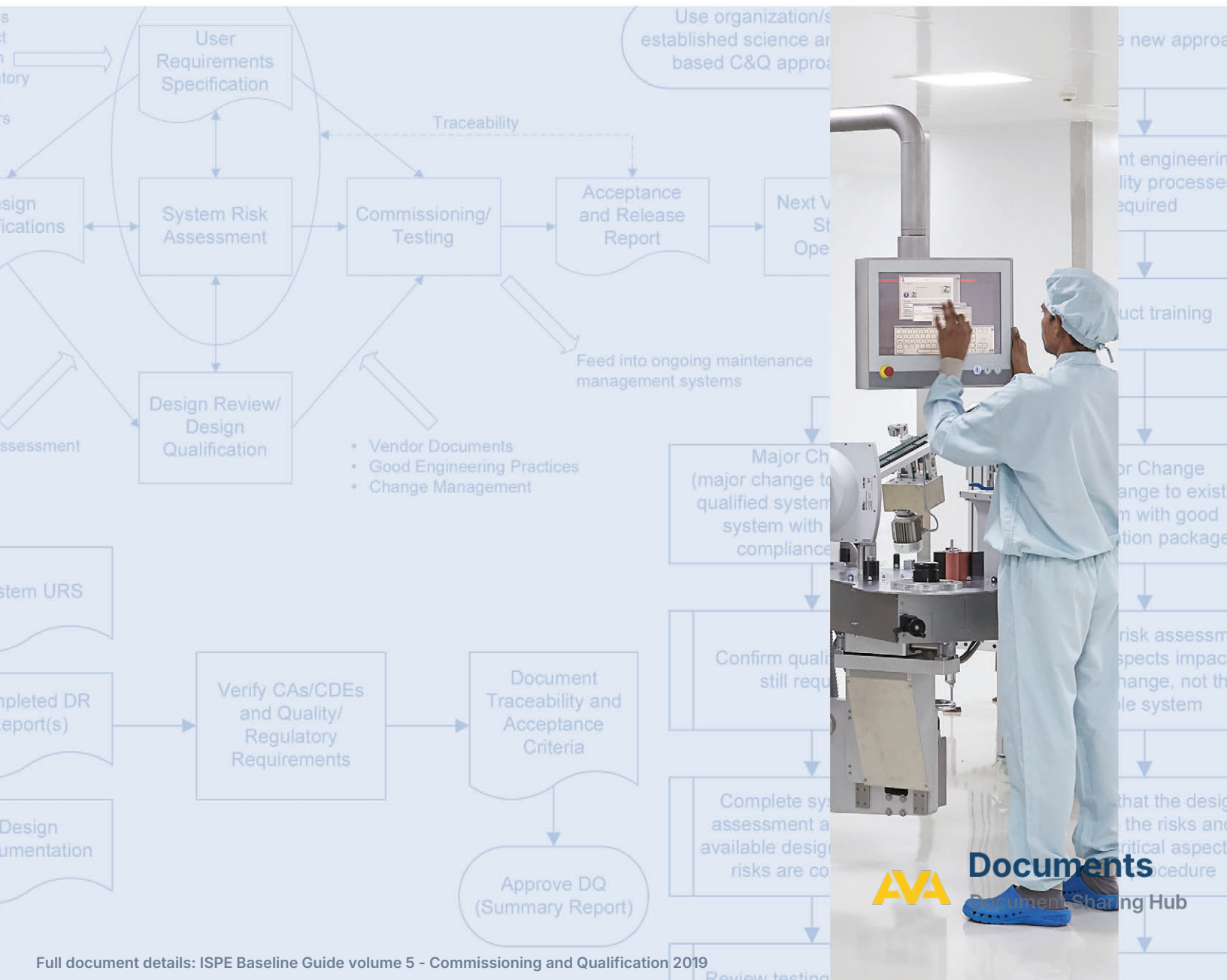


VOLUME 5

Commissioning and Qualification

Second Edition



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Commissioning and Qualification

Second Edition

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Preface

The history of commissioning, qualification, and validation practices in the pharmaceutical industry has witnessed competing priorities over the last thirty years. These priorities include perceptions of global and country specific regulatory requirements, Good Engineering Practice applications, project delivery cost and schedule demands, and successful technology transfers. For many years, organizations have defined their own Good Engineering Practices and technology transfer processes, with the priority of delivering projects as fast and as cost-effective as possible while meeting regulatory requirements.

This second edition of the *ISPE Baseline® Guide: Commissioning and Qualification* provides practical guidance to industry on the implementation of a science and risk-based approach to commissioning and qualifying pharmaceutical manufacturing facilities, systems, utilities, and equipment to demonstrate that they are suitable for the intended purpose. This Guide defines a process that incorporates current industry best practices for commissioning and qualification and that intends to comply with regulatory requirements.

Any uncertainty about the requirements for regulatory compliance may drive up costs and discourage innovation and technological advancements. Neither of these outcomes benefits public health. This Guide intends to offer a compliant, integrated science and risk-based approach to make the commissioning and qualification process efficient and cost-effective. It is intended to align with regulatory guidances, including EU GMP Annex 15 Qualification and Validation (October 2015) [1], US FDA Guidance for Industry: Process Validation (January 2011) [2], and ICH Q9 Quality Risk Management (November 2005) [3].

The intent of this revision to the Guide is to help the pharmaceutical industry simplify and improve the commissioning and qualification process by bringing the “best of the best” together into one document. The following ISPE guides are superseded with this revision:

- *ISPE Baseline® Guide: Volume 5 – Commissioning and Qualification (First Edition)*
- *ISPE Guide: Science and Risk-Based Approach for the Delivery of Facilities, Systems, and Equipment*
- *ISPE Good Practice Guide: Applied Risk Management for Commissioning and Qualification*

The authors of this Guide have brought together a wealth of experience and knowledge to describe a simplified commissioning and qualification process, with supporting templates and example documents to illustrate the concepts. In addition, this Guide helps to clarify definitions and address common challenges that may arise during the process.

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1 Introduction

1.1 Background

It is a universal regulatory expectation that pharmaceutical manufacturing facilities, systems, utilities, and equipment are designed, constructed and qualified to be suitable for the intended purpose. Regulatory authorities have indicated in their guidances and regulations that organizations must build quality into their processes and products.¹ This Guide intends to offer a compliant, integrated commissioning and qualification process that is based on a science and risk-based approach. This process supports Quality by Design [4] and ensures that risks to product quality from the systems² are adequately addressed.

It is recognized that the terminologies for the commissioning and qualification process are varied. The overall process has traditionally been called commissioning and qualification; ASTM E2500-13 [5] refers to the process as verification. This second edition of the Baseline® Guide focuses on the approach; the terminology used is not as important as the approach. For the purposes of this Guide, the term **Commissioning and Qualification (C&Q)** is used to describe the *process* for establishing that facilities, systems, utilities, and equipment are suitable for the intended purpose. The term **verification** is used to describe an *activity* performed during the C&Q process to establish suitability for the intended purpose.

Commissioning and qualification differ only in that the qualification process has oversight by the Quality Unit, focused on the system risk to product quality. The Quality Unit ultimately decides whether systems are suitable for the intended purpose, based on the identification, testing, and documentation of the system features deemed critical to product quality.

1.2 Purpose and Objectives

This Guide intends to offer a compliant, integrated C&Q approach to making the qualification process efficient and cost-effective. The approach includes a **System Risk Assessment** process that identifies the **Critical Aspects (CAs)** and/or **Critical Design Elements (CDEs)**. CDEs are system functions and features identified as having the potential to control risks to product quality and therefore ensure patient safety. Qualification confirms that the CDEs and design risk controls identified through the System Risk Assessment have all been checked, tested, and found to be installed and operating as specified. This approach demonstrates that the systems are suitable for the intended purpose and can be accepted and released for the next stage (performance qualification or manufacturing operations, as appropriate).

The approach described in this Guide involves utilizing properly performed and documented verification or testing completed at any project phase to establish that the system is qualified (suitable for the intended purpose). The utilization of commissioning tests as well as vendor testing can yield an efficient compliant program. The benefits of this approach are maximized with a strong trusting relationship between vendors, service providers, and pharmaceutical organizations.

This Guide recognizes industry best practices regarding C&Q and presents concepts that can assist organizations in meeting current regulatory expectations for system qualification by:

- Providing guidance on how to apply the Quality Risk Management (QRM) [3] process to C&Q to establish CDEs
- Defining the focus of an integrated C&Q effort to be the CAs/CDEs and Critical Process Parameters (CPPs) which provide the ability to deliver the product Critical Quality Attributes (CQAs)

¹ Further information about the regulatory basis for this Guide is provided in Chapter 15 (Appendix 1).

² For the purposes of this Guide, the term systems is used to refer to facilities, systems, utilities, and/or equipment.



- Defining best practices for User Requirements Specification (URS), Design Review (DR), Design Qualification (DQ), and acceptance and release of the system
- Clarifying the change management processes required to support the C&Q process
- Providing Good Engineering Practice (GEP) documentation standards
- Describing where testing should be duplicated and where it is acceptable to test once
- Addressing integration of equipment automation systems
- Providing examples of appropriate C&Q deliverables

The authors of this Guide believe that there is value in employing the concepts described in the individual chapters even if all aspects of the program are not implemented, e.g., identification of CAs/CDEs through System Risk Assessments, better definition of the URS, etc.

1.3 Scope

This Guide applies to systems used by pharmaceutical manufacturers of human and veterinary drugs, including biological drug products.

Medical devices have separate regulatory requirements and are outside of the scope of this Guide. For combination devices, this Guide can be applied to the manufacturing equipment for the combination device, but not to the device itself.

