



## Commissioning and Qualification

Second Edition

# QRM Addendum – C&Q Delivery Process

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# 1 Introduction

The purpose of this Addendum is to provide an overview of the Commissioning and Qualification (C&Q) delivery process, as described in *ISPE Baseline® Guide: Commissioning and Qualification (Second Edition)* [1], along with implementation recommendations for the application of Quality Risk Management (QRM) supporting qualification of facilities, systems, utilities, and equipment. This Addendum is based on surveys conducted by the ISPE Global C&Q Community of Practice in 2023 and 2024 to gather data on the adoption of QRM-based C&Q within the pharmaceutical industry and the need to identify and further describe key elements of the quality systems supporting the C&Q execution process. Survey results indicate inconsistencies in how the QRM process is applied for the purposes of achieving qualified systems<sup>1</sup> (i.e., suitable for the intended purpose) to support Process Performance Qualification (PPQ) for Process Validation (PV) and Performance Qualification (PQ) for critical utilities, environments, etc. In addition, this Addendum provides additional focus on the lifecycle deliverables associated with the QRM C&Q process and addresses four areas of supplemental guidance including:

- Better definition of and the relationship between Critical Quality Attribute (CQA), Critical Process Parameter (CPP), Critical Aspect (CA), and Critical Design Element (CDEs)
- Established Conditions (ECs), as defined in ICH Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management [2], and how to apply QRM C&Q to CPPS designated as ECs controlled during pharmaceutical manufacturing
- Insight into the risk assessment process in the application of QRM for C&Q including:
  - Definition of how the C&Q risk assessment aligns with the principal ICH Q9(R1) [3] elements of risk identification and risk control
  - Risk assessment scope definition as applied to CPP manufacturing control support versus other risk assessments needed to support the Control Strategy (ICH Q8(R2) [4]) in support of commercial manufacturing operations
- Introduction/overview of Process Control System (PCS) qualification in support of manufacturing systems

Inadequate application of *C&Q Baseline Guide* guidance for implementing QRM-based C&Q may increase the risk of deficiencies identified during regulatory inspection. The *C&Q Baseline Guide* guidance and this Addendum are intended to clarify regulatory expectations associated with compliance with both the internal site Pharmaceutical Quality System (PQS)/Quality Management System (QMS) and regulatory requirements.

Product quality and patient safety are the key drivers for industry adoption of the implementation approaches defined within the *C&Q Baseline Guide*. Speed to patient can also be achieved through optimized QRM-based project delivery and represents a significant opportunity to address product shortages and the need for quality life-changing products, while providing a business rationale for changes to traditional project delivery and C&Q methodologies. The application of the industry consensus-led *C&Q Baseline Guide* has saved companies time and effort, helping achieve optimized project deliverables and timely product launches. The impact is tangible and supports taking a hard look at current practices relative to the QRM-based integrated approach described in the *C&Q Baseline Guide*.

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<sup>1</sup> For the purposes of this Addendum, the term systems is used to refer to facilities, systems, utilities, and/or equipment.

## 2 Overview

The Second Edition of the *ISPE Baseline® Guide: Commissioning and Qualification* [1], published in June 2019, provides guidance on implementing QRM-based integrated C&Q for systems. The Guide incorporates the elements contained in ICH Q8(R2) Pharmaceutical Development [4], Q9(R1) Quality Risk Management [3], and Q10 Pharmaceutical Quality System [5]. The Guide describes the process by which systems can be verified as suitable for the intended purpose (qualified) through robust application of Good Engineering Practice (GEP) during project execution in support of commercial pharmaceutical manufacturing.

Additional details related to the QRM-based C&Q lifecycle process and associated deliverables and approvals can be found in the *C&Q Baseline Guide* and are not repeated in this Addendum.

### 2.1 Background

The purpose of PV is to verify/prove that the control strategy (ICH Q8(R2) [4]) established for a commercial manufacturing process will routinely deliver products meeting their CQAs.

As related to the qualification of systems, the focus for the QRM application is to develop an operational risk profile of the system for the chosen manufacturing train for a designated product type or for the manufacturing platform/process in the case of no selected product (i.e., CMOs with preliminary assigned CQAs). This prospective assessment associates the potential CQAs and CPPs for each step of the manufacturing process through the identified systems to be installed and determines the risk to product quality on the CQA if CPP is not under control.

CPPs are identified based on their potential impact on CQAs, independent of the robustness of the control strategy ultimately applied. The application of Quality by Design (QbD) principles serves to reduce the probability of CPP-related risks but does not negate the inherent criticality of a process parameter whose variability can affect product quality. Consequently, reducing residual risks to acceptable levels through controls/CAs, CDEs, or procedural measures does not constitute declassification of a CPP to a non-critical parameter.

Refer to Section 2.2 of this Addendum for additional information when designating a process-related CPP as an EC in a regulatory filing as opposed to CPP. CDEs are then identified to control the process designated EC and included in the design of the system. Where the risk is determined to be unacceptable, controls/CAs are added to the equipment design requirements. In addition, CAs associated with acceptable risk are identified, documented, and included in the design requirements.

By applying the principles of QbD during design development, the CDEs are identified, incorporated into the design, and fabricated into the system. If CDEs cannot be identified/applied to eliminate the risk associated with the CPPs keeping CQA at risk, a procedural control may be put into place.

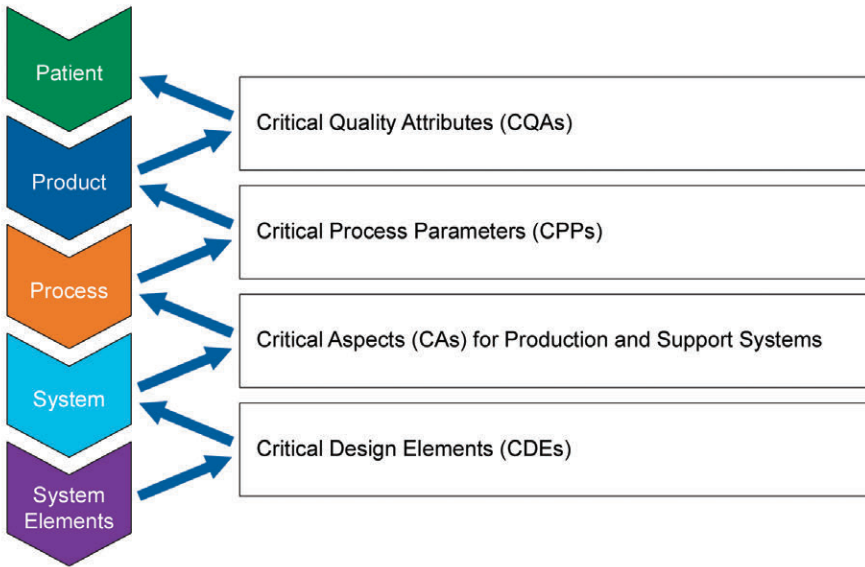
The desired output of System Risk Assessment (SRA) is that the CA/CDE and/or procedural control established to mitigate the risk of CPP control failure to an acceptable level (low). If the identified CAs/CDEs and/or procedure(s) cannot mitigate the risk to an acceptable level (low), the CPP and EC control design approach may need to be revised or the team may recommend to management to accept the risk within the system's defined risk profile.

CDEs can include engineering design elements such as components, instruments, and materials of construction. Automation CDEs can include data management and critical alarms.

The element of the ICH Q8(R2) [4] control strategy related to CPP control during manufacturing is referred to as the **Manufacturing Process Control Strategy (MPCS)** in this Addendum. The MPCS identifies the controls/CAs that then serve as inputs (i.e., user requirements) for the design and delivery of the systems needed to achieve the desired level of quality.

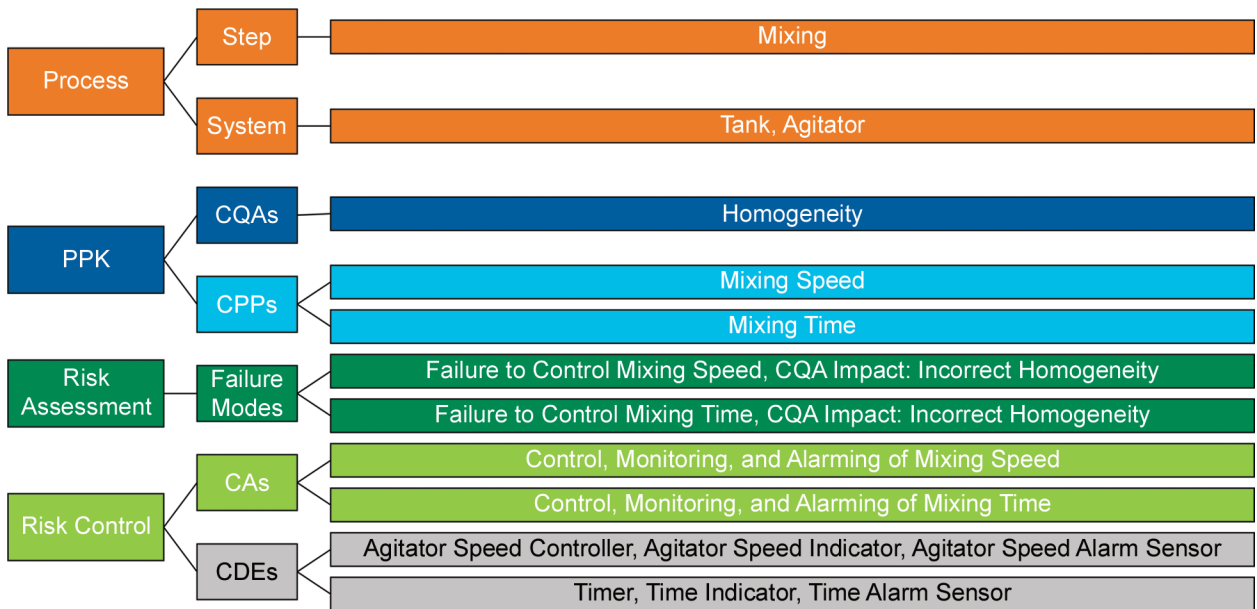
CQAs and CPPs are typically part of the Product and Process Knowledge (PPK) delivered by the product development teams. It is not the role of the C&Q team to develop CQAs and CPPs but rather collect the information from the development teams and appropriate Subject Matter Experts (SMEs) as a starting point to apply QRM and conduct risk assessments. The alignment of CQAs, CPPs, CAs, and CDEs to product quality and patient safety is shown in Figure 1.

