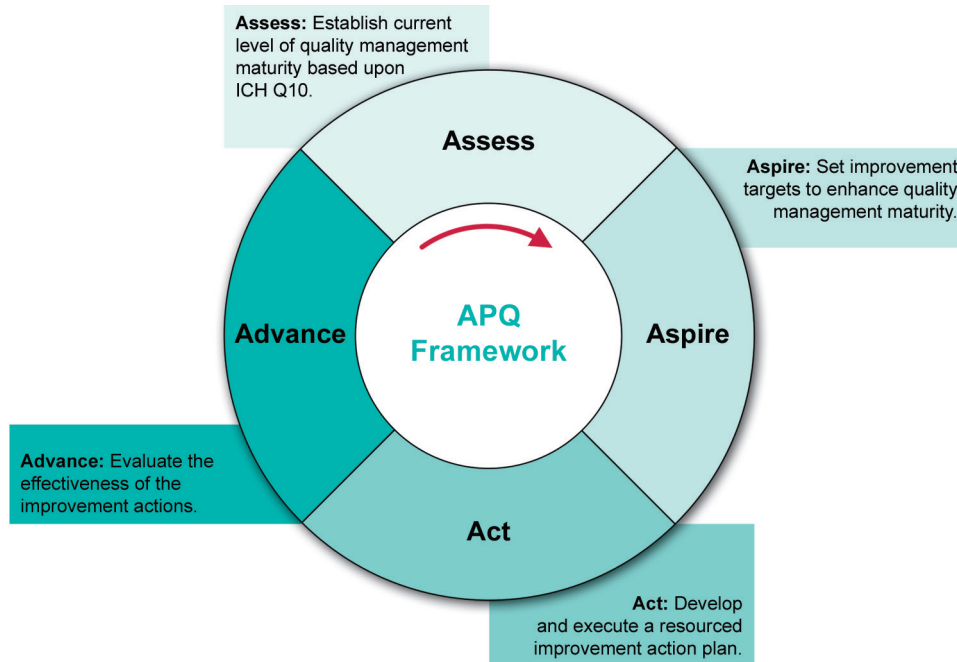
The APQ Assess, Aspire, Act, and Advance framework provides deep diagnostic tools for each of the four PQS elements based on ICH Q10 [1]:

- CAPA system
- Management responsibilities and management review
- Change management system
- Process performance and product quality monitoring system

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

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

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



3.1 APQ Framework Process

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

1. Assess Phase

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

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

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

2. Aspire Phase

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

3. Act Phase

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

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

4. Advance Phase

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

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

3.2 APQ Self-Assessment Tool

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

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

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

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

Figure 3.2: APQ 5-Level Maturity Model

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

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

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

Level 1 Undefined

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

Level 2 Defined

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

Level 3 Managed

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

Level 4 Improved

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

Level 5 Optimized

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

3.2.2 Quantitative and Qualitative Aspects

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

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

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

Maturity Rating

Maturity Criteria

Level 1 Undefined	Compliance risk	<ul style="list-style-type: none"> • Undefined • Uncontrolled • Not monitored • No evidence 	☐ No SOPs. ☐ No formal process for documenting CAPA. ☐ No monitoring or traceability oversight.
Level 2 Defined	Partially meets ICH Q10 requirements	<ul style="list-style-type: none"> • Partially defined • Not formally controlled • Not formally monitored • Person dependent 	☐ SOP provides high-level overview and expectations (lacks details for defined responsibilities, process, and expectations). ☐ Formal process to document CAPA exists. ☐ CAPAs are monitored, however the process is not defined in an SOP.
Level 3 Managed	Fully meets ICH Q10 requirements	<ul style="list-style-type: none"> • Defined policy and processes • Meets requirements for application • Process monitoring and controls in place 	☐ SOP defines process, expectations, and responsibilities across individual site or functions. ☐ Process for documenting CAPA is applied, however may have inconsistencies in execution from record to record. ☐ Monitoring process is defined in an SOP.
Level 4 Improved	Demonstrates improved/ optimized execution	<ul style="list-style-type: none"> • Defined policy and processes • Routine application • Routine monitoring, advancing improvements 	☐ SOP defines process, expectations, and responsibilities across the organization's entire network. ☐ Process for documenting CAPA is executed consistently from record to record, across the PQS (Pharmaceutical Quality System). ☐ Robust and defined monitoring ensuring successful KPI performance for the CAPA quality system.
Level 5 Optimized	World class/industry leader	<ul style="list-style-type: none"> • Proactive • Continual improvement • Predictive 	☐ CAPA documentation process is periodically reviewed and proactively enhanced. ☐ Process for documenting CAPA includes full integration with PQS processes, seamless network collaboration, and proactive actions to drive continual improvement. ☐ CAPA Key Performance Indicators and Key Behavioral Indicators are engrained within the CAPA quality system. ☐ Monitoring process is proactive and assesses real time data. May include evaluating stress points and forecasting of upcoming CAPA; further granularity of CAPA for trending (category or effectiveness) is included within the documented process.