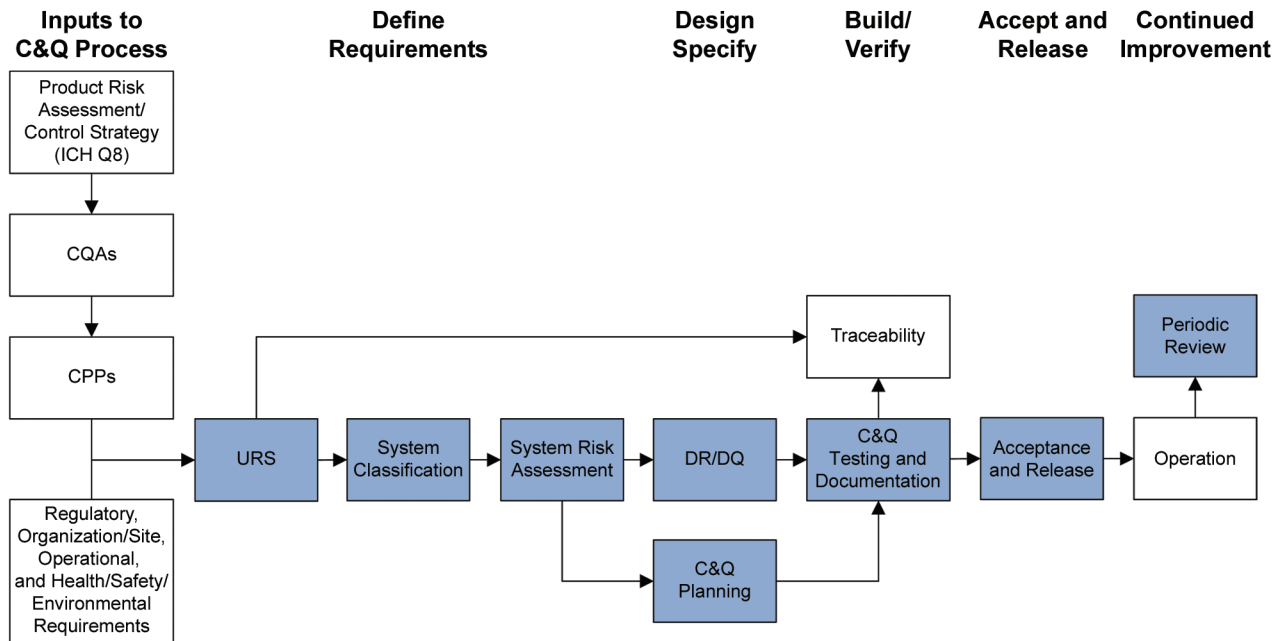
The following areas are not in the scope of the C&Q process as described in this Guide:

- Product and process development, including identification of any process requirements that influence system design
- Computerized systems software development and testing (refer to *ISPE GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems* [6])
- Process validation, including Process Performance Qualification (PPQ) and Continued/Ongoing Process Verification (refer to *ISPE Good Practice Guide: Practical Implementation of the Lifecycle Approach to Process Validation* [7])
- Cleaning validation
- Sanitization and sterilization validation
- Analytical procedures and methods validation
- Decommissioning activities (refer to *ISPE Good Practice Guide: Decommissioning of Pharmaceutical Equipment and Facilities* [8])

1.4 Process Overview and Structure of the Guide

An overview of the integrated C&Q approach is shown in Figure 1.1.

Figure 1.1: Science and Risk-Based C&Q Process Map



Note for Figure 1.1: Shaded boxes indicate the major blocks within the process maps that are addressed by chapters in this Guide.

The inputs to the integrated C&Q process include product and process CQAs/CPPs (established through research and development and/or the technology transfer process) and the application of QRM to define the control strategy.

The steps in the integrated C&Q process are:

- URS (Chapter 2)
- System Classification (Chapter 3)
- System Risk Assessment (Chapter 4)
- DR/DQ (Chapter 5)
- C&Q Planning (Chapter 6)
- C&Q Testing and Documentation (Chapter 7)
- Acceptance and Release (Chapter 8)
- Periodic Review (Chapter 9)

Also included in this Guide are the support programs and strategies for implementation:

- Vendor Assessment for C&Q Documentation Purposes (Chapter 10)

- Engineering Quality Process (Chapter 11)
- Change Management (Chapter 12)
- Good Documentation Practices for C&Q (Chapter 13)
- Strategies for Implementation of Science and Risk-Based C&Q Process (Chapter 14)

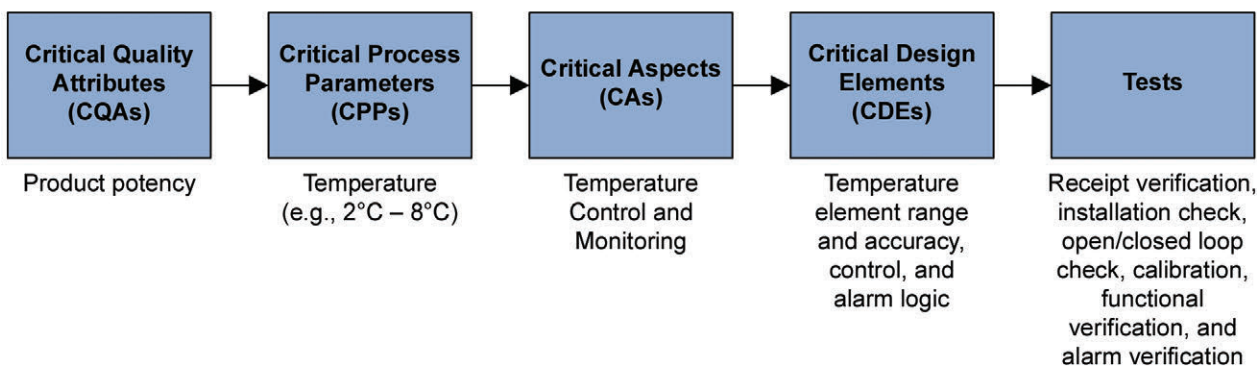
The process begins with the development of the URS (Chapter 2). This includes defining the product quality related user requirements that must be met for a system to be suitable for the intended purpose.

The next step in the process is system classification (Chapter 3). The system is categorized as direct impact or not direct impact, depending on its potential impact to product quality. Either the system has direct product quality impact or it does not. A system classification tool is provided to facilitate this determination and to document the results. Direct impact systems are commissioned and qualified while systems that are not direct impact are commissioned.

The next step in the process is System Risk Assessment (Chapter 4), the application of QRM in which a risk assessment of the direct impact system is used to examine the system product quality risk controls and to identify CDEs. It is important for the System Risk Assessment to be performed by Subject Matter Experts (SMEs) that understand the science of the process. CDEs are identified by examining the CPPs that need to be controlled to ensure product quality, as defined by the CQAs. CPPs are not only those that control delivery of drug substance or drug product CQAs, but can also be related to CDEs of packaged materials (e.g., ensuring inclusion of product inserts or variable data such as lot number and expiration date on labeling). The CAs of the process can be identified from the CPPs, and the CDEs of the system can be identified from the CAs. CDEs can also include features such as product contact materials of construction. Unacceptable risks are mitigated through the application of risk controls, which include the CDEs.

Figure 1.2 provides an example that illustrates the relationship between CQAs, CPPs, CAs, CDEs, and the associated testing.

Figure 1.2: Example of Automated Temperature Control and Monitoring of a Process Step



A C&Q Plan (Chapter 6) or strategy can be initiated once sufficient design information exists. The plan/strategy can be modified as more information is collected during the project execution lifecycle. Design finalization of the system can be performed in parallel with C&Q planning based on the system-specific design requirements that include CDEs, safety, capacity, and all other requirements.

While the C&Q Plan is being created, DR (Chapter 5) is conducted iteratively during the design process to ensure all user requirements and CDEs are addressed in the design. Aspects of the design impacting product quality are confirmed in DQ (also Chapter 5) for direct impact systems. The Quality Unit approves the DQ. Once the DR/DQ is completed, the C&Q Plan can be finalized.

C&Q testing and documentation (Chapter 7) is initiated once construction (including fabrication of equipment at vendor facilities) has reached a point that the testing is meaningful and all prerequisites are met. Testing and verification do not have to wait until construction is completed. This may include pre-delivery or receipt inspection, Factory Acceptance Testing (FAT), construction quality document verification, and Site Acceptance Testing (SAT). C&Q planning should identify aspects of the FAT and SAT that will be utilized to satisfy qualification requirements. C&Q testing can include clean utilities performance testing and room environmental qualification, also known as Performance Qualification (PQ), per organization/site policies and procedures.

Completion of testing leads to acceptance and release (Chapter 8), the last phase of C&Q. Completion of this phase acknowledges that the system is suitable for the intended purpose and can be released for PPQ or for commercial use, depending on the system type. PPQ is outside of the scope of this Guide.

It is important to ensure that systems remain suitable for the intended purpose after acceptance and release, and while in use. This is accomplished by various management systems (such as calibration, maintenance, and change control systems) and a periodic review program (Chapter 9).

The additional programs necessary to support the C&Q process are described in Chapters 10 through 13 and are used throughout the C&Q process.

The vendor assessment for C&Q documentation (Chapter 10) is used to help identify vendor documentation that can be used for C&Q purposes. It should be performed prior to finalizing the C&Q Plan.

The overall quality program supporting the C&Q process is the Engineering Quality Process (Chapter 11). This addresses the quality practices for the C&Q process and is intended to be part of the overall Pharmaceutical Quality System (PQS) [9] and QRM.

It is important to implement a change management program (Chapter 12) to capture changes as they are identified, assessed, and implemented.

Good Documentation Practices (Chapter 13) are important in all C&Q process steps and in other support programs to demonstrate data integrity.

This revision to the Guide is not intended to drive companies to repeat qualification for their existing systems, but to identify an efficient, science and risk-based approach for future C&Q efforts and provide strategies for implementation (Chapter 14). Guidance is also provided for modifying existing systems with legacy qualification documentation.

It should be noted that the process, as described in this Guide, is scalable. Depending on the project size, complexity, and novelty, the documents and deliverables may be combined. As appropriate, this should be documented in the C&Q Plan.

The appendices provide additional details and examples to the C&Q program. The examples have been included in the Guide to enhance understanding of the principles. The reader is encouraged to utilize the examples for illustrative purposes. These examples are not intended to be the only way to execute the process; the intent is to demonstrate the concepts as applied to example systems. Individuals creating documentation for their systems should involve those in their organization/site to adapt the examples to meet their needs.

1.5 Rationale for this Second Edition

This Guide, the second edition of the *ISPE Baseline® Guide: Commissioning and Qualification*, has been designed to present industry best practices for C&Q. It also combines concepts from regulatory guidances (e.g., from EMA [10], FDA [11], ICH [12]) and the following ISPE documents that are superseded with this revision:

- *ISPE Baseline® Guide: Volume 5 – Commissioning and Qualification (First Edition)*
- *ISPE Guide: Science and Risk-Based Approach for the Delivery of Facilities, Systems, and Equipment*
- *ISPE Good Practice Guide: Applied Risk Management for Commissioning and Qualification*

Certain aspects of the C&Q approach described in the previous edition of this Guide are retired and replaced with QRM and GEP. These include:

- *Component Criticality Assessment*

Since CDEs are identified as an output of the System Risk Assessment, assessment of the criticality of each system component is unnecessary.