**Figure 1: Relationship Between CQA, CPP, CA, and CDE**



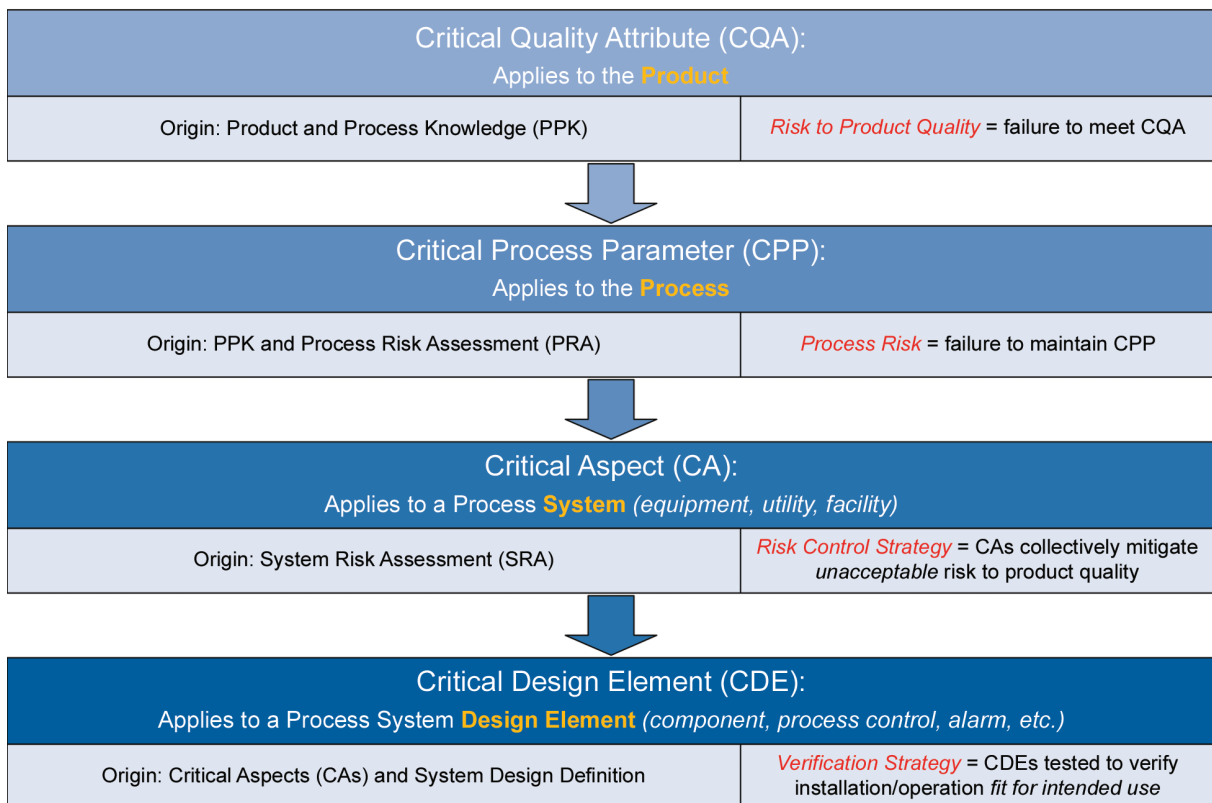
An example of the CQA, CPP, CA, and CDE relationship when applied to manufacturing equipment, such as a mixing tank for the CQA of homogeneity can be seen in Figure 2.

**Figure 2: Example QRM Application to C&Q – Mixing Operation with CQA = Homogeneity**



Collectively, the controls/CAs associated with manufacturing process systems constitute the MPCs, a sub-element of the overall control strategy defined within ICH Q8(R2) [4]. While the CDEs identified through QbD provide the focus for C&Q verification activities, CPPs remain lifecycle process attributes. CPPs continue to be subject to monitoring, trending, and change impact assessment during PPQ, continued process verification, and routine commercial manufacturing. Translation of CPPs into engineering controls does not remove the need for ongoing process-level ownership and governance. In effect, the prospective application of QRM on the process CPPs leads to identifying the controls/CAs defining an MPCs with an acceptable risk profile, resulting in delivery of a more robust manufacturing process. The CDEs provide the focus for the verification strategy, as shown in Figure 3.

**Figure 3: Sequence of Risk Identification and Control Strategy Development**



**Note:** A Process Risk Assessment (PRA) is usually conducted during Research and Development, PV Stage 1 (per FDA 2011 Guidance for Industry: Process Validation – General Principles and Practices [6]) to identify the Critical Control Points (CCPs) and identify CPPs having a direct impact on CQAs through the sequential steps of the selected manufacturing process. An SRA is performed on the selected direct impact manufacturing systems to identify control elements supporting the MPCs and to identify incorporated existing controls and CDEs supporting acceptable risk and any additional controls needed to mitigate unacceptable risk associated with CPP control/failure. The SRA aligns with ICH Q9(R1) [3] section 4.4, “Risk control includes decision-making to reduce and/or accept risks. The purpose of risk control is to reduce the risk to an acceptable level.” The SRA incorporates the elements of risk reduction and risk acceptance.

## 2.2 Impact of ICH Q12 Established Conditions on User Requirements

ICH Q12 provides a framework to facilitate the management of post-approval CMC (Chemistry, Manufacturing, and Controls) changes in a more predictable and efficient manner. ECs were introduced as a key element of the ICH Q12 guidance. ECs can be defined as elements (e.g., parameters, attributes, controls, specifications) “necessary to assure product quality and therefore would require a regulatory submission if changed post-approval.” [2]

ECs are further defined as follows:

- “Are legally binding information considered necessary to assure product quality” [2]
- A change to an EC requires submission to the regulatory authority that is consistent with regional regulations or guidance, or as agreed upon during review and approval of the marketing application
- Are contained in a regulatory submission, submitted, and justified by the applicant, and approved by the regulatory authority
- Are based on existing regulation and guidance, and can be further targeted based on science and risk-based approaches described in ICH Q12 [2]

In terms of defining critically and risk assessment, ICH Q12 [2] notes the following when defining ECs (e.g., CPP/ CMA) and reporting categories:

- Initial impact assessment of material and process inputs
- Identification of potential CPPs
- Evaluation of impact of process parameters on quality
- Final risk assessment of impact on quality when changing CPPs and material attributes in context of control strategy

While applying the ICH Q12 [2] guidance, industry may choose to define designated process parameters with the potential to impact product quality in their regulatory filings as ECs. There will be a defined range of operation and approach for control associated with the EC. As applied to the process/equipment used for manufacturing, an EC designated as a quality impacting process parameter would be subject to the same QRM C&Q approach as described for CPP control failure in determining the supporting MPCS. If a company follows ICH Q12 and classifies specific process parameters as ECs, then the designated ECs should be listed using the “quality” classification in its associated User Requirement Specification (URS) or other Quality-approved user requirements document. During manufacturing equipment design, the QRM process will address EC process parameter control failure and establish an acceptable risk profile incorporating the identified controls and supporting CDEs. In the context of this Addendum, references to CPPs may include process parameters designated as ECs in accordance with ICH Q12 [2], where applicable. However, designation of a parameter as an EC addresses regulatory change management and reporting requirements and does not replace or negate its scientific classification as a CPP. EC status defines how changes are managed post-approval; CPP designation defines the parameter’s relationship to product quality and CQAs. These concepts are complementary but not interchangeable.

### **2.3 Science and Risk-Based Approach to C&Q**

A science-based approach to C&Q starts with an understanding of the product, its impact on patient safety, and the definition of what constitutes quality through identification of the product’s CQAs. It also requires an understanding of the process design basis and systems selected to achieve its intended purpose, as well as the relationship between the identified CQAs and the quality-supporting process parameters, the CPPs. This foundation provides the basis, the PPK, for the identification of the manufacturing process systems/equipment controls to ensure safe and efficacious products. These controls are then translated into specific equipment and automation requirements for running the processes.

A risk-based approach to C&Q applies the principles of QRM, as defined in ICH Q9(R1) [3]: identifying, assessing, and evaluating process risks and developing a risk control strategy (as defined in ICH Q8(R2) [4]) that mitigates risks of CPP control loss to an acceptable level. The *C&Q Baseline Guide* [1] describes a risk assessment tool, the SRA (discussed in Section 5 of this Addendum), that can be used to identify and evaluate CPP control failure while concurrently identifying any controls and design elements (CAs/CDEs) already incorporated into the system design. The assessment is done by a knowledgeable team of SMEs who can recommend the addition of additional controls to mitigate any unacceptable risk to CPP control failure. The SRA tool therefore allows the evaluation and control considerations to be conducted simultaneously, and as a sequential activity, by the SMEs. The SRA tool can also be used to identify critical alarms and supporting procedures. As noted, in Section 2.1, the element of control strategy related to CPP control is referred to as the MPCS in this Addendum. The MPCS identifies the controls/CAs that then serve as inputs (i.e., user requirements) to the design and delivery of the systems so that CDEs can be identified and fabricated into the system to achieve the desired level of quality.

The most frequently applied types of controls/CAs for establishing the MPCS related to CPP include:

- Interaction between the equipment (fabrication) elements and the automation software to control CPPs as specified (e.g., setpoint, range, tolerance, exposure, flow, etc.)
- Management of data used to verify CPP control was maintained
- Activation of critical alarms when CPP control is lost

**Note:** The use of warning or alert alarms is recommended so remedial action can be taken before CPP control loss.

- Associated procedural controls (e.g., operation, cleaning, maintenance, calibration)

**Note:** The identified procedural controls are included within the scope of qualification and approved by Quality as part of acceptance and release, but are not included in the scope of C&Q execution (i.e., GEP-based testing and documentation (verification) of systems to establish suitability for the intended purpose).

The controls/CAs identified and documented during the risk assessment and risk mitigation part of the QRM process are added to the defined system boundary user requirements. QbD applied during design development will identify the CDEs to be fabricated/constructed into the system. Refer back to Figure 1 for the relationship between CQA/CPP/CA/CDE and Figure 3 for the basis of the process risk control strategy (MPCS/CAs) and verification strategy (CDEs).

Figure 4 illustrates the C&Q delivery process across the progression of a project execution lifecycle. The four shaded inputs on the left reflect typical project level related user requirements that are likely to lead to additional user requirement input to one or more manufacturing systems. For example, the project level associated risk assessments identify risk controls that need to be added to specified systems. Examples of CQAs associated with elements of the holistic manufacturing control strategy providing the basis for defining the scope of additional supporting risk assessments can be seen in Figure 5. As appropriate, identified CQAs can be associated with specific CPPs or process requirements that will be included in specific system boundaries and linked to controls incorporated in the system and identification of the CDEs associated with the system.