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

3.3 Cross-Functional Team Approach

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

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

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

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

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

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

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

It is strongly recommended that the cross-functional assessment team practice the Gemba method of “Go, Look, Ask, Coach” as part of the inquiry and assessment process. This approach ensures a full understanding of the current situation, identification of potential improvement opportunities and issues, and opportunity to provide constructive feedback to the department or function under review. The location of the Gemba walks should include observing front line activities including engagement with a cross-section of process users (e.g., attendance at CAPA meetings run by the CAPA system owner) and participation in the relevant oversight and review meetings conducted by the process and/or functional owners. For additional recommendations on how to conduct an effective Gemba activity refer to the ISPE Cultural Excellence Report [2].

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

3.3.2 Improvement Team (Act and Advance)

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

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

4 APQ Benchmarking

The APQ program incorporates a pre-assessment and post-action benchmarking questionnaire tool developed by the St.Gallen OPEX Benchmarking team specifically for use with the APQ program.⁶ 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).⁷

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 [7].

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)

⁶ 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.

⁷ For information about participating in the external benchmarking study, contact the St.Gallen OPEX Benchmarking team at benchmarking@unisp.ch. St.Gallen may collect a fee for the benchmarking service.

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

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

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

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

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

St.Gallen APQ Benchmarking Tool			
Maintenance	Quality	Delivery	People
1. Share of Unplanned Maintenance 2. Maintenance FTE / Total FTE	3. Rejected Batches 4. Recurring Deviation 5. Quality FTE / Total FTE 6. IOOS rate (Lab) 7. Deviation Closure Time	8. Service Level – Delivery (OTIF) 9. Service Level – Supplier (OTIF) 10. Customer Complaint Rate 11. Adherence to standard lead time	12. Safety level 13. Sick leave
Enabler		Contextual Factors	
<ul style="list-style-type: none">• Organization enablers• Social and employee enablers• Technical and tool enablers		<ul style="list-style-type: none">• Site type and size• Production technology platforms and size• Days on Hand (DOH)	
ICH Q10 Maturity Assessment			
<ul style="list-style-type: none">• Management Responsibilities• Knowledge Management• CAPA System• Quality Risk Management		<ul style="list-style-type: none">• Process Performance and Product Quality Monitoring System• Change Management System• Management Review	

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

4.2 APQ Pre-Assessment Benchmarking

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

4.3 APQ Post-Action Benchmarking

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

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

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

5 Introduction to APQ-CAPA

Part 2 of this Guide covers the practical application of the APQ framework to the Corrective Action and Preventive Action (CAPA) system. It provides guidance on how to use the APQ framework to:

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

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

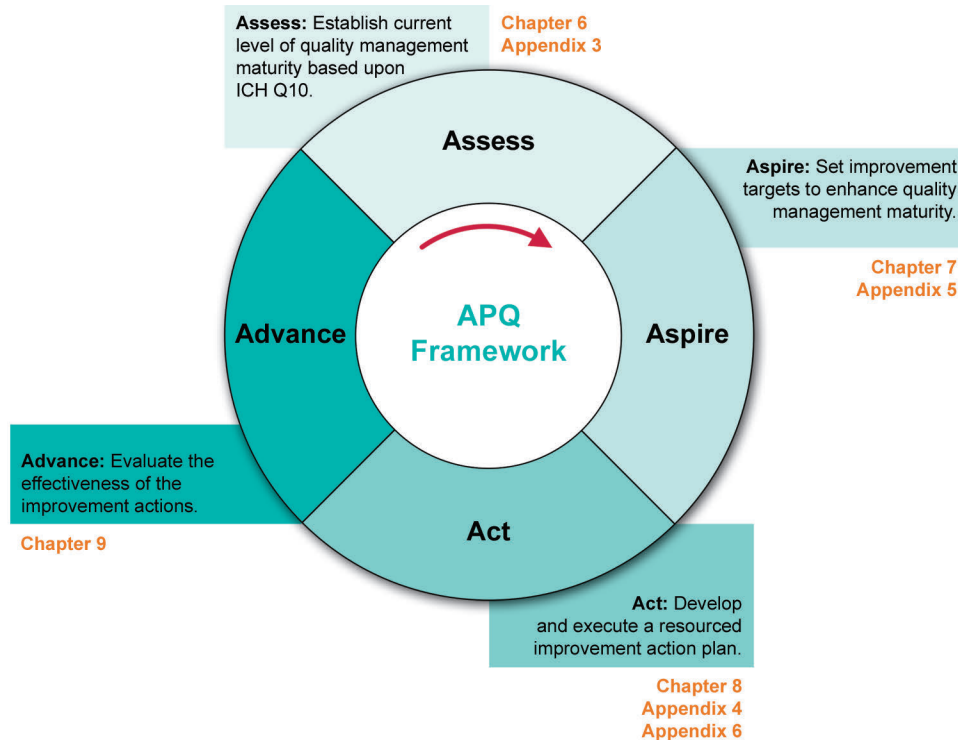
The following resources are provided in the APQ-CAPA Appendices:

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

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

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

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



5.1 Key Concepts of the CAPA System

The quality and quantity of CAPAs may be considered key indicators of an organization's health. The CAPA system demonstrates whether issues are acknowledged, tracked, and ultimately remedied in an effective manner to eliminate or reduce the risk of a recurrence. The timeliness and robustness of these processes and records also indicate whether an organization demonstrates effective planning and/or has sufficient resources to manage, resolve, and correct past issues and to prevent future issues. In this way, the effectiveness of an organization's CAPA system plays a crucial role in the ability of an organization to apply effective continual improvement strategies.

FDA guidance [10] describes the CAPA system as *"one of the most important quality system elements"*. EU GMP Volume 4, Chapter 1: Pharmaceutical Quality System [11] further recommends:

"The effectiveness of [CAPA] actions should be monitored and assessed, in line with Quality Risk Management principles."

CAPAs are defined in ICH Q10 [1] as follows:

"Corrective Action:

Action to eliminate the cause of a detected non-conformity or other undesirable situation. NOTE: Corrective action is taken to prevent recurrence whereas preventive action is taken to prevent occurrence. (ISO 9000:2005 [12])"

"Preventive Action:

Action to eliminate the cause of a potential non-conformity or other undesirable potential situation. NOTE: Preventive action is taken to prevent occurrence whereas corrective action is taken to prevent recurrence. (ISO 9000:2005 [12])"

In addition to these formal definitions, this Guide includes one further category of action, as follows:

Correction:

Immediate action taken to correct the identified problem or reduce the significance.

The distinction between these three potential actions and how they might be assigned is covered in further detail in Section 6.4.

A robust CAPA system should be designed to both:

- Capture and record CAPA activities; and
- Draw from multiple inputs across the organization to identify signals, review trends, and seek improvement opportunities.

This depth of scope of the overall CAPA program represents an important distinction between it and other related but separate units within an organization's PQS. For example, the CAPA system should not be mistaken with the deviation management system. Figure 5.2 illustrates the multitude of inputs to an effective CAPA system.

Figure 5.2: Inputs to an Effective CAPA System



The fundamental objectives of the CAPA system are to:

- Implement immediate corrections as necessary to correct the identified problem or reduce the significance or risk of the event
- Implement corrective actions by addressing root causes and preventing recurrence
- Proactively implement preventive actions to eliminate potential root causes to prevent future occurrence