- *Enhanced Commissioning*

This Guide describes how the level of testing can be aligned with criticality and intended purpose of the system.

- *Enhanced Design Review*

This Guide describes an approach for performing effective DRs using the System Risk Assessment to achieve DQ.

- *Enhanced Documentation*

Good Documentation Practices are defined in the Guide.

- *Indirect Impact*

The term is not used. The Guide describes C&Q for systems based on whether a system has direct product impact or not.

- *V-Model*

The integrated C&Q approach provides a lifecycle C&Q approach and is represented by a different process map (see Figure 1.1). The V-model appropriately represented the links between the design process and testing, but did not incorporate a risk assessment process based on product quality.

1.6 Key Concepts

1.6.1 Efficient Approach without Redundant Testing

The foundation of this Guide is based on the expectation that engineers and system vendors ensure systems are installed and operate to meet the design specifications and user requirements. This is commonly referred to as commissioning. Best industry practice is to utilize such an approach when installing any new system. However, the level of testing and documentation for commissioning is variable within the industry. This Guide establishes the rationale and a methodology for aligning testing and documentation expectations with the intended purpose of the system.

When a system has direct impact on product quality (direct impact system), the CDEs of the system can be verified by the approach described in this Guide. This approach ensures that identified CPPs are maintained; CPPs ensure that CQAs are attained. Testing of system CDEs is utilized to support qualification of the system. Thus, the documentation of the testing performed in commissioning needs to be acceptable to be presented in a regulatory audit or inspection. The acceptance of that documentation is based on adherence with Good Documentation Practices fundamentals (as described in Chapter 10).

1.6.2 Terminology for Product Impacting Attributes

A common source of debate is regarding the terminology for CPPs and CQAs. For systems that are directly used to manufacture pharmaceutical products, these terminologies are easily identified and supported. However, there is also a recognition that critical utilities, such as Water for Injection (WFI) systems, may not have product CQAs but do have compendial requirements and CPPs. There is a recognition that the output of upstream processes (e.g., fermentation) and utilities (e.g., WFI system) need to meet specific quality attributes as defined by process definition or in compendial requirements. These parameters can directly influence the system's ability to deliver product meeting those attributes.

These parameters can be termed critical parameters but not in the context of final product quality attributes. The authors of this Guide continue to use the terminology of CPPs and CQAs for all systems, including WFI and upstream equipment. It is important for individual organizations/sites to define what is critical for their products, processes, and systems (e.g., CQAs, CPPs, Critical Parameters, Key Operating Parameters, System Process Parameters, etc.). The criticality designation should drive the activities related to design, installation, and operation throughout the system lifecycle.

1.6.3 Quality Unit Oversight

Another common source of debate within the C&Q effort is which group should approve what document. The Quality Unit is expected to have oversight of the entire validation lifecycle including qualification. Because the Quality Unit is not expected to have expertise in all aspects of pharmaceutical manufacturing systems, identified SMEs (including system vendors) should be responsible for determining how best to design and test systems to ensure they are suitable for the intended purpose. It is important that the SMEs have sufficient knowledge of the processes and systems to ensure the systems are properly designed, tested, and operate as designed. The Quality Unit needs to be engaged in the process, be considered part of the C&Q team, approve the appropriate testing plans and documents for systems that directly affect product quality, and approve the final acceptance of the qualified state and release to support pharmaceutical manufacturing operations. The authors see this as a Quality Assurance (QA) role, not a documentation quality control role. An example approval matrix is provided in Chapter 6.

1.7 Key Terms

This section introduces key terms as they are used in the context of this Guide. Refer to Chapter 31 (Appendix 17) for an expanded listing of definitions.

Acceptance Criteria

As defined in WHO Annex 5 [13]:

"Measurable terms under which a test result may be considered acceptable"

Commissioning

A well-planned, documented, and managed engineering approach to the start-up and turnover of facilities, systems, utilities, and equipment to the end-user that results in a safe and functional environment that meets established design requirements and stakeholder expectations.

Critical Aspects (CAs)

As defined in ASTM E2500-13 [5]:

“Functions, features, abilities, and performance or characteristics necessary for the manufacturing process and systems to ensure consistent product quality and patient safety.”

Critical Design Elements (CDEs)

Design functions or features of an engineered system that are necessary to consistently manufacture products with the desired quality attributes. Examples of automation design functions include alarms and data management. Examples of engineering design features include components, instruments, and materials of construction. CDEs are identified and documented based on technical understanding of the product CQAs, process CPPs, and equipment design/automation. CDEs are verified through C&Q.

Critical Process Parameter (CPP)

As defined in ICH Q8 [4]:

“A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality.”

Critical Quality Attribute (CQA)

As defined in ICH Q8 [4]:

“A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.”

Design Qualification (DQ)

A documented process that verifies the proposed design of the facilities, systems, utilities, and equipment is suitable for the intended purpose.

Design Review (DR)

As defined in ISO/IEC/IEEE 24765 [14]:

“Formal, documented, comprehensive, and systematic examination of a design to determine if the design meets the applicable requirements, to identify problems, and to propose solutions.”

Deviation

In the context of this Guide, a departure from specification, or a critical discrepancy that cannot be corrected, that affects a CA/CDE. Deviations require Quality Unit approval prior to closure.

Direct Impact System

A system that directly impacts product CQAs, or directly impacts the quality of the product delivered by a critical utility system. All other systems are considered to be not direct impact.

Discrepancy

As defined in FDA 2006 Quality Systems Guidance [15]:

“Datum or result outside of the expected range; an unfulfilled requirement; may be called non-conformity, defect, deviation, out-of-specification, out-of-limit, out-of-trend.”

Expected Results

The result that the test case should produce based on the requirements.

Installation Qualification (IQ)

A documented *process* that verifies that the facilities, systems, utilities, and equipment, as installed or modified, comply with the approved design and the manufacturer’s recommendations.

Installation Verification (IV)

The *activity* of reviewing, inspecting, testing, checking, auditing, or otherwise establishing and documenting whether items, processes, services, or documents conform to specified requirements.

Legacy Systems

For the purposes of this Guide, the term used to describe systems previously qualified using methodologies other than those presented in this Guide.

Operational Qualification (OQ)

A documented *process* that verifies that the facilities, systems, utilities, and equipment, as installed or modified, perform as intended throughout the anticipated operating ranges.

Operational Verification (OV)

The *activity* of reviewing, testing, checking, or otherwise establishing and documenting that a system operates according to written and pre-approved specifications throughout all specified operating ranges.

Performance Qualification (PQ)

A documented *process* that verifies that the facilities, systems, utilities, and equipment, as connected together, can perform effectively and reproducibly, based on the approved process method and product specification.

Qualification

For the purpose of this Guide, a *process* to demonstrate and document that the critical manufacturing facilities, systems, utilities, and equipment are suitable for the intended purpose.

Quality Risk Management (QRM)

As defined in ICH Q9 [3]:

“A systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle.”

Suitable for the Intended Purpose

The system requirements are defined, the design is appropriate for control of the manufacturing process, and the system is fabricated and installed as designed, and performs as intended throughout the anticipated operating ranges.

Systems

For the purposes of this Guide, the term used to refer to facilities, systems, utilities, and/or equipment.

Vendor (also known as a Supplier)

For the purposes of this Guide, the term used to describe the organization providing the system or providing the contract services to execute the C&Q program for the organization that owns the system.

Verification

An *activity* that is performed within the C&Q process to document that the manufacturing facilities, systems, utilities, and equipment are suitable for the intended purpose.

2 User Requirements Specification

2.1 Introduction

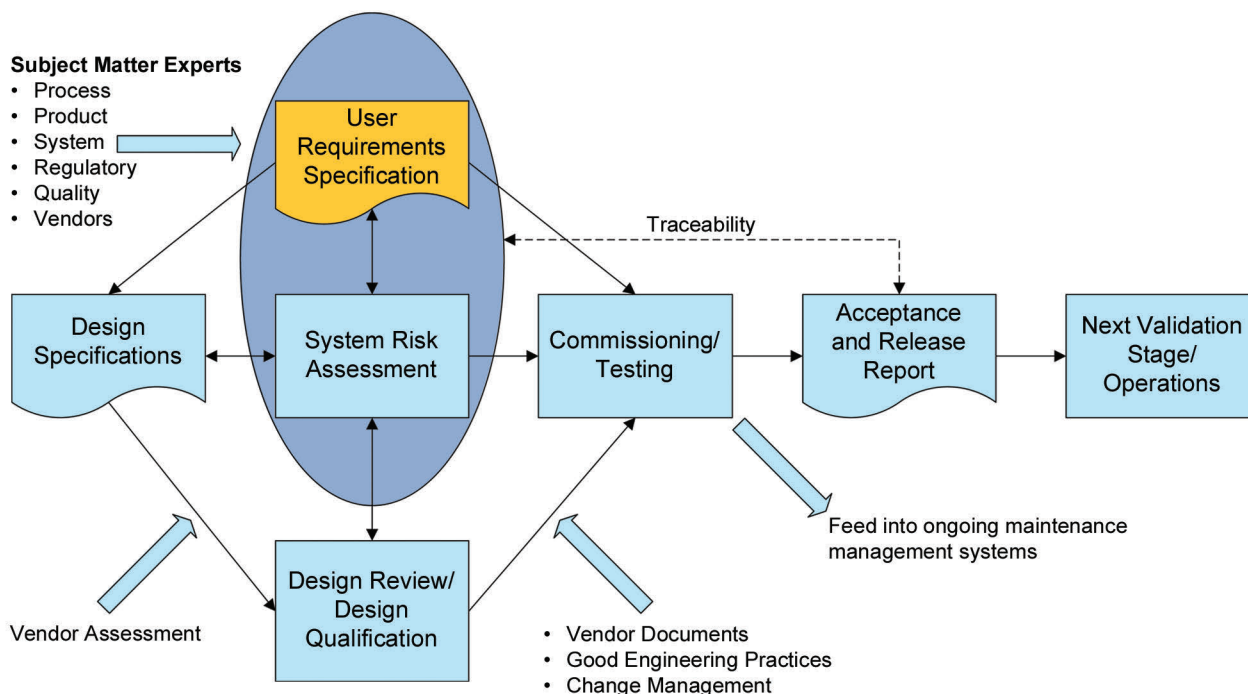
The User Requirements Specification (URS) brings together system requirements from multidisciplinary sources to support system design, C&Q, operations, and maintenance. Within the C&Q process, it is a foundational document that identifies the product and process requirements for the system. These product quality related user requirements are based on product knowledge (CQAs), process knowledge (CPPs), regulatory requirements, and organization/site quality requirements. The product and process requirements in the URS are inputs to the C&Q process; they provide the science-based knowledge that forms the basis for applying QRM to C&Q.