The balance of Figure 4 expands upon the *C&Q Baseline Guide* Figure 1.1 Science and Risk-Based C&Q Process Map [1] and is structured to capture the dynamic nature of the execution process, during which additional PPK is obtained, potentially influencing the initial risk profile of the MPCS. Changes to the MPCS are managed through the Engineering Change Management (ECM) system and supported by the enablers of design review/design qualification and risk review/risk assessment.

Figure 4: C&Q Delivery Process

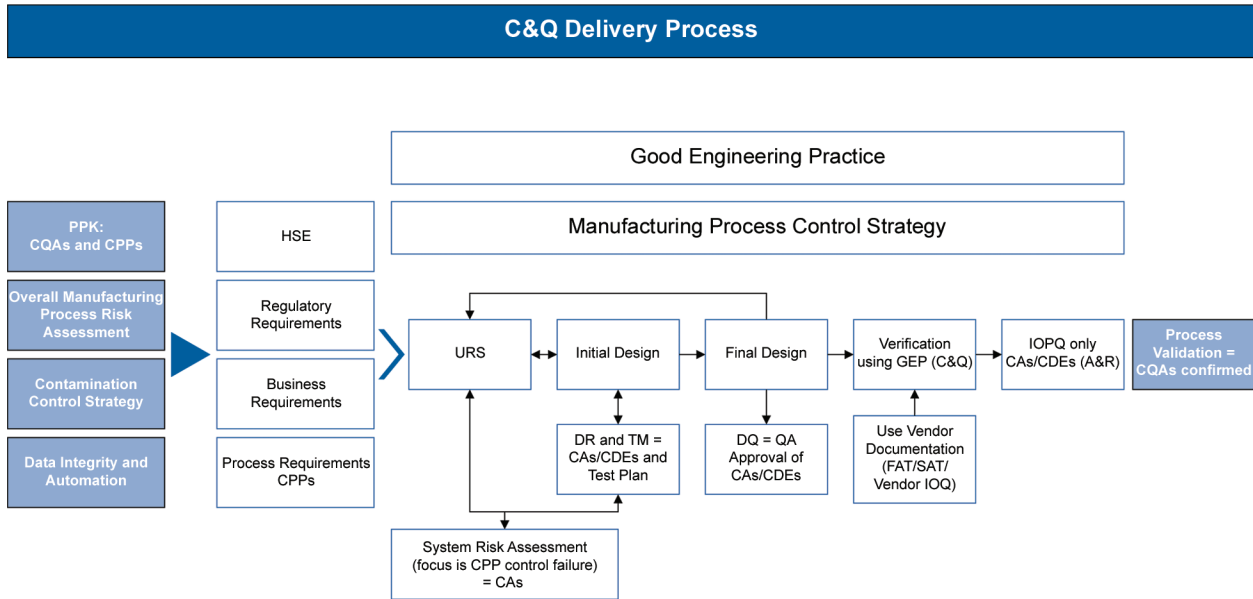


Figure 5: Process Relationship of CAs to CPPs and CQAs

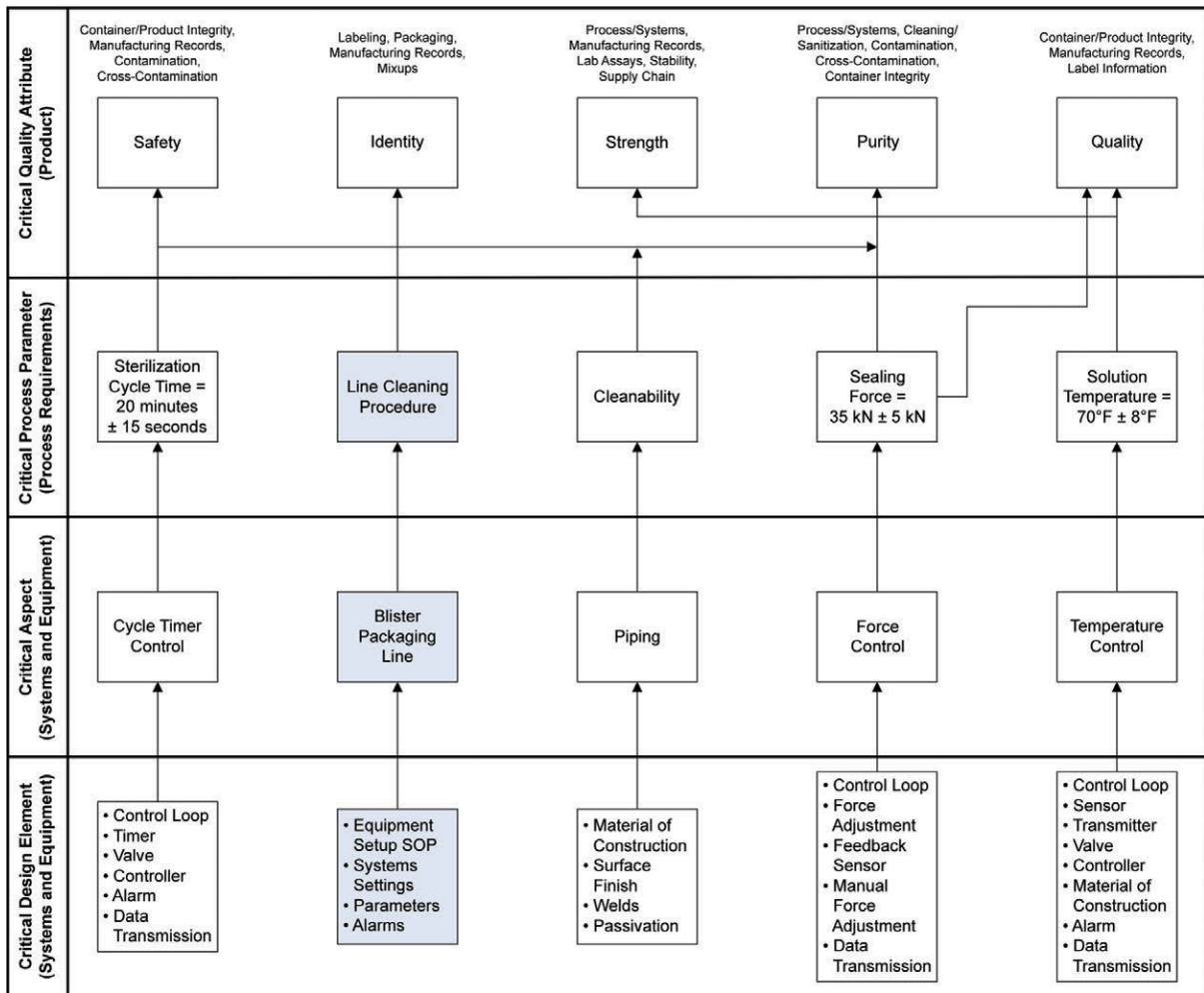
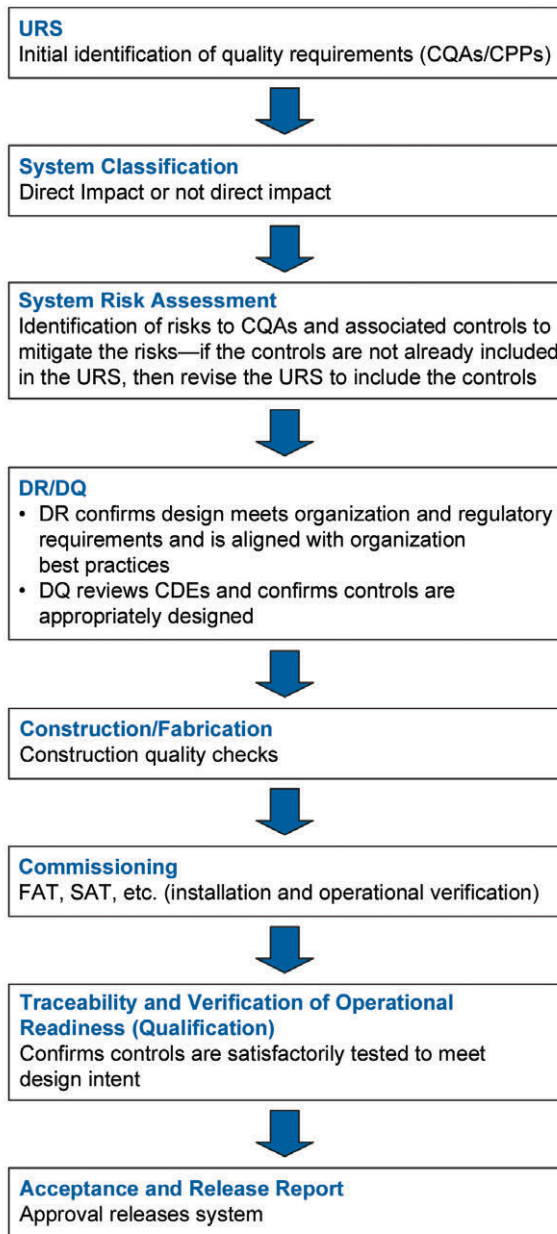


Figure 1.1 and Figure 4.2 (shown in this Addendum as Figure 6) from the C&Q Baseline Guide provide an overview of the QRM-based C&Q process for delivery of quality impacting systems (i.e., direct impact systems suitable for the intended purpose/qualified) and provide detail on the sequential steps and deliverables using pharmaceutical industry best practices and aligned with regulatory expectations (e.g., FDA 2011 Guidance for Industry: Process Validation – General Principles and Practices [6], EU Annex 15 [7], and WHO [8]). Notwithstanding, many in the pharmaceutical industry have had difficulty in identifying and incorporating the necessary elements of a QRM-based C&Q delivery process into their site quality systems. This is crucial for providing the proper quality focus as well as identifying and implementing the necessary site quality system elements to provide a site PQS that supports the use of GEP, as outlined in the *ISPE Good Practice Guide: Good Engineering Practice (Second Edition)* [9], to deliver qualified systems meeting GMP requirements. The C&Q Baseline Guide refers to this process as the Engineering Quality Process (EQP). The EQP can be viewed as a philosophy that fosters modifications of the appropriate site quality systems—such as engineering, Quality Assurance (QA), validation, and manufacturing—to enable the site PQS to accept the application of GEPs during project execution, for the purpose of meeting GMP needs for qualification.