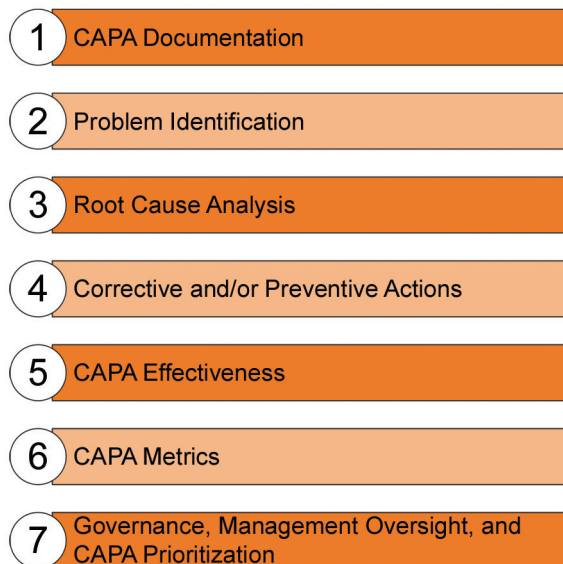
- Develop action plans to identify the root causes of issues to enable appropriate remediation
- Collect signals from across the operations to identify issues that indicate a need for improvement

The approach and the implementation details may differ across organizations, based on the nature or size of the business. However, the fundamental objectives of the CAPA system remain the same.

5.2 Seven Sub-Elements of the APQ-CAPA System

For the APQ program, the CAPA system is categorized into seven distinct sub-elements as shown in Figure 5.3. These sub-elements were determined using feedback from a wide range of inputs from regulatory bodies, academia, and industry (through engagements, focus groups, and pilot studies).

Figure 5.3: APQ-CAPA System Sub-Elements



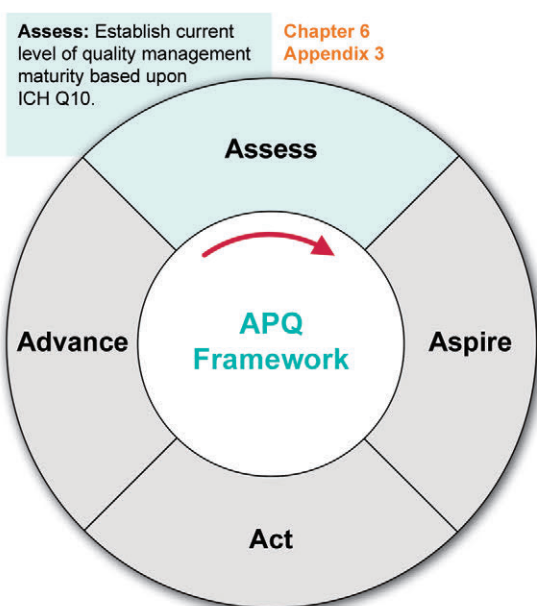
Detailed qualitative evaluation criteria for these seven sub-elements are provided in the APQ-CAPA Maturity Assessment Tool, discussed in detail in the next chapter (Chapter 6) and provided in Appendix 3.

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 the CAPA system. Using the APQ Maturity Assessment Tool, the team evaluates the current state of maturity, establishes objective evidence of organizational capability, and assigns an appropriate maturity rating for each CAPA system sub-element. This chapter covers the self-assessment tool in depth, explaining the rationale for the criteria. The full APQ Maturity Assessment Tool for the CAPA System 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-CAPA 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.

6.1 Assessing Sub-element 1 – CAPA Documentation

Good practices for CAPA documentation include having a governing document that captures the objectives and key elements of the CAPA system that include, but are not limited to:

- Scope of the CAPA system
- Definition of what qualifies as a CAPA record in the organization
- High-level flow chart and description of each step in the CAPA process
- Descriptions of the CAPA governance activities (e.g., review boards, internal audits, self-assessments) used to ensure the quality and consistent execution of relevant CAPA documentation and specific documentation associated with the oversight, monitoring, and review processes (e.g., performance management KPIs)

Other CAPA documentation may include corporate policies, Standard Operating Procedures (SOPs), forms and checklists, electronic audit trails of phased CAPA activities, associated risk or impact assessments, meeting minutes or electronic records of review and approval processes, evidence of effectiveness checks, trend data, documented monitoring behaviors, etc.

Assessment Criteria for CAPA Documentation

When evaluating the CAPA documentation sub-element of the CAPA system, the assessment team should seek evidence of the following:

- Availability and level of formality of the existing CAPA documentation
- Quality and consistency of the execution and use of that documentation
- Robustness and effectiveness of the oversight and documentation review processes

The detailed maturity assessment criteria for CAPA documentation are provided in Table 6.1.