It is recommended that a URS is developed for each system that has the potential to impact product quality, or a direct impact system (as determined through system classification described in Chapter 3). A formal URS document is not always necessary. A statement of the URS may be contained in various forms, e.g., purchase request, functional specification, change request, or data sheet. For standard off-the-shelf or simple catalog systems, a statement of the URS may be a purchase order, vendor cut sheet, or catalog data. The system would be verified against this document.

Figure 2.1 shows the relationship between the activities and documents in the C&Q process for direct impact systems.

Figure 2.1: Relational Diagram for C&Q Activities and Documents – User Requirements Specification

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2.2 Development of the User Requirements Specification

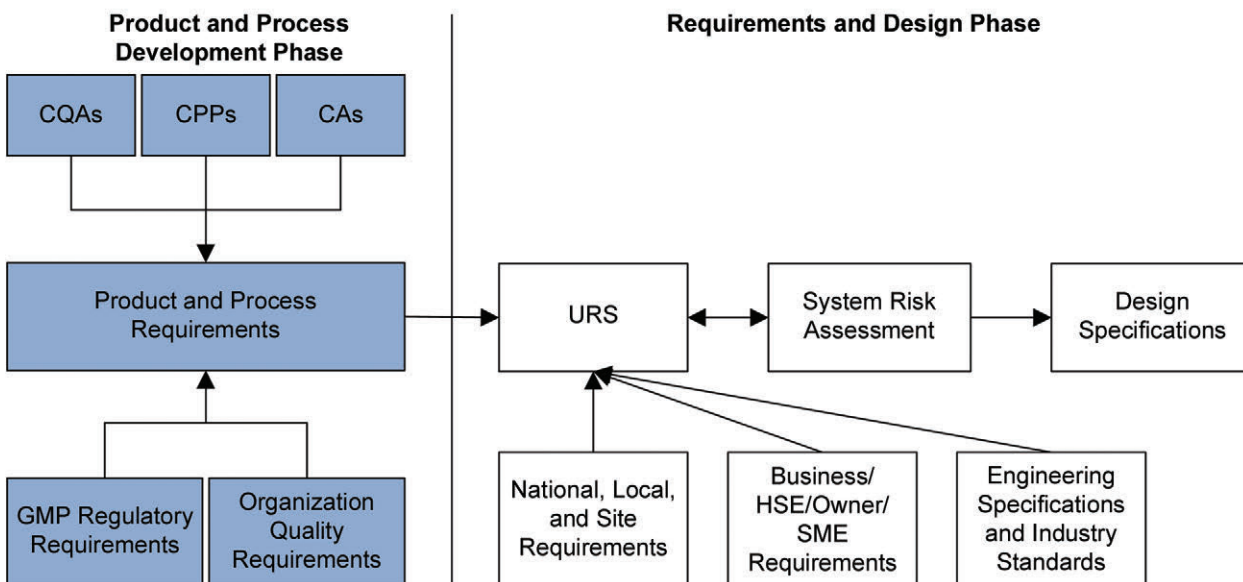
The URS defines the requirements that must be met for a system to be suitable for the intended purpose; it should not detail how those requirements are met. The URS is developed by a project team that includes SMEs (refer to Section 6.4 for an example approval matrix). It can be revised throughout the system lifecycle.

The URS document should:

- Describe the intended purpose of the system
- State the requirements in verifiable terms without describing how the requirements will be met
- State the category and source of each requirement
 - Categories may include, for example:
 - > Quality
 - > Business
 - > Health, Safety, and Environmental (HSE)
 - Sources may include, for example:
 - > Product and process requirements which are derived from:
 - Product and process knowledge (CQAs, CPPs, CAs)
 - GMP regulatory requirements
 - Organization/site quality requirements
 - > System Risk Assessment (includes CAs and associated CDEs)
 - > Range and accuracy for any controlled parameters
 - > National, local and site requirements, as applicable
 - > Business, HSE, system owner, and SME requirements
 - > Engineering specifications and industry standards (e.g., ASME [16], ASTM [17], ISO [18])
 - > Project requirements document or project charter
 - > Legacy system evaluations

Figure 2.2 shows the data sources typically used as inputs to an individual system URS.

Figure 2.2: Data Sources Used to Develop the User Requirements Specification



Note for Figure 2.2: Shaded boxes indicate product and process requirements and sources.

The URS should also include the following:

- Data integrity requirements
- Data storage/display requirements
- Alarm requirements, with identification of the critical alarms
- System automation requirements
 - If there are any connections (e.g., data archiving) and interactions (e.g., alarm initiation) to a larger automation control system, then that system can have a separate URS. There needs to be clearly defined boundaries between the systems.

Note: System software development and testing is outside of the scope of this Guide. Refer to *ISPE GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems* [6].

The URS, which may be further detailed during early project phases, provides the foundation for the Basis of Design (BOD) and becomes a reference used to establish that a system is suitable for the intended purpose. To be suitable for the intended purpose, systems need to meet their URS.

The URS should not include the following information as requirements:

- How a requirement is to be met
- Detailed design specifications
- Sequence of operations
- Generic statements (e.g., must comply with local codes, must meet all GxPs)

- General references to government/national standards (e.g., nonspecific reference to ASME [16] code, ISO [18] standards)
- Contractual terms and deliverables
- Unverifiable parameters
- Standard functionality of the equipment type

Refer to Chapter 16 (Appendix 2) for an example URS template. It is the responsibility of the organization/site to designate quality impacting elements of their URS in a manner that is most appropriate for their integrated C&Q process.

2.3 Approval of User Requirements Specification and Changes Post-Approval

The URS should be approved by the system owner, an appropriate SME, and the Quality Unit. However, if the Quality Unit has already approved the source documents from which the quality requirements within the URS were obtained, then the Quality Unit does not need to approve the URS. Refer to Section 6.4 for an example document approval matrix.

The URS should be updated through the system lifecycle (from development through sustaining operations) until decommissioning of the system. After approval of the URS, changes or additions with the potential to impact product quality are evaluated against the System Risk Assessment (refer to Chapter 4) to confirm if risks are acceptable or to determine if additional risk controls are required. Changes to the URS are performed through change management (refer to Chapter 12).

2.4 Legacy Systems

For a legacy system without a documented URS, a URS for any scope changes may be developed and incorporated into the C&Q Plan (see Chapter 6) or change record.

Based on the magnitude of the change and the extent of the C&Q required, it may be beneficial to create a new URS. Refer to Chapter 14 for implementation recommendations.

3 System Classification

3.1 Introduction

This Guide presents an approach for classifying systems into two categories depending on the system capability to impact product quality. System classification establishes whether a system is commissioned and qualified or only commissioned, as follows:

- **Direct impact** systems are commissioned and qualified
- **Not direct impact** systems are commissioned

Note: In the previous edition of this Baseline® Guide, component classification could be carried out as a subset of system classification. Component classification is no longer necessary since the System Risk Assessment (as described in Chapter 4) identifies CDEs for the system in a more efficient manner.

For systems that are not direct impact, the scope of commissioning is determined by SMEs and is based on the business and HSE criticality of the system. For example, a chilled water system serving an administrative building (not direct impact) may be balanced only. Meanwhile, a chilled water system (not direct impact) serving direct impact process equipment may be balanced, with the balancing confirmed at the minimum and maximum design flow rates to ensure reliable system performance during operation.

3.2 System Boundaries

Projects are commonly divided up into systems to facilitate construction management, document collation, turnover, and C&Q. System boundaries are markings on design drawings to distinguish systems from one another; this includes all components and piping to logically define what is included and what is not included within the system. System boundaries should be defined and documented early on in the project (at the BOD phase) to enable development of the systems list and subsequent execution of System Risk Assessments. The systems are usually listed in the C&Q Plan (refer to Chapter 6). System boundaries should be defined such that the systems cover the entirety of the project scope; this is typically documented in the system Process and Instrumentation Diagram (P&ID) or Process Flow Diagram (PFD).

The scope of supply from vendors is often used as the basis for defining system boundaries; however, these boundaries should be carefully reviewed as there may be benefits in defining the boundaries differently. For example, boundary considerations for a direct impact compressed air system are as follows:

- A Point of Use (POU) filter is typically outside the vendor scope of supply for a compressed air system but may or may not be included in the system boundaries.
- The POU filter could be included within the boundaries for the compressed air distribution system. All compressed air testing and verification activities would be part of the compressed air system.
- Alternatively, the POU filter could be included in the process system for which the air is being supplied to. All compressed air testing and verification activities for the POU filter would then be part of the process system.

During the early stages of a project, system boundaries may also be subdivided to facilitate development of C&Q documentation by different suppliers. For example, the URS for a compressed air system can include generation and distribution sections, each of which may have its own set of C&Q documentation.

The optimum approach for the project should be evaluated and then defined in the C&Q Plan. In the compressed air system example discussed earlier, it may be simpler to provide a URS/C&Q package for the generation system from one supplier and a separate URS/C&Q package for the storage and distribution system that is built on-site by a separate supplier.

Regardless of the C&Q documentation strategy, systems need to meet their URS.

3.3 Criteria for System Classification

This Guide presents criteria for system classification that consist of eight questions; a YES response to at least one question indicates that the system is a direct impact system. Table 3.1 lists the questions that can be used to determine system classification for a given system.

Table 3.1: Criteria for System Classification

These criteria should be used to inform a judgment based on a comprehensive understanding of the product, process, and the nature of the system. They should not be used to replace the exercise of informed judgment by appropriately qualified personnel.