**Figure 6: Sequence of Activities for Direct Impact Systems (Figure 4.2 from the C&Q Baseline Guide [1])**



GEP applied during the project lifecycle execution (e.g., requirements definition, design development, fabrication, installation, commissioning, and turnover) provides the foundation of an integrated C&Q approach. The concept of an EQP is not intended to call out or diminish the value of any existing engineering Standard Operating Procedures (SOPs) or GEPs. Instead, it is meant to enhance and embrace those activities such that they are well-defined, understood, and accepted as part of the project delivery process and the PQS. Refer to the *ISPE Good Practice Guide: Good Engineering Practice (Second Edition)* [9] for additional information and Chapter 11 of the *C&Q Baseline Guide* [1] for a detailed explanation of the EQP.

The following sections of this Addendum provide additional details and current industry best practices for the sequential lifecycle steps in structuring an efficient QRM-based C&Q process, expanding on Figures 4 and 6.

General success factors:

- **Project Team Knowledge of Qualification/Validation Strategy:** Presentation and orientation of the team on critical concepts.
- **URS:** This document is the foundation for implementation of the risk-based approach. The URS should contain the “what” not the “how” and is the description of the process operation strategy/approach.
- **QRM Approach and Risk Assessment Strategy:** Scope definition for system/equipment or process area SRA, and identification of potential linkage to other QRAs (e.g., overall process risk, contamination control, data integrity) that result in identifying additional risk mitigation elements. Typically, the project risk assessments are an input to the site risk register.
- **Understanding that the application of GEP to systems for qualification addresses both quality impacting and non-impacting user requirements and verifies conformance to all supporting engineering specifications.**
- **Post acceptance and release GEP application ensures that systems remain suitable for the intended purpose as applied through supporting quality systems such as maintenance, calibration, and change management using approved procedures.**
- **Robust Project Delivery Process:** Project-specific procedures or standard ways of working within the engineering space are needed (e.g., vendor data requirements, vendor quality assessments, drawing management, change management, and integrated (via interactive planning) C&Q execution plan that drives system boundaries and DQ).

## 3 URS – C&Q *Baseline Guide* Chapter 2

Industry continues to face challenges producing appropriately sized URSs. Key lessons learned for URSs emphasize focusing on what is truly required for the unit operation, while balancing the level of detail according to system novelty and complexity. The approach described in this section refocuses SMEs on what truly impacts product quality and patient safety, positioning the URS as a key project deliverable within a QRM approach. URS documents become overly detailed when GEP-driven engineering standards are not developed. A better approach is to develop GEPs and appropriate engineering standards as part of the EQP.

User requirements are the foundational starting point for any project. When applied to pharmaceutical manufacturing projects, the user requirements are dependent on defining the type of product (e.g., oral solid dosage, biologic, injectable, advanced therapy medicinal product, etc.) and process equipment identified for manufacturing (i.e., defined process flow, unit operations). To initiate the QRM-based C&Q process, representative CQAs for the product type and representative CPPs for the identified systems/equipment can be documented, depending on the status of the R&D process in defining PPK. This consideration is particularly relevant for contract development and manufacturing organizations and can be referred to as a platform approach. Even when a product/process has been identified, there may not be sufficient PPK initially to define the CPP operational/control needs; however, this knowledge can be added during the project execution lifecycle as it becomes available and can be used to establish C&Q acceptance criteria. As a point of clarification, CQAs and CPPs are inputs to the QRM-based C&Q process. They cannot be developed by the project execution team applying QRM as part of the scope of project execution for the identified manufacturing operation. In some cases, due to the specific function and control aspects of a system, a new CPP may be identified and a risk acceptable control strategy will need to be determined.

The acronym URS is recognized as a GEP engineering document associated with defining requirements for the system. Note that the associated GAMP QRM process for automation/software development begins its lifecycle process with a planning phase followed by preparing a user requirement/functional specification. The scope for a URS should not be confused as the means for defining the system boundary for the purpose of classifying systems as direct impact or not-direct impact. Depending on the size, complexity, and vendor supply scope, the system boundary for C&Q may contain elements from multiple URSs. Major projects will have numerous URSs based on system/equipment type, vendor/supplier, or other defined system boundaries.

For the purpose of applying QRM to C&Q, it is necessary to add a classification column in the URS template so that each user requirement can be classified as either product quality-impacting or non-impacting. There are four categories of quality impacting requirements: product CQAs, process CPPs or ECs designated for CPPs, regulatory, and company quality. A single classification of “Quality” in the URS can be used for these four quality impacting requirement types.

The primary focus for QRM-based C&Q is on product CQAs and process CPPs. In support of vendor design development, the key URS focus is identifying the CPPs linked to delivering CQAs. CPP documentation is crucial since CPPs are central to the application of QRM. After the application of QRM and with focus on CPP control failure, all controls associated with risk mitigation are identified. Additional controls/CAs added to reduce high risk to an acceptable level are also identified. All identified controls associated with low, medium, and high-risk control are added to the user requirements/URS. In effect, these controls/CAs are additional URS elements of the control strategy (MPCS).

The other two quality impacting categories are regulatory and company quality. Regulatory refers to requirements defined in regulations such as the CFRs for FDA [10] and EU Directive 2001/83/EC [11]) and is usually associated with patient safety. Company quality approved requirements include, for example, tablet color, viscosity of a gel, etc. Regulatory and company quality requirements may not have an associated CPP, but they will require identification of supporting risk controls (CAs/CDEs) that need to be incorporated into the MPCS.

Non-quality impacting requirements can be listed using two classifications: HSE (Health, Safety, and Environmental) and business or owner. Business or owner requirements usually address desired logistical/operational needs associated with the manufacturing process (e.g., single door versus pass through autoclave, Clean-In-Place (CIP) versus manual tank cleaning, vacuum loading versus hand scooping, system capacity). After the system type or operational approach has been chosen, the approach will be evaluated to that system/equipment product quality impacting elements. For example, for both CIP and manual tank cleaning, appropriate controls need to be identified and incorporated to reduce the risk of contamination.

At a minimum, the Quality Unit, system owner, and SME approve the URSs for direct impact systems. If the Quality Unit has previously approved all the product quality-impacting user requirements in a separate document (such as a project charter or project requirements brief), then Quality approval is not required on individual direct impact system URSs.

Off-the-shelf systems (systems that cannot be physically modified) require documented user requirements, but they do not need a formal URS deliverable if the design and configuration/customization of CPP control and operation are documented elsewhere. A DQ or SRA can be performed to designate the CPPs that need to be controlled for the process and to determine if the equipment as designed or the configurable control strategy is adequate for the process. Vendor specifications can be assessed in the DQ to confirm that risk control strategies are incorporated into the engineering design, or a simple cover sheet to the off-the-shelf system cut sheet can be applied to cover CPP designation and configuration and any data integrity requirements.

In some circumstances, large pharmaceutical manufacturing companies with multiple sites running similar processes have established engineering specifications that define features and elements of how systems should be controlled and built. If approved within the company quality system, these specifications are included in the URS.

It is important to note that for automated systems, the system URS and GAMP UR/Functional Specification (when used) must be aligned to define the CPP operational/functional needs, data management needs, and critical alarm identification. An integrated approach is applied for the final operational/functional verification when the system, including its automation/software, has been completed (including start-up, test, and adjustment) and the final operational configuration/parameters are known.

Key takeaways:

- The URS is a foundational start of the project C&Q lifecycle.
- A robust URS with defined and classified quality/regulatory requirements (e.g., product/process knowledge, CPP, CQA) and general requirements (HSE and business) will set up a good framework for the overall success of project C&Q execution.
- Differentiate quality/regulatory requirements (product quality-impacting) from general requirements (non-impacting) to ensure alignment with QRM principles.
- Design details should be excluded from the URS and instead included in a design specification document.
- CAs (risk controls) identified as an output of the SRA are added to the URS to identify associated CDEs during design development (QbD).
- A Traceability Matrix (TM) can be used as a lifecycle tool to capture the outputs of the four principal QRM C&Q process documents (i.e., URS, system classification, SRA, DQ), showing which CPPs support which CQAs, and which CAs and CDEs support which CPPs and thus the related CQAs. Post URS approval, CQAs and their supporting CPPs are entered into the TM.

## 4 System Classification – C&Q Baseline Guide Chapter 3

The purpose of system classification is to distinguish between systems that have an impact on product quality (direct impact) versus those that do not impact product quality (not-direct impact). Direct impact systems are commissioned and qualified, whereas not-direct impact systems are commissioned only. There are two objectives for system classification:

- To identify the direct impact systems since these will undergo an SRA
- From a project management and project controls perspective, to provide the necessary focus in order to access, define, and utilize vendor testing and documentation during C&Q execution

The first step in the system classification process is to define the system boundaries. Within the scope of the project, all boundary adjacencies are defined. As noted in Section 3 of this Addendum, the URS scope is determined by factors such as system size, complexity, and vendor supply scope. This often results in the defined system boundary, for classification purposes, incorporating user requirements from multiple URSs. System boundary definition provides an opportunity to incorporate quality impacting elements of a support system (CAs/CDEs) into the direct impact system, thereby having the supporting system classified as not-direct impact. A well-known application of this concept is establishing the boundary for a classified room around the room containing the terminal HEPA filters (CDE) so the Air Handling Unit (AHU) can be classified as not-direct impact.

After the system boundary has been defined, a set of questions is answered to identify—within the system boundary—if the system includes CAs/CDEs that are traceable to product quality impacting requirements. These mostly include the CPPs, regulatory, and/or company quality approved requirements. SMEs familiar with the product and process are selected to execute the system classification process.

The Quality Unit approves the system classification assessment, classifying each boundary-defined system within the project scope as direct impact or not-direct impact. This system classification list is often included in a project-related master plan.

Key takeaways:

- Using one system classification form for all systems creates efficiency and standardization, enabling ease of stakeholder assessment.
- Well-defined user requirements, aligned with QRM principles (CPP, CQA, CA, CDE and other quality and regulatory impacting requirements), form the basis for the system classification process.
- CPPs can be identified in FDA R&D Stage 1 via PPK or a PRA. Lacking PPK knowledge, CPPs can be assumed generically using a platform approach or within systems/equipment chosen by a Contract Development and Manufacturing Organization (CDMO) to conduct a manufacturing process.
- The outcome of successful system classification determines which systems have direct impact and require a risk assessment for identifying risks and control strategies. It also outlines the scope of systems that only require commissioning, i.e., the not-direct impact systems.
- For direct impact systems with an associated PCS, a list of such systems along with the supporting boundary definition documentation should be supplied to the Computerized System Validation (CSV) team to be used as an input to their CSV GxP classification process. Refer to *ISPE GAMP® Good Practice Guide: GxP Process Control Systems (Third Edition)* [12].