Table 6.1: Assessment Criteria for CAPA Documentation

CAPA System Sub-element 1: CAPA Documentation			
Level 1 Undefined	Compliance risk	<ul style="list-style-type: none"> • Undefined • Uncontrolled • Not monitored • No evidence 	☐ No SOPs. ☐ No formal process for documenting CAPA. ☐ No monitoring or traceability oversight.
Level 2 Defined	Partially meets ICH Q10 requirements	<ul style="list-style-type: none"> • Partially defined • Not formally controlled • Not formally monitored • Person dependent 	☐ SOP provides high-level overview and expectations (lacks details for defined responsibilities, process, and expectations). ☐ Formal process to document CAPA exists. ☐ CAPAs are monitored, however the process is not defined in an SOP.
Level 3 Managed	Fully meets ICH Q10 requirements	<ul style="list-style-type: none"> • Defined policy and processes • Meets requirements for application • Process monitoring and controls in place 	☐ SOP defines process, expectations, and responsibilities across individual site or functions. ☐ Process for documenting CAPA is applied, however may have inconsistencies in execution from record to record. ☐ Monitoring process is defined in an SOP.
Level 4 Improved	Demonstrates improved/ optimized execution	<ul style="list-style-type: none"> • Defined policy and processes • Routine application • Routine monitoring, advancing improvements 	☐ SOP defines process, expectations, and responsibilities across the organization's entire network. ☐ Process for documenting CAPA is executed consistently from record to record, across the PQS (Pharmaceutical Quality System). ☐ Robust and defined monitoring ensuring successful KPI performance for the CAPA quality system.
Level 5 Optimized	World class/industry leader	<ul style="list-style-type: none"> • Proactive • Continual improvement • Predictive 	☐ CAPA documentation process is periodically reviewed and proactively enhanced. ☐ Process for documenting CAPA includes full integration with PQS processes, seamless network collaboration, and proactive actions to drive continual improvement. ☐ CAPA Key Performance Indicators and Key Behavioral Indicators are engrained within the CAPA quality system. ☐ Monitoring process is proactive and assesses real time data. May include evaluating stress points and forecasting of upcoming CAPA; further granularity of CAPA for trending (category or effectiveness) is included within the documented process.

6.2 Assessing Sub-element 2 – Problem Identification

The strength of the overall CAPA system relies on a rigorous capture of all potential inputs. It is important that the problem identification process is clearly defined and that there are routine mechanisms to capture these inputs. These mechanisms may include, but are not limited to:

- Periodic Product Reviews
- Senior management reviews of quality systems
- Reviews of facilities, utilities, equipment, and computer systems
- External audits and regulatory inspections
- Observations from audits and issues from self-inspections
- Trends from process performance and product quality monitoring
- Deviations
- Product rejections
- Recalls and complaints

For problem identification to operate effectively, initial capture for the issue/problem should allow for the details of the event to be captured as contemporaneously to the event as possible. Those present at the event, most familiar with the event, or responsible for the area/function under review should be directly involved. The use of visuals, photographs, or diagrams can help to describe the issue in a way that enables the CAPA reviewer to fully understand the problem. Training in structured writing to capture the issue/problem (as well as all other CAPA system sub-elements) is extremely important. This focus may support the use of advanced data tools to detect trends, e.g., artificial language processing.

Clarity in the problem identification phase will assist in more accurate investigations, root cause identification, and ultimately support a more timely close out of the issue. Early assumptions of impact or root cause should be discouraged in the problem identification phase to reduce the impact of bias. The provisions of supporting data, evidence of the timeline of the event, and relevant recurrence trends should be facilitated to enable a full review.

Assessment Criteria for Problem Identification

When evaluating the problem identification sub-element of the CAPA system, the assessment team should seek evidence of the following:

- Variety of sources of inputs that are routinely captured
- Consistency of capture of issues/problems within the CAPA system
- Quality of the problem statements, descriptive details, supporting evidence, data, etc.
- Linkages between other PQS and business processes
- Ratio of reactive versus proactive issue identification

- Cultural aspects such as percentage of problems related to human error

The detailed maturity assessment criteria for the problem identification sub-element are provided in Table 6.2.