Number	Question	Additional Information
Q1	Does the system contain CAs/ CDEs or perform functions that serve to meet one or more process requirements (CQAs) including CPPs?	- There are two inputs to this question: product and process knowledge (CQAs and CPPs) - If the system controls or monitors a CPP, then the answer to this question should be a YES
Q2	Does the system have direct contact with the product or process stream and does such contact have the potential to impact the final product quality or pose a risk to the patient?	- Risk factors to consider: - GMP requirement that product contact materials are non-reactive, non-additive, and non-absorptive such that the safety, identity, strength, quality, or purity of the drug product is not affected [19] - Whether the materials that contact the manufacturing process can corrode and impart corrosion products into the manufacturing process - If any of these risk factors is an inherent part of the system, then the answer to this question should be a YES
Q3	Does the system provide an excipient or produce an ingredient or solvent (e.g., WFI) and could the quality (and compliance with the required specifications thereof) of this substance impact the final product quality or pose a risk to the patient?	- Risk factors to consider: - Whether the excipient, ingredient, or solvent needs to be of defined requirements in order to produce a quality product - Whether the excipient, ingredient, or solvent can introduce contaminants into the process stream (e.g., microbial contamination, corrosion products, residues from improper cleaning of the system) - If any of these risk factors is an inherent part of the system, then the answer to this question should be a YES

Table 3.1: Criteria for System Classification (continued)

Number	Question	Additional Information
Q4	Is the system used in cleaning, sanitizing, or sterilizing, and could malfunction of the system result in failure to adequately clean, sanitize, or sterilize such that a risk to the patient would result?	- Risk factors to consider: - Whether proper functioning of cleaning, sanitizing, and sterilizing systems is critical to product quality (YES in most cases) - Whether the quality of the substance used to perform the cleaning, sanitizing, or sterilizing (e.g., WFI, purified water, pure steam, cleaning or sterilizing chemicals): - Imparts any impurities to the process equipment - Impacts the effectiveness and repeatability of the cleaning, sanitizing, or sterilizing process - If any of these risk factors is an inherent part of the system, then the answer to this question should be a YES
Q5	Does the system establish a proper environment (e.g., nitrogen blanket, closed process, exposed filling zone air quality, maintenance of temperature, humidity when such parameter is part of the product CPPs) for the process and could failure of the system to function properly pose a risk to the patient?	- At different stages of a process, there may be requirements for a controlled temperature, humidity, aseptic, oxygen-free, or pressurized environment; systems that provide this environment (including providing sterile air, unidirectional flow/HEPA filtered air in a clean room or nitrogen that contacts a process stream) would fall into this category - If failure of the system to function properly or to provide the required environment of requisite quality means that a risk to product quality exists, then the answer to this question should be a YES
Q6	Does the system use, produce, process, or store data used to accept or reject product, CPPs, or electronic records subject to 21 CFR Part 11 [20] and EU GMP Vol. 4, Annex 11 [21] or the local equivalent?	This criterion is aimed at firmware, software, PLC, SCADA, PCS, BAS, networks, spreadsheets, and databases
Q7	Does the system provide container closure or product protection, the failure of which would pose a risk to the patient or degradation of product quality?	- Risk factors to consider: - Whether the system provides the closure or seal - Whether the system controls or provides the outside environment during shipping or product movement - If any of these risk factors is an inherent part of the system, then the answer to this question should be a YES
Q8	Does the system provide product identification information (e.g., lot number, expiration date, counterfeit prevention features) without independent verification or is the system used to verify this information?	- Risk factors to consider: - Whether any packaging components, if compromised, would lead to an impact on product quality or identity - Systems that perform operations such as label verification of lot number/expiration date and proper packaging insert - If any of these risk factors is an inherent part of the system, then the answer to this question should be a YES
Note: BAS, Building Automation System; PCS, Process Control System; PLC, Programmable Logic Controller; SCADA, Supervisory Control and Data Acquisition.		

Refer to Chapter 17 (Appendix 3) for an example system classification form. Refer to Chapter 18 (Appendix 4) for an example list of direct impact systems with typical CQAs and CPPs.

4 System Risk Assessment

4.1 Introduction

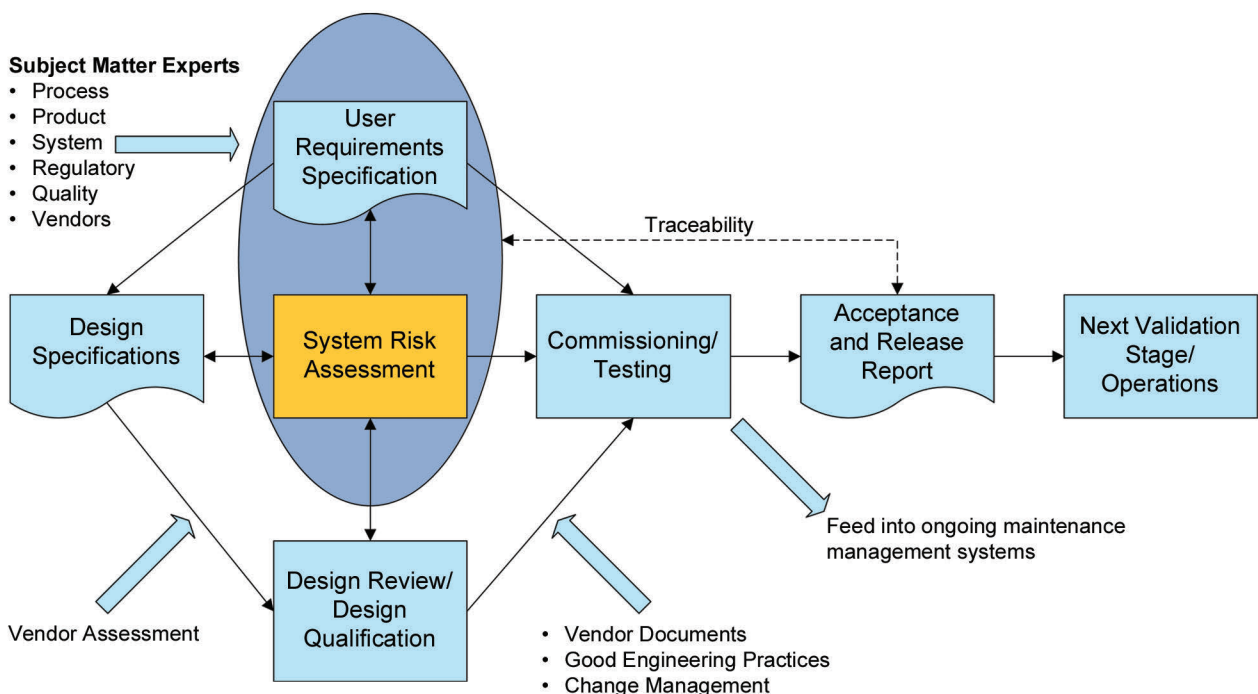
The System Risk Assessment is the application of QRM to examine the product quality risk controls for direct impact systems. This assessment identifies the critical design controls (CAs/CDEs) and procedural controls that are required to mitigate system risks to an acceptable level. It is important for the project team performing the System Risk Assessment to include technical SMEs that understand the science behind the process and the risks associated with the CQAs.

System Risk Assessments should be developed for direct impact systems (as determined through system classification described in Chapter 3). For standard off-the-shelf or simple catalog systems, some organizations may consider it unnecessary to perform the System Risk Assessment; a simple protocol or report (e.g., Installation and Operational Verification) could be used to provide the documented evidence that the installation and operation meet the system requirements.

Figure 4.1 shows the relationship between the activities and documents in the C&Q process for direct impact systems. C&Q inspection and testing activities can take place during fabrication and construction as well as during the commissioning/testing activities.

Figure 4.1: Relational Diagram for C&Q Activities and Documents – System Risk Assessment

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After the System Risk Assessment is completed, the URS should be checked to ensure that the CAs/CDEs have been included; if they are not included, then the URS should be revised to add them. Procedural control elements should be added to the C&Q scope.

Acceptance and release of the system (described in more detail in Chapter 8) involves confirming that the controls identified in the System Risk Assessment are in place as follows:

- The design controls (CAs/CDEs) have been shown to operate as specified
- The procedural controls are in place

4.1.1 Rationale

The traditional approach to qualification did not directly utilize commissioning documentation; instead, it often relied on an additional set of documents, the Installation Qualification (IQ) and Operational Qualification (OQ) protocols. These protocols provided the documented evidence that the system was installed and operating according to its specification. The scope of the IQ/OQ was determined by various elements such as organization/site established guidelines, vendor specifications, user requirements, and regulatory and guidance documents.

This traditional approach to qualification often resulted in IQ/OQ activities covering more scope than was necessary and repeating successful tests already performed during engineering start-up and commissioning. Furthermore, commissioning activities were commonly not robust enough or well documented since engineering teams anticipated that additional or repeat testing would be performed during qualification activities.

This Guide proposes a more streamlined approach to C&Q. Engineering documentation (i.e., commissioning inspection and testing documentation) is used to provide the documented evidence that the system has been installed and operates to meet the specifications. The CQAs and related CPPs are documented for the system, and a System Risk Assessment is developed to define potential risks to the CQAs and identify design (CAs/CDEs) and procedural controls used to mitigate these risks. Qualification confirms the system is suitable for the intended purpose and that the risk controls (design and procedural controls) are in place and functioning as specified.

4.1.2 Purpose and Benefits

The System Risk Assessment has multiple purposes and is a means to:

- Identify, assess, and record the quality risks to CQAs and associated controls
- Identify and document the design and procedural controls that are required to control and manage the identified risks
 - The rationale for these controls can also be documented in the System Risk Assessment
 - Testing of the design controls (CAs/CDEs) and verification of procedural controls provides the documentation used to support system qualification
- Provide guidance for the scope of the DQ, i.e., the scope covers the design of the CAs/CDEs
- Provide the information that is required for the basis of acceptance and release
- Provide a focus for Quality Unit oversight

The System Risk Assessment establishes (if not available in other documents) and documents the CAs/CDEs of the system operation and design that can impact product quality. It identifies the design and procedural controls that would mitigate those risks to product quality to an acceptable level. By verifying these controls, the system is confirmed to match that risk profile.

4.2 System Risk Assessment Process

As a prerequisite, the CQAs and associated CPPs should be identified and documented in the URS.

This Guide presents the following approach to performing the System Risk Assessment:

- A small team develops an initial baseline draft that includes development of the process description and identification of design and procedural controls
- A broader team reviews this initial baseline draft, making any necessary revisions to ensure the information is correct and no risks or controls have been omitted, and assigns the system risk profile

As a general guide, the initial session by the small team and the review session by the broader team should not exceed more than a few hours each if the preparation work is complete and teams with the correct level of expertise are used.

An example System Risk Assessment format is presented in Section 4.4.

4.2.1 Developing the Baseline Draft

The small team that develops the initial baseline draft should consist of the following:

- Experienced facilitator to guide the process
- Quality Unit representative
- Process/system SME (may be one SME or could additionally include a system vendor representative)

Refer to Chapter 19 (Appendix 5) for an example baseline System Risk Assessment.