## 5 System Risk Assessment – C&Q *Baseline Guide* Chapter 4

The SRA applies QRM principles to prospectively identify and evaluate the risks of failures during system operation, such as CPP control failures, which may put product quality (CQA) at risk. Another example is a failure in product lot code printing that may put patient safety at risk. As noted in Section 3 of this Addendum, when unacceptable risk is identified, controls/CAs are added to the system user requirements/URS to define the system operational/control strategy requirements to ensure product quality and patient safety. Also discussed in Section 2 of this Addendum, the controls/CAs collectively define the MPCS that leads to the CDEs identified via QbD during design development. The identified controls will require an update to the URS if an initial URS was given to the vendor, designating the CPPs and other non-quality impacting process parameters, to begin design development. The CDEs, documented at the completion of design development, provide the quality focus for integrated C&Q testing and documentation (verification) leading to qualification and suitability for the intended purpose. As noted in Section 2.3 of this Addendum, the SRA tool has been designed to simultaneously address risk identification, evaluation, and control and is conducted by the appropriate SMEs using defined PPK as the basis for evaluation.

The SMEs conducting the SRA need to be aware that many systems used for pharmaceutical manufacturing and packaging are standard systems that have been in use for a reasonable period of time, have built-in control strategies, and are developed by experienced vendors with established engineering quality systems. The SRA will also document and include existing CAs/CDEs identified to support acceptable risk control. The SRA output will also be entered into the TM if used.

When defining the scope of the risk assessment, it is important to exclude elements that are the focus of other supporting quality system development risk assessments, such as maintenance and calibration program requirements. Failures related to system breakdown, major component failures, calibration out-of-tolerance, thermocouple failures, and similar issues should be excluded from the scope of CPP control failure. These types of failures are normally addressed through the robust application of GEP during design development and the application of QbD in achieving the design intent and acceptable risk profile of the documented user requirements.

Another aspect that is out of scope for individual systems is the contamination control risk for the overall manufacturing area where the system is located. The contamination control strategy (see EU Annex 1 [14]) should define the associated controls, supported by a separate risk assessment focused on contamination control for the specified process stage/step or area. It is important to note that certain results or outputs of the contamination control risk assessment may identify additional controls that are recommended to be included in a system URS to support the overall contamination control strategy.

SRA scope determination is scalable. The boundary for the SRA effort can be a single complex type of equipment, a system with multiple pieces of equipment, or a designated manufacturing area such as fermentation, purification, primary or secondary packaging.

The SRA is conducted for direct impact systems and can be performed as soon as the system boundaries have been identified and the CPPs or other quality impacting requirements contained therein are documented. For off-the-shelf equipment, the SRA objective can usually be achieved by performing a DR/DQ to identify/document which process parameters are CPPs and evaluate the operational control ranges and configuration for the intended process. Examples of SRAs are available in Appendix 19 of the *C&Q Baseline Guide* [1] and additional examples for download can be found on the ISPE website [13].

It should be noted that if a PRA was completed earlier or as an element of R&D, the PRA can be modified and updated to evaluate the selected process equipment for scale-up and tech transfer. This updated PRA can then be associated with identified system CPPs for failure identification and evaluation. If a PRA has not been completed, a PRA can be done that includes system evaluations.

When properly completed, the SRA document and template will identify and document any:

- Existing CAs/CDEs already incorporated by the vendor into the system standard design
- Additional controls/CAs needed to mitigate unacceptable risk
- Procedural controls required for risk reduction
- Critical instrument/alarm relationships to CPPs

Completed SRAs are approved by the Quality Unit, system owner, and SME at a minimum.

Key takeaways:

- Lesson learned:
  - Industry is implementing the concept of risk assessment and risk-based approaches to C&Q without a true focus on CPP control failure. As noted in EU Annex 15, paragraph 5.7: *“The basis by which process parameters and quality attributes were identified as being critical or non-critical should be clearly documented, taking into account the results of any risk assessment activities.”* [7] The previous method of component criticality assessment lacks the ability to link risk mitigations (CDEs) to the ability to control CPPs; therefore, there is no clear link between risk mitigations and product quality (CQAs). SMEs should challenge their existing methods by asking: Do we truly assess and mitigate risks associated with identified product CQAs and process CPPs (PPK), or are we relying on categorization and previous experience to designate components and functions as potentially quality impacting?
  - The SRA is a qualitative risk assessment focused on system operational control, aligned with C&Q, and does not result in a Risk Priority Number (RPN). Instead, the SRA uses SME judgement to assign the risk level (High/Medium/Low). This approach is used because there is typically inadequate data to support a quantitative assessment (e.g., probability of occurrence). Quality teams may review the SRA process and other deliverables within the *C&Q Baseline Guide* and express concerns that it is not quantitative or does not address all risks. This is true, and it highlights the importance of an early effort that is associated with an overall manufacturing PRA, where the focus is on the manufacturing process and the type of equipment/systems selected for commercialization and not on the actual equipment eventually selected for commercial manufacturing. An overall PRA does result in a quantitative analysis and associated RPN. It is at this early stage that key decisions, CQA and CPP determination, and risk mitigations are evaluated. An overall PRA precedes the scope of the *C&Q Baseline Guide* which is focused on CPP control failure based on the manufacturing process identified by its unit operations and its equipment train, supporting systems, and utilities.
  - CPPs may be prioritized based on severity of impact to CQAs, complexity of control, detectability, and available PPK. Prioritization supports effective allocation of control and verification efforts; however, prioritization does not equate to removal or declassification of CPPs to “non-critical” parameters. All identified CPPs retain their linkage to CQAs and should be governed accordingly throughout the lifecycle.
  - A determination that a manufacturing process has no CPPs would imply that no process parameters have the potential to impact CQAs, which is inconsistent with the fundamental assumptions of GMP, PV, and QRM. QRM-based C&Q is intended to manage and reduce risk associated with CPPs, not to eliminate the existence of CPPs.

- FMEA, frequently applied during maintenance quality system development, is not the recommended approach to replace the SRA as it is overly focused on system failure and not focused on CPP control failure. Instead, process knowledge can be used as a basis for brainstorming to determine hazards and hazard pathways. The SRA tool can then be applied to evaluate the harms, hazards, and mitigations associated with the failure of CPP control.
- The SRA can be initiated as soon as PPK is identified (CQAs and CPPs) and when system classification and system boundaries are available. The URS and SRA inform each other, and it is an iterative process for both deliverables. In support of process design and full determination of unit operations, systems, and automation, an overall manufacturing PRA is performed using a Preliminary Hazards Analysis (PHA) and focused on hazards and hazard pathways that could impact product quality and patient safety.
- In alignment with QRM principles, the outcome of a successful SRA determines risk control measures and defines the system risk profile where both controls supporting an acceptable risk level and added controls mitigating unacceptable levels of risks (to product quality and patient safety) are identified. The identified risk control measures (CA/CDE) are incorporated into the final engineering design (QbD), and this sets the framework for DQ deliverables and verification.
- For direct impact systems with an associated PCS, the controls/CAs and any identified CDEs should be provided to the CSV team as user requirement inputs to their GAMP risk assessment process.
- Risks that have a low residual risk determination still require verification activities to confirm that the associated risk mitigation CAs/CDEs are in place.

## 6 Design Review and Design Qualification – *C&Q Baseline Guide Chapter 5*

Design Review (DR) is a GEP conducted iteratively during design development of complex systems to verify traceability of the design elements/features back to the user requirements. For less complex systems, a single DR can be performed at the completion of design. For pharmaceutical manufacturing systems, the DR is inclusive of the product quality impacting and non-impacting user requirements as well as the controls/CAs identified during the SRA for the direct impact systems. During design development, the engineering design elements (components, instruments, materials of construction, etc.) are identified and an engineering specification is developed. If the design element specification is traceable to a control/CA, it is “tagged” (or identified) as a CDE and will provide the focus for qualification. At the completion of design development, a DR summary is generated and approved by the system owner and the appropriate SMEs.

Design Qualification (DQ) is a document that is generated using the final DR summary. It provides verification that the design of the risk controls is robust prior to fabrication. The scope of DQ consists of the CDEs and their associated acceptance criteria (generally the engineering specification), CAs, and quality impacting requirements. The DQ is approved by the Quality Unit and is the last component of the C&Q Plan. From a project execution perspective, system procurement/fabrication is normally initiated post-DQ approval.

At the end of design development and inclusive in the DQ scope, PPK should have been sufficiently developed to document the operational, control, and tolerance ranges related to the CPPs. These will be documented in the DQ and approved by the Quality Unit, unless previously approved by the Quality Unit in the SRA, as elements of the verification acceptance criteria. If data is not available to document product-specific CPP operation and control ranges, it is recommended to obtain vendor documentation stating the maximum control range for the system’s capabilities for the process parameters that have been identified and documented by the manufacturer. This range can be established as the PAR (Proven Acceptable Range, for anticipated CPP control) and used in the scope of initial qualification. Post qualification, if additional PPK results in CPP control ranges that exceed the previously documented PAR, then modification of the system may be required under change control.

Note that for off-the-shelf equipment, a DQ can be performed in lieu of the SRA (and URS) to identify and document equipment containing process parameters as CPPs and to verify their operating range and control as appropriate.

Key takeaways:

- The scope and objective of DR is to confirm both direct impact and not-direct impact systems have been reviewed by appropriate SMEs to ensure that systems have been designed to meet all user requirements.
- The scope and objective of DQ is to confirm risk control measures for supporting both acceptable risk and unacceptable levels of risk to product quality and patient safety are incorporated into the final engineering design and to determine the associated acceptance criteria. DQ is performed only for direct impact systems.
- The timing of DQ includes the expectation that the engineering design specification associated with the engineering design element (e.g., component/instrument/material type) used for fabrication or construction has been selected. The engineering specification and design element descriptive data provide an input to the basis for the acceptance criteria verified during C&Q.
- DR and DQ are not separate work efforts. DQ is extractable from a completed DR summary and approved by the Quality Unit.

- DQ represents the culmination of the URS, SRA, and DR. The Quality Unit reviews the proposed design and risk mitigations and verifies that the system design is suitable for the intended purpose and that the C&Q Plan is established and agreed upon.
- For direct impact systems with an associated PCS, a listing of the CDEs that interconnect/support PCS functions as well as their associated specification/acceptance criteria should be given to the CSV team as inputs to their DR process.