Table 6.2: Assessment Criteria for Problem Identification

CAPA System Sub-element 2: Problem Identification			
Level 1 Undefined	Compliance risk	<ul style="list-style-type: none"> • Undefined • Uncontrolled • Not monitored • No evidence 	☐ No SOP definition of what types of issues/problems require the initiation of a record in the CAPA quality system. ☐ Issues/problems are not initiated as records in the CAPA quality system. ☐ There is no linkage between CAPA and other quality systems.
Level 2 Defined	Partially meets ICH Q10 requirements	<ul style="list-style-type: none"> • Partially defined • Not formally controlled • Not formally monitored • Person dependent 	☐ An SOP definition of what types of issues/problems require the initiation of a record in the CAPA quality system exists; however, its application is inconsistent. ☐ Issues/problems are inconsistently initiated as records in the CAPA quality system; the same type of problem inconsistently results in the initiation of a record in the CAPA quality system. ☐ All of the records initiated are reactive; potential problems/issues (preventive actions) are not identified. ☐ There are some linkages between CAPA and other quality systems and operational processes; however, the inputs are not defined procedurally.
Level 3 Managed	Fully meets ICH Q10 requirements	<ul style="list-style-type: none"> • Defined policy and processes • Meets requirements for application • Process monitoring and controls in place 	☐ An SOP definition of what types of issues/problems require the initiation of a record in the CAPA quality system exists; its application is consistent. ☐ Issues/problems are initiated as records in the CAPA quality system; the same types of issues result in the initiation of a record in the CAPA quality system the majority of the time. ☐ The majority of records initiated are reactive; potential problems/issues (preventive actions) are sometimes identified. ☐ There are linkages between CAPA and other quality systems and operational processes, and they are defined procedurally; however, the inputs may not always be clear.
Level 4 Improved	Demonstrates improved/ optimized execution	<ul style="list-style-type: none"> • Defined policy and processes • Routine application • Routine monitoring, advancing improvements 	☐ A clear SOP definition of what types of issues/problems require the initiation of a record in the CAPA quality system exists; its application is consistent. Defined examples exist in SOPs and/or training materials. ☐ Issues/problems are always initiated as records in the CAPA quality system. The same types of issue always result in the initiation of a record in the CAPA quality system. ☐ > 25% and < 50% of the records initiated are reactive and the balance are initiated for potential problems/issues (preventive actions). ☐ There are linkages between CAPA and other quality systems and operational processes, and they are defined procedurally. These inputs are clear and may contain some of the following: <ul style="list-style-type: none"> ☐ Events/nonconformities ☐ Complaints ☐ Suspect results ☐ Audits ☐ Trends ☐ Reviews
Level 5 Optimized	World class/industry leader	<ul style="list-style-type: none"> • Proactive • Continual improvement • Predictive 	☐ A clear SOP definition of what types of issues/problems require the initiation of a record in the CAPA quality system exists; its application is consistent. In addition, the SOPs from other systems/processes define when a record must be initiated in the CAPA quality system (the linkages between systems are clearly defined). ☐ At least 50% of the records initiated in the CAPA quality system are for potential problems/issues (preventive actions). ☐ Process for problem identification for CAPA includes full integration with PQS processes, seamless network collaboration, and proactive/ predictive actions to drive continual improvement.

6.3 Assessing Sub-element 3 – Root Cause Analysis

The root cause analysis process should clearly define when a full investigation must be initiated to determine the underlying cause(s) and assign appropriate actions. It is extremely important to extend the scope of the investigation to include a review of impact on related products, processes, and sites across the organization. Alternatively, if the cause is immediately evident and the issue represents an isolated incident, then the CAPA review team may determine that a correction alone is sufficient and no root cause analysis is initiated. Post-implementation effectiveness checks will confirm that the appropriate actions have been applied, whether corrections, corrective actions, or preventive actions. A supporting decision tree or similar tool should clearly outline when a full root cause analysis must be triggered, for example:

- Periodic reviews (Periodic Product Reviews, quality system senior management reviews):
 - If data from the periodic review identifies an adverse trend with unknown root cause
 - If there is a series of individual nonconformances that is indicative of a trend
- Internal and external audits and inspections:
 - If the finding is from an external regulatory agency
 - If the finding is categorized as major or critical
- Deviations, trends, complaints, recalls, and product rejection:
 - If the issue results in an impact to a CQA
 - If the issue results in being outside a regulatory specification, commitment, or market authorization
 - If the issue results in being outside of the controls to ensure product quality
 - If the issue results in a GMP compliance concern

The root cause analysis process should also provide the appropriate level of guidance to ensure the investigation is complete, thorough, and successful. For example, references should be included for key procedures, tools, and specialized investigator resources, as applicable. Refer to the ISPE and PDA joint publication on Root Cause Analysis [13] which highlights commonly used approaches and provides guidance on how and when to use each.