4.2.2 Performing the System Risk Assessment

After the initial baseline is completed, a broader team reviews the document and determines the risk profile. This review team generally consists of representatives from a broader group with different experiences to provide a balanced perspective; this team could include:

- Operations (Production)
- Maintenance
- Engineering
- Process development
- Vendor representatives

Note: The time taken for the review generally increases with the number of people in the team, thus maintaining a balance between experience and the number of team members is important.

Prior to determining the risk profile, the team identifies the sources of the risks (potential failure modes) along with design aspects and/or procedural controls that would mitigate or eliminate the risk. Risk profiles are assigned per definitions shown in Table 4.1.

Table 4.1: Risk Level Definitions

Risk Level	Definition
Low	Considered acceptable with no actions needed. The likelihood of the risk occurring with the defined controls operating is considered low, and the detection is robust.
Medium	Normally considered unacceptable and requires mitigation through design (CAs/CDEs) and/or procedural controls. However, the SME reviewers may consider a medium risk as acceptable for the specific process/system and decide to accept the risk.
High	Considered unacceptable and requires mitigation through design and/or procedural controls. In certain situations, the SME reviewers may determine that these controls are not appropriate, e.g., implementation costs outweigh the incurred costs if the risk occurred, operational challenges, or other reasons. The SMEs may recommend acceptance of the system with the high risk; in this case, the assessment needs to be accepted by high-level management.

Note: The risk level is defined considering the overall process; thus, if the process is changed, the System Risk Assessments may need to be reviewed/updated. This aspect should be addressed through change management (see Chapter 12).

Determination of the risk profile should also be based on the SME's experience with the process/system. While defining the risk of the failure or hazard occurring, the SME should consider that the controls listed are in place and operating as intended.

The design controls (CAs and/or CDEs) defined during the System Risk Assessment are considered part of the system requirements and should be included in the URS. After the System Risk Assessment is completed, the URS should be updated to include these controls. If a Traceability Matrix is used as a tool to manage the C&Q execution process, the CDEs could be added to the Traceability Matrix only and updating the URS would not be needed.

Procedural controls identified during the System Risk Assessment need to be included in the C&Q Plan scope and could also be added to the Traceability Matrix.

4.2.3 Using Completed Assessments as a Starting Point for New System Baseline Drafts

The experience and documentation gained from completing System Risk Assessments can be applied to future systems. In addition, 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. Therefore, any new systems that are identical to or similar to existing systems can utilize the completed System Risk Assessments as a starting point.

The small team that develops the baseline draft (as described in Section 4.2.1) should assess the new system against the completed System Risk Assessment for the existing system that is identical/similar. The SMEs should determine if the system under review has different functionality and/or components. If the SMEs determine that these differences may introduce additional or different risks, then the baseline draft needs to be updated to include the risks and associated risk controls.

The remainder of the System Risk Assessment process would proceed as described in Section 4.2.2. The broader team reviews the baseline draft and determines the risk profile for the new system.

The use of completed assessments as a starting point for new system baseline drafts can improve the efficiency and consistency of the process.

4.3 Timing of System Risk Assessments

4.3.1 Development of the System Risk Assessment

The System Risk Assessment can be developed after completion of concept design and prior to the start of detailed engineering. It can be updated later as required. The System Risk Assessment can be completed when the Issued for Construction (IFC) design drawings and specifications are available, whether for new or modified systems. These drawings and specifications represent what will be built including any incorporated changes made through the DR/DQ process. Therefore, the System Risk Assessment can be confirmed and approved at this stage.

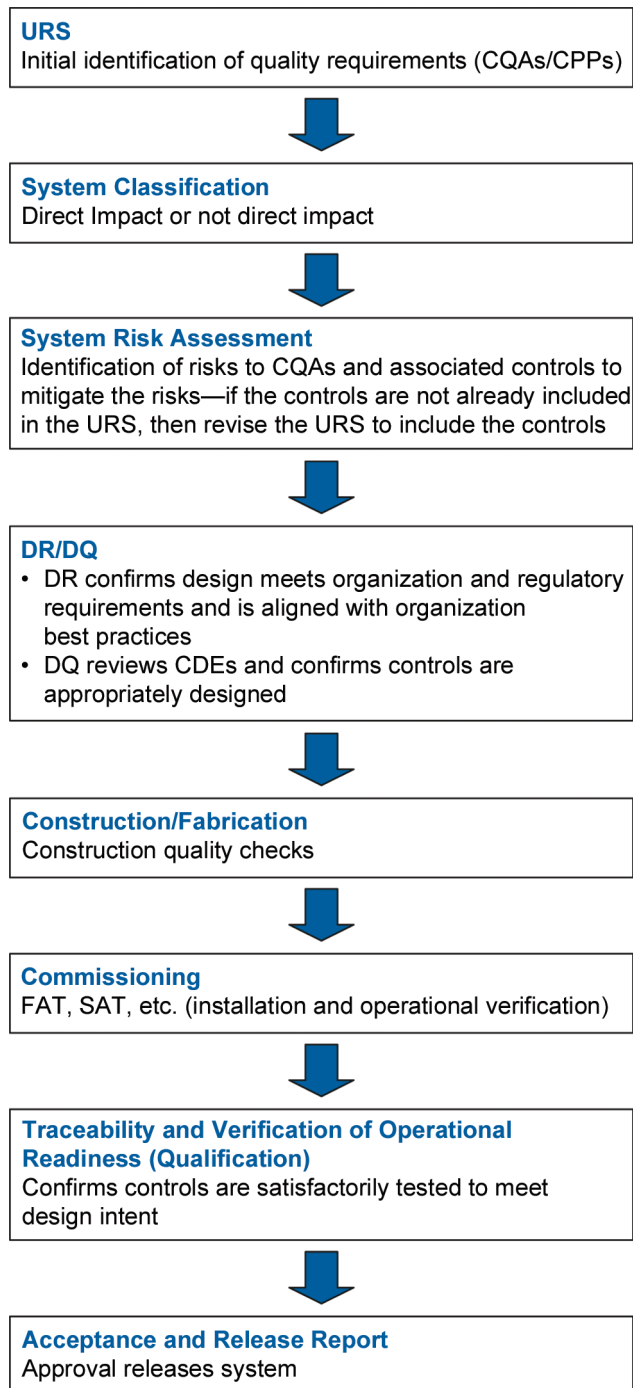
Note: Depending on the level of product and process knowledge, some of the CDEs associated with CAs may be known while the balance of the CDEs will be identified during the engineering design lifecycle (and can be documented as part of the DQ). All CDEs should be listed in the System Risk Assessment.

The System Risk Assessment defines the system risk profile, i.e., what it will be after the risk controls have been verified to be in place and operating as specified. Until the verification is completed, it is considered a provisional risk assessment.

For novel systems, starting the System Risk Assessment earlier in the design process can be beneficial since this allows for any identified risks to be controlled by design. Most risk control is achieved through system design; a procedural control is not considered as robust.

For standard or catalog systems where the potential risks are well understood and design controls are built in where possible, the System Risk Assessment could be performed at any time before the final DR of the system. Alternatively, an Installation and Operational Verification document could be used. DQ can also confirm that the system risk controls are adequate.

The sequence of activities for direct impact systems is shown in Figure 4.2.

Figure 4.2: Sequence of Activities for Direct Impact Systems

4.3.2 Lifecycle of the System Risk Assessment

Depending on the project size, timing, and complexity, additional product/process or system knowledge may become available after completion of the System Risk Assessment. If this additional knowledge impacts the system risk profile, the System Risk Assessment needs to be reviewed and updated.

System Risk Assessments are not subject to time-based periodic review; it is more efficient to reassess the risk profile in the event of a deviation related to the system performance and determine if an update is required. The System Risk Assessment can also be used as a reference document for assessing potential changes to a system.

For any changes to the system, the URS and System Risk Assessment should both be reviewed as part of the change management process (refer to Chapter 12). If the proposed change introduces additional risks or impacts existing risk controls, the System Risk Assessment (and associated URS) needs to be reviewed and updated.

4.4 Example System Risk Assessment Format

This Guide presents an example System Risk Assessment format that consists of thirteen columns. Table 4.2 summarizes the risk assessment process and how the contents of the example System Risk Assessment are developed.

Refer to Chapter 19 (Appendix 5) for an example of a baseline System Risk Assessment.

Table 4.2: Contents of Example System Risk Assessment Format

Column Number	Column Name	Description
1	Reference Number	Item reference number.
2	Operations Sequence/Process Flow	List the entire operational sequence of the system if the system operates in a sequential manner. Include cycles such as Clean-in-Place (CIP) or Sterilize-in-Place (SIP). When the system operates continuously (e.g., for a critical utility system), then a process flow is appropriate.
3	Process Description	Add a brief description of the process that applies to the sequence.
4	CQA*	List the CQA that is relevant for this step of the sequence/process. If none at this point, enter N/A.
5	CPP	This entry should map to the corresponding CQA in the same row. List the CPP whose variability has an impact on the CQA and can be monitored or controlled for that row. If none, enter N/A.
6	Impact on CQA	Enter direct or indirect, based on the impact of the established CPP on the CQA. For example, direct impact is where the CPP directly impacts the CQA. This entry is used to establish the criticality of any associated alarms.
7	How CQA can be Impacted	Add a brief description on how the CQA can be impacted at this step of the sequence/process, e.g., due to incorrect or out of range conditions of the CPP. This entry is used to define the possible hazard(s) to the CQA at this point of the sequence/process; it serves as an aid in the SME determination of risk.
*Regulatory requirements (e.g., labeling, dating, batch coding) can be addressed in the same manner as CQAs. Controls will normally be incorporated into the design and verified to work to ensure the regulatory requirement is met.		

Table 4.2: Contents of Example System Risk Assessment Format (continued)

Column Number	Column Name	Description
8	Design Controls (CAs/CDEs)	List any elements of the system design or operation that are built into the system. The design controls can be comprised of CAs and/or CDEs as defined in this Guide. These are the elements of the system that can be verified through inspection or testing, and are key to the risk-based C&Q approach. Examples include: an interlock that stops the machine upon certain conditions to protect the system product, an alarm alerts an operator that a CPP is outside the normal operating range, a setpoint that is defined by a recipe and is not operator adjustable, etc.
9	Recipe Parameter	List the recipe parameter (if applicable). Recipe parameters are usually product specific and established through product characterization studies; these are considered to be a risk control. It can be associated with an alarm for the machine operation. This entry is used to determine if the parameter is a fixed setting that would be established during characterization of the system. If none, enter N/A.
10	Associated Alarm	Enter yes or no, depending on the step in the sequence/process, the system design, and any requirements to establish the alarm. An alarm is considered as a risk mitigation element.
11	Procedural Controls	List the procedural controls that are in place or that should be established to mitigate risk to system product. Procedural controls can be part of SOPs, sampling procedures, or other.
12	Comments	Any comments are entered here.
13	Residual Risk Determination	List Low, Medium, or High. This entry represents an assessment by the appropriate SME(s) to set a risk profile based on the severity of the risk, the related controls (CAs/CDEs or procedural), and the reliability of the detection mechanisms. Refer to Table 4.1 for guidance on defining the risk level.