## 7 Construction/Fabrication

Using GEP, the project team performs appropriate quality checks during the construction/fabrication process to verify that the system/facility is being built per the approved specifications and issued for construction drawings.

Any changes that occur during this project phase are formally managed under change management. Changes need to be assessed for potential impact on product quality or to the initially established risk profile documented during the SRA for direct impact systems. Changes assessed to have the potential to change a CDE, modify a control/CA, or impact CPP operation are subject to Quality Unit review and approval. Such changes may require an update to the URS and/or SRA.

The design authority needs to assess the proposed changes to ensure that they agree with the design intent. The proposed change also needs to be evaluated for its impact on compliance with relevant regulations. Complex novel systems require additional vendor oversight prior to Factory Acceptance Testing (FAT).

Key takeaways:

- GEP should be the basis for how SMEs review and confirm engineering designs are incorporated during fabrication and construction. The successful implementation of GEP and the EQP are crucial for the effective delivery of systems suitable for the intended purpose.
- During the construction phase, equipment, instruments, and materials must comply with the approved engineering specification which becomes the basis for C&Q, and in support of maintenance and calibration with associated identification documentation included in the as-built final document set.
- Changes that are also within the scope of an associated system PCS must be coordinated with the CSV team.
- The design authority should provide periodic oversight of on-site construction activities.

## 8 Integrated C&Q – *C&Q Baseline Guide* Chapter 7

Commissioning is a GEP and defined as a planned, managed and documented approach to the setting to work, start-up, regulation and adjustment, and installation/operation/performance verification necessary to bring equipment, automation, and systems to a fully operational state meeting safety and end-user requirements. As applied in the pharmaceutical industry for QRM C&Q, commissioning incorporates qualification testing, and the supporting documentation, to confirm that the systems/equipment have been installed and are operating correctly in accordance with specifications. Note that EU Annex 15 [7] positions FAT and Site Acceptance Testing (SAT) within qualification. Commissioning is a process with multiple deliverables covering all project phases that is executed within the overall qualification effort for direct impact systems. Commissioning incorporates, but is not limited to, those CDEs, CAs, and quality user requirements associated with product quality and patient safety as well as general engineering, HSE, business requirements and supporting engineering specifications. A systematic approach is defined to commission the manufacturing systems, whether acting singly or in combination.

In support of qualification, commissioning is conducted over the project lifecycle using GEP documents. The document format and title may vary depending on the system type. For example, it may comprise an HVAC testing and balancing report, FAT at the vendor, SAT on-site after installation including any purchased vendor test packages, or Installation and Operational Verification (IOV) for on-site construction. Note that the *C&Q Baseline Guide* [1] uses IOV to describe the integrated C&Q testing for systems constructed/fabricated on-site. The scope of the IOV testing is the same as that done at the vendor site for FAT and when the vendor representative supports the on-site SAT testing post system installation. For direct impact systems, the scope (system or area), approach (list of tests and when performed), focus for testing (CDEs), and acceptance criteria (engineering specification and identification data) are defined in a C&Q Plan. This plan is drafted by SME(s) and approved by the Quality Unit. Refer to Chapter 6 in the *C&Q Baseline Guide* for information on the C&Q Plan approach and content. Because the content of this plan incorporates all quality impacting deliverable documents (URS, system classification, SRA, and DQ with associated acceptance criteria), prepared by an SME and previously approved by the Quality Unit, it is not necessary for Quality to approve the GEP testing documents. For plans that include PCSs within their scope as an integrated lifecycle testing strategy, input from the CSV team validation plan should be included.

Since the majority of the testing, including that intended to support qualification, is done during FAT and SAT, utilization of vendor performed testing and documentation allows for efficient integrated C&Q execution and focus on right-first-time testing. A prospective risk-based approach (such as a vendor audit) should be applied to assess the vendor's capability for conducting and documenting the testing. If gaps or issues are detected in the vendor capability and/or quality system, control measures need to be put in place to mitigate the risk of using the supplied vendor data in support of right-first-time testing. Refer to Chapter 10 of the *C&Q Baseline Guide* for more information on vendor audits.

Often, there is misunderstanding in the interpretation of the risk-based approach related to the amount of CA/CDE testing required. All documented controls and their associated CDEs are tested regardless of the risk level. For example, if three controls are added for CPP control of a high risk versus one control for a low risk, then there will be more documentation and testing associated with testing the three controls versus the one control. Another concern is the level of Good Documentation Practice (GDP) applied to the GEP commissioning documents. The acceptable standard for GDP from a regulatory perspective is ALCOA (Attributable, Legible, Contemporaneous, Original, Accurate). It should be noted that elements related to GAMP qualification documentation, such as audit trails and data integrity, will apply ALCOA+ (Attributable, Legible, Contemporaneous, Original, Accurate, Complete, Consistent, Enduring, Available). Additional information on GDP for GEP is in Chapter 13 of the *C&Q Baseline Guide*.

There is also misunderstanding in defining the type of enhanced testing for a design element designated a CDE through QRM from a commissioning perspective versus what is needed for qualification. Consider a simple example system with ten instruments in which four of have been tagged as CDEs and are the focus for qualification. The GEP commissioning process applied to all ten instruments is to verify and document the correct instrument, proper installation, and initial calibration. For the four instruments used in conjunction with CPP control, an extra verification should be done to confirm they are in the calibration quality system, have a current calibration, and include a loop calibration if the instrument is managed by the PCS. Following this installation verification, any GEP based start-up and adjustment associated with CPP operation would be addressed to establish the system user requirement-based configuration. Subsequent testing in support of qualification would be to verify that the CPP is controlled as specified (e.g., setpoint, range, duration, ramp rate as applicable). If the instrument data is used to support risk control mitigations supporting data management and critical alarms, these would also be verified.

It should be emphasized that during the latter stages of the commissioning process, sufficient resources need to be allocated for startup/testing/adjustment and engineering runs as appropriate. Activities may include initial system activation, water runs, and waste product runs. The engineering runs allow for establishment of the system final operational configuration and include verification of operational ranges and durations associated with worst case conditions anticipated during manufacturing operations. The final configuration can be documented and approved by the Quality Unit in a formal OQ, SOP, or other quality approved document. This documented configuration is verified in PQ/PPQ.

A standardized process must be in place to address test results that do not meet acceptance criteria. System modifications are managed through the ECM process. The majority of such changes typically do not have an impact on product quality and are managed through ECM. Changes that have the potential to impact product quality (e.g., change to an approved CDE, CA, or CPP acceptance criteria) must be elevated to Quality. Both quality impacting and non-impacting changes should first be reviewed by an appropriate SME who can assess if they can be accepted as-is (i.e., having no negative effect on the normal operation of the system and meeting the design intent).

#### Key takeaways:

- For direct impact systems, the scope of the integrated C&Q process includes all product quality impacting and non-impacting user requirements. For a system to be accepted as suitable for the intended purpose, all engineering specifications must be verified and a summary report approved.
- The approved DQ documenting GEP-based system specifications sets the focus for the C&Q testing plan. A robust testing plan (including CDE engineering specification acceptance criteria from DQ, CDE identification criteria obtained during fabrication, and determination of which stage to be tested) and alignment of the plan with the project and vendor team will ensure successful execution of testing. Lack of team alignment can lead to confusion and delays during the testing phase.
- Post-DQ approval, ECM should be applied to ensure appropriate management of changes during the project lifecycle. Robust ECM will help manage both product quality impacting and non-impacting changes in a more agile and flexible way during the project lifecycle. The absence of ECM and Quality Change Control (QCC) or lack of any change management during C&Q testing will lead to potential complications and delays during the project lifecycle.
- Where vendor execution and documentation are integrated to support qualification efforts, a vendor assessment program is a key element. By approving the vendor quality program, the project team, including Quality, is authorizing the vendor to execute C&Q deliverables. In the absence of a vendor quality assessment, the project team may experience challenges including needing to repeat testing post-acceptable vendor execution.

## 9 Traceability and Verification of Operational Readiness (Qualification)

At completion of the integrated C&Q testing using GEP documents (FAT/SAT/IOV) with scope including both specifications associated with non-quality impacting design elements and those associated with CDEs supporting CAs for qualification, the data is reviewed by an SME who has not performed the testing. A summary report is then issued confirming that all user requirements and associated engineering specifications have been verified, and the system is suitable for the intended purpose. The SME review verifies that the system(s) performs as intended throughout the anticipated operating ranges, including worst case conditions and control durations. Post C&Q systems are then further verified using integrated line testing and performance testing via PPQ/PV to confirm effective and reproducible operations such that CPPs are controlled and CQAs are achieved.

There are two ways to approach documentation of traceability. The first approach involves referencing the GEP testing data back to the approved URS (quality impacting user requirements for direct impact systems), the SRA that identified and documented the controls/CAs, and the DQ which listed the CDEs and acceptance criteria. The review process includes confirmation that the C&Q Plan (which was approved by the Quality Unit) was completed, all acceptance criteria were met, and any test failures were investigated, corrected, and retested. The second approach is to use a TM to demonstrate the relationships/linkages of CQA/PPP/CA/CDE as a prospective tool throughout the project execution lifecycle. A TM applied in this manner will initially enter the user requirements from the URS(s), then the controls/CAs are added after the SRA. The TM is then used to verify traceability of the CDEs during the design lifecycle. At the completion of design, the CDEs and associated acceptance criteria are added to the TM (i.e., references to the design documents and traceability back to user requirements). At this point, a DQ summary report is done and approved by the Quality Unit. A TM is also used to designate where the lifecycle testing will occur and designate as appropriate FAT, SAT, IOV, IQ, OQ, PQ (e.g., for critical utilities) and applicable test scripts. A TM is an engineering tool used during project execution. It is periodically updated and is not a Quality-approved document.

The QRM C&Q system TM should not be combined with the TM used for GAMP automation lifecycle development since the execution lifecycle deliverables are different. However, it is important to note that if a process control element is directly associated within a boundary defined system, then the system URS requirements related to CPP control (e.g., CPP control/tolerance, data management, critical alarms, any other identified automation controls/CAs) and the GAMP user requirement/functional specification need to be aligned. An integrated approach should be applied for final C&Q testing of the fully functional and adjusted system.