Assessment Criteria for Root Cause Analysis

When evaluating the root cause analysis sub-element of the CAPA system, the assessment team should seek evidence of the following:

- Adequate training and experience for those performing the root cause analysis
- A range of root cause analysis tools available
- Effective and consistent application of the root cause analysis tools
- Selection of the right tool ensuring the correct depth of the investigation
- Root cause analysis documentation that clearly and succinctly identifies the identified root cause(s)
- Cultural aspects such as percentage of identified root causes related to human error

- Assignment or recommendations for actions appropriate to the identified root cause(s)
- Lessons learned being applied in subsequent investigations

The detailed maturity assessment criteria for the root cause investigation sub-element are provided in Table 6.3.

Table 6.3: Assessment Criteria for Root Cause Analysis

CAPA System Sub-element 3: Root Cause Analysis			
Level 1 Undefined	Compliance risk	<ul style="list-style-type: none"> • Undefined • Uncontrolled • Not monitored • No evidence 	☐ No SOPs exist that defines and requires a root cause investigation. ☐ Approval is not required or performed to confirm the root cause has been identified. ☐ There are no employee training programs for root cause investigations.
Level 2 Defined	Partially meets ICH Q10 requirements	<ul style="list-style-type: none"> • Partially defined • Not formally controlled • Not formally monitored • Person dependent 	☐ SOP exists that defines and requires a root cause investigation but does not provide guidance on how it should be performed. ☐ Approval is not required; however, it is sometimes performed to confirm the root cause has been identified. ☐ There are employee training programs for root cause investigation execution; however, they are not required.
Level 3 Managed	Fully meets ICH Q10 requirements	<ul style="list-style-type: none"> • Defined policy and processes • Meets requirements for application • Process monitoring and controls in place 	☐ SOP defines and requires a root cause investigation and provides guidance and tools on how it should be performed. ☐ Approval is required to confirm the root cause has been identified and there is evidence of it being performed. ☐ Root cause investigation guidance and tools are sometimes used. ☐ There are required employee training programs for root cause investigation execution.
Level 4 Improved	Demonstrates improved/ optimized execution	<ul style="list-style-type: none"> • Defined policy and processes • Routine application • Routine monitoring, advancing improvements 	☐ SOP defines and requires a root cause investigation and provides guidance and tools on how it should be performed. ☐ Approval is required. Quality is embedded in the root cause investigation team and ensures that the identified root cause is appropriate and there is evidence of it being performed. ☐ Root cause investigation guidance and tools are always utilized. ☐ There are required employee training programs for root cause investigation execution. ☐ Select resources are trained on Lean, Six Sigma, or other tools to aide in the identification of root cause.
Level 5 Optimized	World class/industry leader	<ul style="list-style-type: none"> • Proactive • Continual improvement • Predictive 	☐ SOP and/or CAPA training defines and requires a root cause investigation and provides guidance and tools on how it should be performed. ☐ Proximal/contributing causes are also identified and evaluated to identify where additional actions/improvements could be made. ☐ Root cause analysis toolkits such as the ISPE – PDA Guide to Improving Quality Culture in Pharmaceutical Manufacturing Facilities (Root Cause Analysis Guide) are embedded into the CAPA processes. ☐ Process for root cause analysis and CAPA determination includes full integration with PQS processes, seamless network collaboration, and proactive actions to drive continual improvement. ☐ There are required employee training programs for root cause analysis execution. ☐ A core curriculum for personnel conducting and approving investigations has been established. All resources involved with conducting and approving investigations are trained on Lean, Six Sigma, or other tools to aide in the identification of root cause. ☐ Lessons learned sessions are held for large investigations to determine whether the investigation process could be further improved or if there are risks for extension to other areas of the PQS or business.