5 Design Review and Design Qualification

5.1 Introduction

This chapter provides guidance for performing and documenting Design Reviews (DRs) and Design Qualification (DQ). This Guide emphasizes the importance of DRs leading to DQ as a continual process throughout all phases in the design of new or modified systems.

DRs provide assurance that the design deliverables are consistent with the URS and the mitigation control strategies developed during the System Risk Assessment. When properly performed, DRs reduce the need for costly design-related change orders.

DQ is performed only for direct impact systems (as determined through system classification described in Chapter 3). DQ involves more formal documentation, with Quality Unit approval, to show traceability of the CAs and relevant CDEs in the design to the CPPs and CQAs.

DR and DQ are not intended to be separate activities, but rather separate documentation in which DQ is focused on CAs/CDEs and involves the Quality Unit as an approver. There should be minimal duplication of work; the final report from DR is a key input into the DQ process.

5.2 Design Process

The design process can be divided into several phases to ensure the design deliverables are sufficiently developed, the risks are identified and mitigated, and the project (as defined) meets financial objectives. The phases of the design process are:

1. Concept
2. Basis of Design (BOD)
3. Detailed Design

The concept and BOD phases define the Scope of Work (SOW) for the project.

In the concept phase, several approaches (scope options) to meeting the URS may be evaluated. These alternatives should be evaluated for their impact on the business objective, project cost, and risk to quality. The project stakeholders should select the preferred scope option; the project then progresses to the BOD phase.

In the BOD phase, additional engineering work provides a more developed SOW. The BOD design package contains Issued for Design (IFD) documents; it is the basis for the detailed design phase which delivers Issued for Construction (IFC) documents.

5.2.1 Importance of Good Engineering Practice

During the design process, it is important to follow GEP to support the integrity of related data and documentation. DR activities include evaluating deliverables against engineering standards and business, operations, and quality requirements as well as identifying gaps and proposing required corrective actions. Documenting these activities using Good Documentation Practice concepts (as described in Chapter 13) supports the overall effort to ensure the system is suitable for the intended purpose.

5.2.2 Science and Risk-Based Approach to Design Reviews

A quality risk assessment of the manufacturing process (including the environmental conditions supporting the process and/or critical systems) is a significant activity outside of the C&Q scope that can influence the early phase of design. Design stage System Risk Assessment typically uses knowledge from process risk assessments and other process knowledge to evaluate system design with respect to process control failure modes. These assessments are an integral part of the science and risk-based C&Q approach.

Design stage quality risk reviews are an iterative process that is linked to the design development of the process system. The review of the System Risk Assessments and how the results affect the proposed design should be included in the scope of DRs.

5.3 Design Review

5.3.1 Objectives of Design Review

DRs are defined in ASTM E2500-13 [5] as follows:

“Planned and systematic reviews of specifications, design, and design development and continuous improvement changes performed as appropriate throughout the life-cycle of the manufacturing system. Design reviews evaluate deliverables against standards and requirements, identify problems, and propose required corrective actions.”

DRs include both quality critical and non-critical aspects of the system design.

The documented results of the DR should be the basis for any design modifications/additions performed to correct any deficiencies in the design under review.

5.3.2 Role of Subject Matter Experts and Quality Unit

Throughout the design process, a cross-functional project team (refer to Section 6.4 for example approval matrix) reviews the design of the system to ensure that the product and process user requirements, GMP, and regulatory requirements are included. Thus, it is important that this team includes technical SMEs that have the appropriate experience and correct knowledge of the process, process equipment, control strategies, and facilities to ensure that the design under review will meet the requirements of the URS, function efficiently, and consistently produce quality product.

If the system being reviewed is direct impact, then the team should also include a Quality Unit representative to ensure that all quality requirements are met. This can help to facilitate the review and approval of the DQ.

5.3.3 Design Review Process

Prior to the DR, design documents should be circulated to the DR project team for their review to ensure a comprehensive review process. It is the responsibility of the project manager and the design leads to ensure that the appropriate participants are part of the DR. Senior management from the Quality Unit, operations, and production are responsible for ensuring the proper representatives with the appropriate experience are present during the DR.

The project team should define the method for conducting DR according to the system type, size, and risk. This method should be documented and approved in applicable plans (e.g., Project Execution Plan, C&Q Plan).

The effort, formality, and documentation of DRs should follow the ICH Q9 [3] principles of being commensurate with the level of risk. DR documentation may take the form of engineering meeting minutes or notes. For highly critical novel systems, DRs may be more focused and detailed.

For off-the-shelf equipment, DR should consider the complexity and/or risk to system or facility operation and to quality. Vendor documents are typically used to conduct these reviews and, if necessary, a technical vendor representative could attend the DR. The focus should be on the CPPs controlled by the equipment and the CAs/CDEs required for the product.

DRs focus on both engineering design and quality aspects of the design.

The engineering design focus is the technical aspects of the system; the objective is to verify the operability, maintainability, and safety aspects of the system. Technical SMEs, system owners, and any other stakeholders need to be present. It is optional for the Quality Unit to attend these reviews that focus on the technical aspects; however, their presence is beneficial and can simplify the DQ step.

The quality focus of the DRs is on compliance elements and the CAs/CDEs of the system design that affect product quality; the objective is to verify that all regulatory requirements are addressed by the design. It is strongly recommended the Quality Unit attends these reviews with quality focus, and that these reviews are documented.

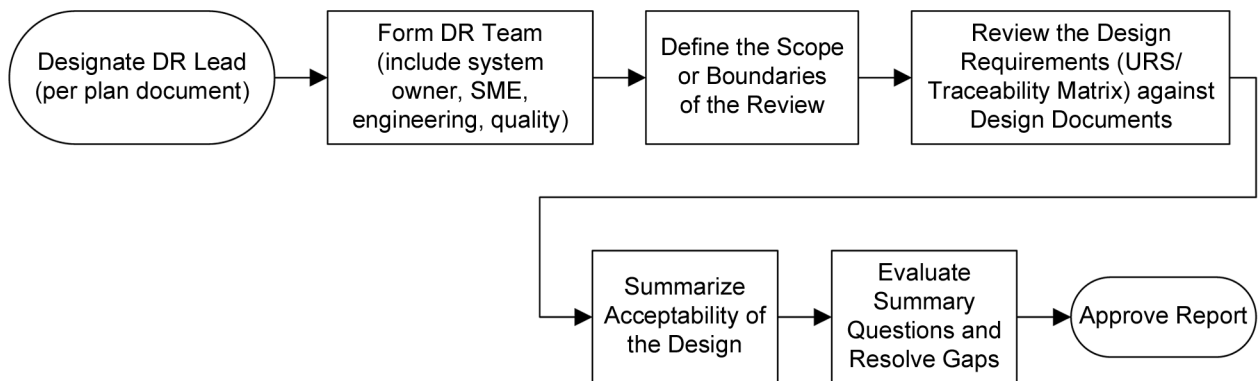
5.3.4 Design Review Outcome

The DR project team should have appropriate methods for recording and distributing the results of the DRs and managing any consequent changes. The results should confirm the continuing suitability of the design and confirm that the design is suitable for the intended purpose.

The team is responsible for communicating to their management any issues affecting design.

Figure 5.1 provides an overview of the DR process.

Figure 5.1: Design Review Process Flow



Note for Figure 5.1: The Traceability Matrix is a document format which compares the product and process requirements for the system with the CAs/CDEs.

Refer to Chapter 20 (Appendix 6) for examples of DR reports.

5.4 Design Qualification

5.4.1 Objectives of Design Qualification

DQ provides documented verification that the design of a new or modified direct impact system will result in a system that is suitable for the intended purpose. The objectives of DQ are to:

- Verify the design will meet the quality user requirements as listed in the URS
- Verify the design will adequately control risks to product quality and patient safety, as identified during the System Risk Assessment
- Verify the CAs/CDEs necessary to implement these requirements and risk controls

5.4.2 Prerequisites

The prerequisites for DQ include:

- Approved URS
- Functional requirements (for automated systems)
- System Risk Assessments with identification of design (CAs/CDEs) and procedural controls that will be used to mitigate the unacceptable risks
- Completed DRs, with verification that all open design issues that affect CAs/CDEs, CPPs, and CQAs are closed and included in the final design

It is the responsibility of the project manager to ensure that all prerequisites have been completed and are made available to the participants prior to the DQ for their review. The DQ should be scheduled to allow adequate time for preliminary review of the material to be covered.

5.4.3 Design Qualification Process

DQ is the documented process for the review and approval of the final system design to verify the following:

- All process and product requirements in the system URS have been incorporated into the design
- Quality and regulatory requirements in the system URS have been incorporated into the design
- Any changes to the design approach for the CAs and any associated CDEs have been reviewed, as appropriate

The DR documentation should be reviewed to confirm the Quality Unit was included in the DR, as defined in the project plan, and has provided the appropriate input to the design.

The approach for performing DQ should be defined in planning documents. For small projects, there may be one DQ performed after all the design is completed. For larger projects, the design may be broken into several areas or functions, with the DQ performed when each design is completed.

A formal protocol document to check requirements against the design is not a regulatory requirement. However, the following information should be defined: plan for conducting the DQ, scope of the DQ, and Quality Unit approval of the DQ. This information could be documented for individual systems or for specified integrated systems.

A Traceability Matrix can be used to document traceability of the CAs and any associated CDEs, and CPPs to the CQAs. The CA and CDE acceptance criteria can also be documented in the Traceability Matrix.