Key takeaways:

- Note that the process described in this section does not require the use of a supplemental Installation and Operational Qualification (IOQ) protocol where additional or repeated field verification is performed for the sake of qualification. This is a paradigm shift in which traditional IOQ protocols containing detailed test script steps are no longer executed. Instead, FAT/SAT/IOV protocols are executed for field integrated C&Q testing under the commissioning process, and they are verified for adequately meeting acceptance criteria for CAs and CDEs within the scope of qualification.
- The scope of the GEP-based commissioning process, documented in the FAT/SAT/IOVs covers both the quality impacting and non-impacting user requirements and engineering-based specifications supporting the non-quality impacting engineering design elements and the quality impacting engineering design elements (CAs/CDEs). Successful completion of all the testing verifies the system is fit for the intended purpose/qualified.

- Based on site maturity, some teams may elect to conduct repeat testing of FAT/SAT/IOV field testing for CAs and CDEs only under a traditional IOQ protocol with QA pre- and post-approval in support of qualification. This is not required or desired by the approach described in the *C&Q Baseline Guide*. Optional approaches may include one of the following:
  - IOV (or FAT/SAT) and IOQ (limited testing focusing on CDEs and any needed post-engineering run configuration verification runs)
  - IOQ report summarizing integrated effort using lifecycle GEP documents (commissioning/FAT/SAT/IOV)
  - Commissioning/IOV summary report with no IOQ deliverable

# 10 Acceptance and Release Report – C&Q

## *Baseline Guide Chapter 8*

Acceptance and release is QA approval that the direct impact system/equipment is suitable for the intended purpose and qualified. Acceptance and release represents the initiation of the “qualified state” and the beginning of QA-managed QCC, continuous performance monitoring, and periodic review. System ownership transitions from the project team to operations/engineering and/or the system owner. It is noted that from a GEP perspective, the design authority has a legal obligation to ensure the system meets codes. That approval is inclusive of all user requirements and is essential prior to turnover to the system owner. The conclusion of acceptance and release is that the system can be released for manufacturing operations—the next stage of qualification (e.g., PQ for a Water for Injection system) or for use in the manufacture of PPQ or commercial batches.

The acceptance and release process is completed through a summary report. The contents and complexity of the report may vary, but it needs to include SME review and approval of the following items:

- Closure of testing documentation (review complete)
- Discrepancies (addressed and satisfied)
- Engineering changes (addressed and closed)
- Implementation of quality system elements to maintain the qualified/validated state, e.g.:
  - Availability of SOPs for operation of the system
  - Calibration/maintenance system and associated procedures
  - Mechanism for tracking system use and maintenance (e.g., logbook)
  - Vendor documentation (e.g., maintenance requirements, spare parts)
  - Drawings
  - Operator training within the training quality system
  - Completion of any other organization requirements to add the system to the operating facility
- Documented formal release of the system

The concept of scalability also applies to acceptance and release. The scope can be a single piece of equipment, a system with multiple pieces of equipment, and a designated area, consistent with the Quality-approved C&Q Plan.

Some companies prefer to use the title of IOQ Summary Report instead of Acceptance and Release Summary Report. Either way, the report contents are the same. Additional elements for acceptance and release may be incorporated into the Change Control system within the organization's PQS related to use and meeting GMP.

Key takeaways:

- The acceptance and release strategy is defined in the C&Q Plan.
  - For systems with an associated PCS, deliverable documents associated with acceptance of the PCS should be identified in the C&Q Plan.
- Systems that are not-direct impact are approved by the SME and system owner.
- Acceptance and release of direct impact systems with non-quality impacting non-conformances can be approved by the Quality Unit if a remediation plan and due date are in place.

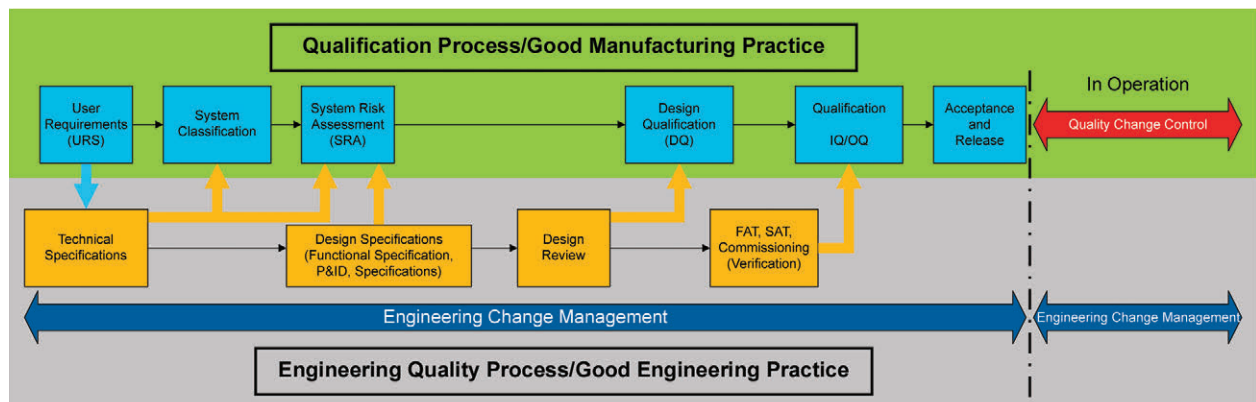
# 11 Good Engineering Practice and the Engineering Quality Process – C&Q *Baseline Guide Chapter 11*

GEPs are an enabler for the QRM-based integrated C&Q process. Engineering is responsible for delivery of the C&Q process, with appropriate Quality oversight. An interface must exist between GEPs established, managed, and performed by engineering and the overall PQS established, managed, and overseen by Quality. The EQP is that interface.

The purpose of establishing an EQP is not to introduce Quality oversight and control of engineering activities performed under established GEPs, but rather to provide a mechanism for appropriate Quality oversight of engineering management and control of GEP processes. This approach allows engineering to apply GEP processes in the delivery of critical systems through the C&Q process, while meeting GMP Qualification.

The EQP can be viewed as the integration of the overall PQS and established GEPs and the linkage between Quality oversight and engineering activities, particularly as applied to the delivery of QRM-based integrated C&Q. In addition, the EQP provides a similar interface to HSE or other site quality systems. The EQP provides the linkage between the Quality Unit and the PQS (engineering and GEP processes, procedures, and practices) as well as establishes the bonds between Quality/PQS and Engineering/GEP based on application of QRM to incorporate QbD enhancements to engineering design and delivery of systems through the integrated C&Q process. The EQP bridges established GEPs to the Facilities and Equipment Quality System as part of the FDA six-system PQS model [15]. The relationship between the qualification process and a GEP-aligned EQP is shown in Figure 7. Additional information on GEP and the EQP can be found in the *ISPE Good Practice Guide: Good Engineering Practice (Second Edition)* [9].

**Figure 7: Linkages Among Quality, PQS, EQP, GEP, and GMP**



Key takeaways:

- GEP and EQP are essential for successful implementation of the QRM-based integrated C&Q approach.
- In the absence of GEP and EQP, an organization is likely to experience various challenges including lack of clarity on Quality versus engineering responsibilities and accountability and resistance from Quality in the acceptance of engineering oversight on C&Q deliverables, acceptance of vendor execution and documentation for qualification deliverables, etc.
- A TM can be used prospectively to manage and make reference to the GEP data and deliverables to support the QRM-based C&Q process for qualification.

# 12 Overview of Process Control Systems Supporting Manufacturing Operations

## 12.1 Features Specific to Process Control Systems

PCSs provide the interface to a physical process being controlled in real time. PCS focus is on the production of quality product, and the PCS is part of the control, measurement, and associated data collection supporting good product quality. This leads to the following considerations:

- The interface to PPK (e.g., CQAs and CPPs for pharmaceutical products or key process inputs for manufacture of medical devices)
- The interface, via sensors and actuators, to the systems being used within the business process

Other aspects that may influence lifecycle activities for a PCS include:

- The extent of embedding of the PCS with the process equipment
  - An example of an embedded system is an autoclave where the equipment and PCS are sold together as a package
- The multiple components and the suppliers providing interfaces between system components, between systems (including those in the manufacturing execution layer and those that support data analytics), and between the different parties involved
- The interfaces introduced by phasing of delivery
- The generation and manipulation of critical data
- The possibility that the system is delivered using a modular plant approach

## 12.2 Leveraging Prior Knowledge

The PCS lifecycle applies preexisting PPK as a starting point for risk management and the subsequent scaling of activities. For a pharmaceutical product, the development process described in ICH Q8(R2) [4] determines the CQAs, CPPs, and the proposed control strategy. For medical device manufacturing, key process inputs are identified as necessary to ensure their required characteristics and performance. The development of the systems required to implement the proposed control strategy (MPCS) leads to identification of CAs of those systems and, in turn, the component/instrument related CDEs and includes the required process controls, alarms, and data captures. It may also identify ECs, e.g., the operating configuration for a CPP which is part of the regulatory submission and therefore will be controlled/monitored as part of the requirements.

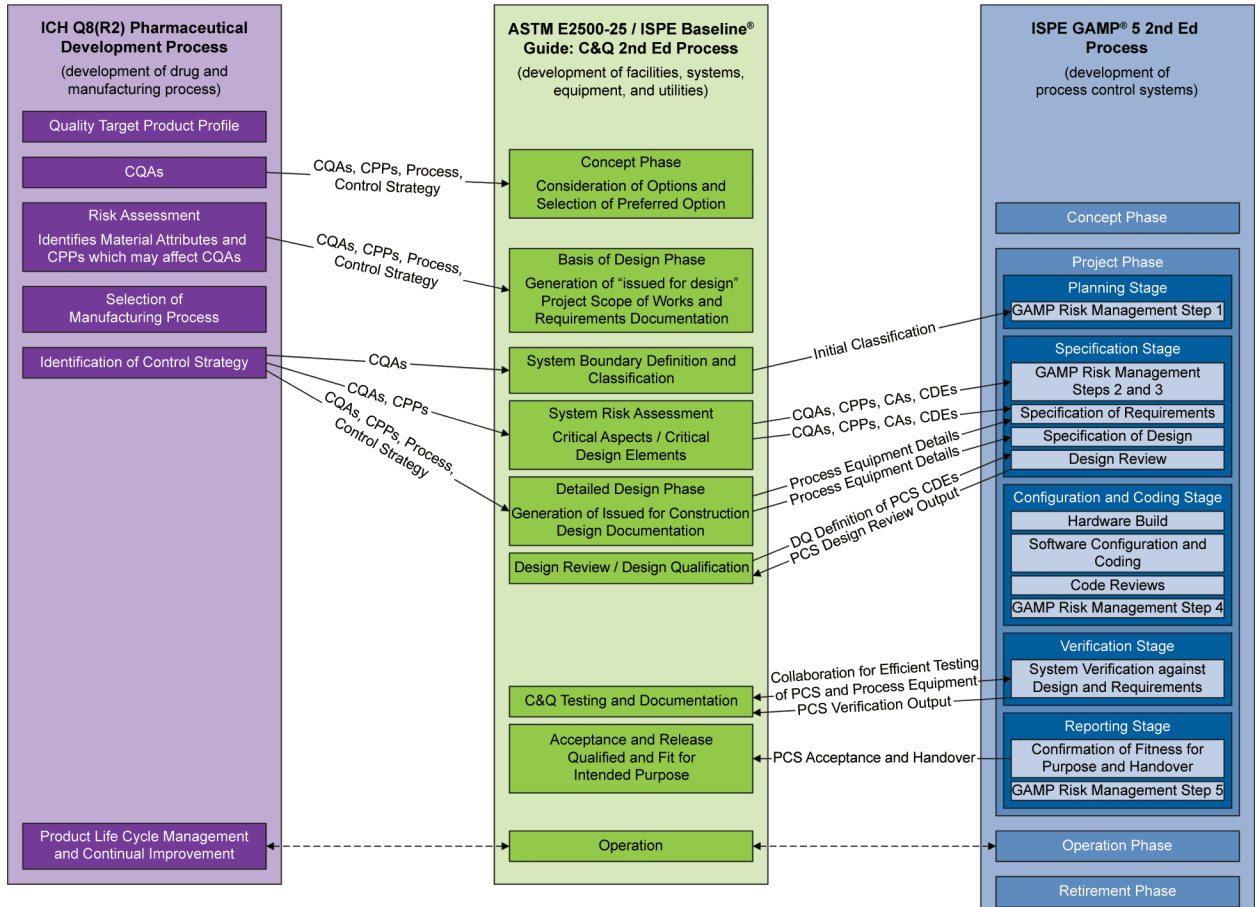
Both PPK and the outputs from the development of the systems can be leveraged to ensure science-based QRM for a PCS. As stated earlier, three types of control/CAs have been identified during these process-focused risk assessments which impact the PCS:

- Those that regulate CPPs to ensure that CQAs of the product are met
- Those that gather data demonstrating that the CPP has remained in a state of control
- Those that draw attention to any loss of control

**Note:** There may also be SOPs relating to the operation of the process, equipment, and control system that form part of risk mitigations and need to be verified alongside the other controls.

Figure 8 provides an example of how prior knowledge may be leveraged during the lifecycle, with each black arrow representing either prior knowledge that may be leveraged for the PCS lifecycle or PCS knowledge that may need to be leveraged by others.

**Figure 8: Example Showing Leveraging of Product, Process, and Process Equipment Knowledge (Figure 3.1 from ISPE GAMP® Good Practice Guide: GxP Process Control Systems (Third Edition) [12])**



Key takeaways:

- Follow a proactive approach to aligning the QRM C&Q and GAMP PCS lifecycle activities:
  - Designate project execution team member(s) with CSV expertise during initial project planning.
  - Consider whether the C&Q SRA and GAMP risk management processes can be usefully combined. Refer to *ISPE GAMP® Good Practice Guide: GxP Process Control Systems (Third Edition)* Appendix E3 [12] for an example of combining risk assessment processes where the PCS is embedded with the process equipment.
  - Be aware that a PCS is likely to have interfaces through which data flows to other systems, for use in GxP critical business processes including product release and product recall. Risks to data integrity need to be considered in addition to risks to patient safety and product quality.
  - Be aware that where modular or plug-and-play / process equipment is selected, there will also be interface requirements relating to modular PCS that need to be considered as part of risk management.

- The SRA focus on a unit operation does not include automation level CDEs. That is covered within the GAMP Risk Management Steps 2 and 3. However, if there is an embedded PCS (e.g., a system with an embedded PCS that was procured with a combined URS with PCS and equipment user requirements) or PLC/VSC (Vendor Supplied Controller) within the unit operation, consider including the scope of access, security, and backup in the SRA for direct impact systems.
- Refer to *ISPE GAMP® Good Practice Guide: GxP Process Control Systems (Third Edition)* [12] for additional information.

# 13 Creating Change and Overcoming Objections

Realization of the full benefits of the *C&Q Baseline Guide* [1] approach requires commitment to organizational change inclusive of focus and realignment. It must also be inclusive of leadership buy-in and sponsorship along with enhanced communication and collaboration. There may be stakeholders and SMEs that are resistant to change and project standards that are not yet updated to align with the approach where GMP Qualification is achieved through the robust application of GEP and its associated commissioning process. There can also be a tendency for some to see this as a push to force engineering to do more and to relabel engineering and commissioning activities as qualification (e.g., leveraging FAT testing into IOQ protocols), as opposed to a GEP-based process that holistically incorporates GMP Qualification into an integrated C&Q process that incorporates right-first-time lifecycle testing beginning at FAT. This thought process is based on a fundamental misunderstanding of the approaches explained within this Addendum. Reference Chapter 14 of the *C&Q Baseline Guide*, Strategies for Implementation of Science and Risk-Based C&Q Process, for additional details.

The key area of understanding is that the application of GEP to qualification addresses both product quality impacting user requirements that support qualification and non-impacting user requirements and verifies conformance to all supporting engineering specifications in support of the manufacturing process systems and equipment being accepted as fit-for-purpose/qualified. The Quality Unit is involved in the approval of quality deliverables as well as the review and audit of the integrated C&Q process, to ensure the proper execution of GEP within the framework of the EQP to meet GMP.

Successful QRM-based integrated C&Q programs include the following:

- Leadership buy-in and support.
- Communication and training of the benefits and drivers behind a risk and science-based (QRM integrated) C&Q approach. Early alignment with Regulatory and Quality teams to ensure understanding of the approach, terminology, timelines, and methods, allowing them to properly convey the new approach for future internal and external assessments.
- Acknowledging that engineering is not seen as the current problem, but rather their expertise and valuable contributions should be recognized and documented.
- Early engagement with the CSV team to ensure an efficient and coordinated effort in ensuring PCS-enabled systems are fit for intended purpose/qualified.
- Robust implementation of GEP and EQP and alignment with Quality and engineering in terms of responsibilities and accountability of their respective deliverables. Lack of robustness can manifest in the following ways which erode the trust in the EQP/GEP process:
  - PPK and CQAs/CPPs not documented as input to the QRM-based C&Q process.
  - Business requirements in the URS inappropriately classified by operations as quality impacting to ensure they get tested.
  - URS content encumbered with design details, procurement requirements, and documentation requirements which should be included in a contractual document to ensure systems/equipment are purchased correctly.
  - DR focused on review of the deliverables (drawings layouts, specifications, etc.) with no consideration for traceability to the user requirements.

- Commissioning documents not delivered to a basic standard of GDP, inadequate system test procedure, and/or unacceptable test acceptance criteria used as a qualification test.
- Commissioning testing of the full requirements/specifications of the system, focusing on a vendor FAT/SAT and ignoring the testing of the full system with its identified and installed control strategy.
- Excessive punch lists generated during commissioning indicating the system design is not robust.
- Lack of a change management system in place, requiring qualification retesting to be performed because of the level of undocumented changes occurring during commissioning.
- Insufficient documented functional specifications reviewed and evaluated prior to OV/OQ, leading to an excessive number of discrepancies.
- Not realizing that the initial SOPs that document the QRM C&Q approach will be updated by lessons learned integrated into program and SOP revisions.
- A concern by site and project teams that a new QRM C&Q approach will not allow for improvements and lessons learned and that this new methodology will not only be a change but also rigid, creating difficulty in gaining acceptance and adoption. It should be clear in plans and SOPs that this is a living program and is subject to continual improvement.

# 14 References

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15. FDA Guidance for Industry: Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations, September 2006, US Food and Drug Administration (FDA), [www.fda.gov](http://www.fda.gov).

# 15 Glossary – Acronyms and Abbreviations

<b>AHU</b>	Air Handling Unit
<b>ALCOA</b>	Attributable, Legible, Contemporaneous, Original, Accurate
<b>ALCOA+</b>	Attributable, Legible, Contemporaneous, Original, Accurate, Complete, Consistent, Enduring, Available
<b>C&amp;Q</b>	Commissioning and Qualification
<b>CA</b>	Critical Aspect
<b>CCP</b>	Critical Control Points
<b>CDE</b>	Critical Design Element
<b>CDMO</b>	Contract Development and Manufacturing Organization
<b>CFR</b>	Code of Federal Regulations (US)
<b>CIP</b>	Clean-In-Place
<b>CMC</b>	Chemistry, Manufacturing, and Controls
<b>CPP</b>	Critical Process Parameter
<b>CQA</b>	Critical Quality Attribute
<b>CSV</b>	Computerized System Validation
<b>DQ</b>	Design Qualification
<b>DR</b>	Design Review
<b>EC</b>	Established Condition
<b>ECM</b>	Engineering Change Management
<b>EQP</b>	Engineering Quality Process
<b>FAT</b>	Factory Acceptance Testing
<b>FDA</b>	Food and Drug Administration (US)
<b>GDP</b>	Good Documentation Practice
<b>GEP</b>	Good Engineering Practice
<b>GMP</b>	Good Manufacturing Practice
<b>GxP</b>	Good “x” Practice
<b>HEPA</b>	High Efficiency Particulate Air
<b>HSE</b>	Health, Safety, and Environmental
<b>HVAC</b>	Heating, Ventilation, and Air Conditioning
<b>IOQ</b>	Installation and Operational Qualification
<b>IOV</b>	Installation and Operational Verification
<b>MPCS</b>	Manufacturing Process Control Strategy
<b>PAR</b>	Proven Acceptable Range
<b>PCS</b>	Process Control System
<b>PHA</b>	Preliminary Hazards Analysis
<b>PPK</b>	Product and Process Knowledge
<b>PPQ</b>	Process Performance Qualification
<b>PQ</b>	Performance Qualification
<b>PQS</b>	Pharmaceutical Quality System
<b>PRA</b>	Process Risk Assessment
<b>PV</b>	Process Validation
<b>QA</b>	Quality Assurance
<b>QbD</b>	Quality by Design
<b>QCC</b>	Quality Change Control
<b>QMS</b>	Quality Management System
<b>QRM</b>	Quality Risk Management
<b>RPN</b>	Risk Priority Number
<b>SAT</b>	Site Acceptance Testing
<b>SME</b>	Subject Matter Expert
<b>SOP</b>	Standard Operating Procedure
<b>SRA</b>	System Risk Assessment
<b>TM</b>	Traceability Matrix
<b>URS</b>	User Requirement Specification