5.4.4 Final Design Qualification Report

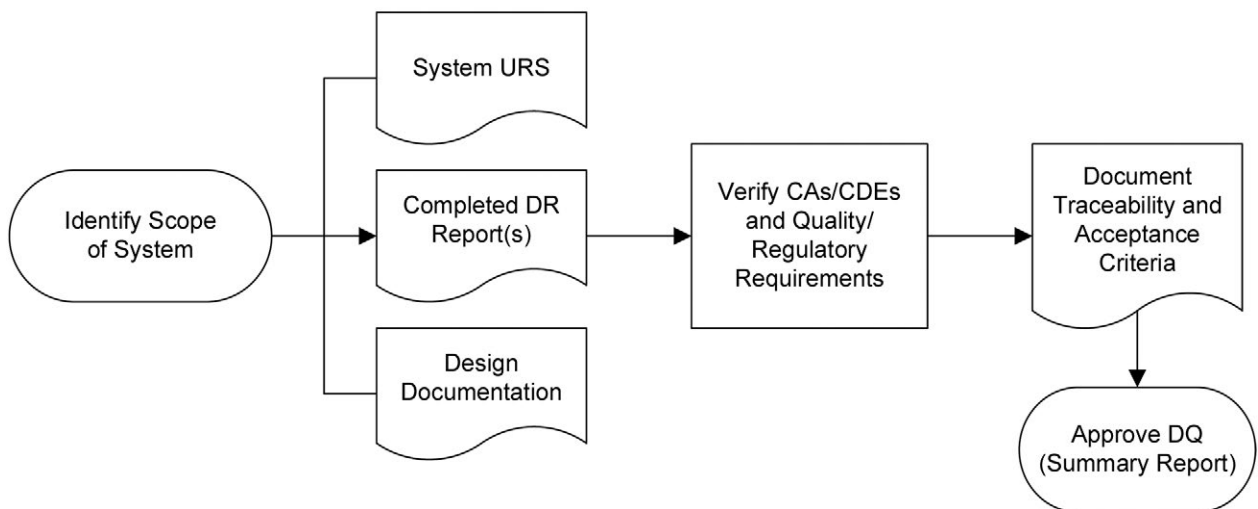
The final DQ report should include or refer to the following, as applicable:

- Any needed risk reviews to document the incorporation of design control elements to support quality product manufacturing
- Identification of each CDE (critical aspect of the physical and functional design) that serves to control identified potential process failures
- Description of each CA and any supporting CDEs in terms that are verifiable through inspections or testing (acceptance criteria)
- The CDEs that serve to meet a product or process user requirement in terms that are verifiable (mainly through performance testing)

A final DQ report should be issued stating the design is suitable for the intended purpose; the report should be approved by representatives (from the appropriate level) in Engineering, Manufacturing and the Quality Unit.

Figure 5.2 provides an overview of the DQ process.

Figure 5.2: Design Qualification Process Flow



Refer to Chapter 20 (Appendix 6) for an example of a DQ summary.

5.5 Timing of Design Review and Design Qualification

The DR is performed during development of the concept and BOD packages and near the completion of detailed design. These design packages should be reviewed to ensure all action items from the DR are included. These actions include business, Quality, and HSE related items.

DR of the construction specifications and drawings continues into detailed design. These reviews may be done at design meetings or off-line with the appropriate SMEs; the end-users would provide comments during approval drawings review. The DQ is completed upon the completion of DR of the final detailed design.

For small projects, these steps can be combined into one of two project steps with a limited amount of DRs and one DQ.

Table 5.1 lists the typical project phases and primary documents that should be available from each phase to support the DR process.

Table 5.1: Project Phases and Associated Deliverables That Support Design Review

Project Initiation	Concept Phase	Basis of Design (BOD) Phase	Detailed Design Phase
• Business objectives • High-level process and quality requirements • Key project assumptions • High-level project risk assessment	• Detailed process and quality requirements • Design options that include quality based on system classification, regulatory, HSE items, cleaning philosophy, and facility layout and flows • Concept design drawings • Updated project risk and key assumptions • Process risk assessment	• BOD level SOW selected option that include quality based on System Risk Assessment, regulatory, HSE items, cleaning philosophy and facility layout and flows • DRs • IFD P&IDs and other design drawings • Equipment and instrumentation specifications • Risk review • Revised cost and schedules • Updated project risk and key assumptions	• Construction drawings and specifications • IFC P&IDs • Risk review

6 C&Q Planning

6.1 Introduction

C&Q is a planned, documented, and managed engineering activity that starts with the establishment of the URS and continues to start-up and acceptance and release of systems. A well-planned program is essential and leads to an efficient, “right the first time”, and cost-effective C&Q effort; the result is the delivery of systems that operate in a safe manner, meet established design requirements and stakeholder expectations, and are suitable for the intended purpose. Planning provides the ties between process understanding and system design; it focuses qualification efforts to enhance the likelihood that the system will deliver quality products while maintaining a controlled operating state. It also acts as a means for communication between members of the multidisciplinary project team.

This chapter focuses on the formal C&Q Plan. There are other plans that can be generated, such as overall project plans or cleanliness plans, which have great value but are not covered in this chapter. Refer to Chapter 21 (Appendix 7) for a listing of supporting plans and general concepts for each.

Regulatory expectations for C&Q planning are described in Chapter 15 (Appendix 1).

6.1.1 Purpose and Benefits

A well-conceived and executed C&Q Plan can greatly facilitate a timely and cost-effective qualification effort. It is essential to have excellent communication, planning, and coordination between the Quality Unit, vendors, operations, automation, engineering, construction, commissioning, and qualification personnel, to name a few, to deliver a project on time, within budget, and meeting all expectations. A C&Q plan facilitates this communication.

An important secondary goal of the C&Q Plan is to foster an interdisciplinary team approach to C&Q. Well-planned project logistics are crucial to the success of every project. A well-coordinated effort leads to a high quality, effective, and efficient C&Q project.

A single, integrated, overall schedule should be developed with input from the entire project team. This schedule should cover all systems (utilizing defined system boundaries as discussed in Section 3.2) and phases of the projects lifecycle from construction to Process Validation/PPQ completion. This schedule should be updated and issued regularly. These updates should not drive a C&Q Plan revision, but the C&Q Plan should identify how the schedule updates will be captured and communicated.

An integrated schedule, using a critical path method, can increase the awareness of dependent activities and provide a clear understanding of the critical path. Including all project team members in the schedule development will engage the team members and foster better planning. All team members should comprehend the schedule format. Ordering long delivery time items early can help timelines, but consideration should be made to ensure the process requirements for those items are understood and included in the requisition. Understanding when to engage support for C&Q helps to support the success of the project.

A well-planned effort can ensure that the user, business, regulatory, and patient expectations are met. All efforts to ensure the system is suitable for the intended purpose (e.g., start-up, balancing, trial runs, establishing maintenance programs) should be included in the planning phase since this is where the formality of the documentation can be established. These expectations include:

- Systems are delivered on time and within budget
- Systems meet approved user requirements and are suitable for the intended purpose
- Stakeholder needs, including speed to market, are met

- Products produced from the systems meet defined quality standards

6.2 C&Q Planning Approach

The amount of planning, documentation, reporting, and level of detail of the C&Q Plan should be based on expectations of the organization/site, size and complexity of the system or project, and the potential impact on product quality and patient safety.

A C&Q Plan should not repeat details that are in other documents but needs to capture the organization of those documents in order to facilitate an efficient project execution.

A separate C&Q Plan is not always necessary. Aspects of C&Q planning can be included with other documents, such as a validation plan or change control. For example, the simple change of adding a small system would not need a separate C&Q Plan; the requirements could be incorporated into a change control plan. More complex systems would benefit from a separate C&Q Plan, for example, the installation of a filling line with terminal sterilization and secondary packaging or the doubling in capacity of a manufacturing site including additional utilities to support the expansion.

6.2.1 *Timing of C&Q Plan*

In an overall scheme, the creation of the C&Q Plan falls in the process map as shown in Figure 1.1 (Chapter 1).

It is important to note that C&Q planning begins prior to the creation of any formal written plans. C&Q planning starts during the planning and design phase of a project and continues through project implementation. A documented strategy may be developed as a precursor to a C&Q Plan, to help align team members with the process and personnel who will be responsible for C&Q.

A C&Q Plan should begin early in a project in the concept or early basic engineering phase.

The C&Q Plan needs to be approved before the respective testing documents (i.e., test instructions) are approved, and such test instructions need to be approved before test execution starts to support qualification. This is recommended for commissioning plans and test instructions. The C&Q Plan should address how existing test documentation and test results from commissioning (including FAT, SAT, etc.) are referenced in qualification documents, as appropriate.

6.2.2 *Lifecycle of C&Q Plan*

The C&Q Plan is not finalized until after the risk management process has reached a point to capture the impact of product quality decisions or of establishing the CDEs.

C&Q Plans are expected to be kept up-to-date as changes to the project are made. Revisions of the C&Q Plan may be necessary as new information is learned or as modifications to the design are made, e.g., changes in scope (additions or removals), timing, or identification of additional CAs/CDEs.

Approval is recommended for these early plans and for subsequent changes made by the revision process; this ensures agreement at various stages of the C&Q approach. Changes to the C&Q Plan should be reviewed and approved by the original approvers (or their designate) and a revision history should be maintained of significant changes to the Plan.

It should be noted that revisions may not always be necessary. Minor departures from the C&Q Plan may be documented in the Qualification Summary Report with appropriate justification and rationale, as deemed appropriate by the project team.

At the end of a project, a written document capturing the completion and closure of the project should be created. See Chapter 8 for more details regarding acceptance and release.

Changes to the C&Q Plan should be handled under change management (as discussed in Chapter 12) to ensure that as changes are implemented, the impact to C&Q efforts is addressed.

6.2.3 Elements to be Addressed

This section is intended to be a discussion of the elements that need to be addressed as part of C&Q planning, not the documents where they are captured.

6.2.3.1 Scope of Testing

System classification (as described in Chapter 3) identifies which systems require qualification. The System Risk Assessment (as described in Chapter 4) identifies which elements in those systems require qualification. The URS (as described in Chapter 2) and System Risk Assessment establish the scope of testing for qualification. The equipment specifications establish the scope of testing for commissioning.

The testing approach is based on the most efficient method to test the system and should be captured in the C&Q Plan. If systems are tested separately, the C&Q Plan should include a final test verifying that all systems are able to work together prior to acceptance and release. If PPQ is included in a separate plan, the linkage to the execution of that critical phase should be captured.

6.2.3.2 Identification of Document Source

Engineering firms, vendors, contractors, quality, engineering, and owners provide the documentation necessary for design, construction, commissioning, qualification, operation, and technical support of the systems. It is important to identify the documentation source early in the process so the impact on the testing of the system is understood and thus the quality of the documentation understood. This understanding will allow for utilization of the documentation to support qualification.

For example, the decision should be made during planning if any FAT, construction, SAT, or commissioning testing results and documentation will be used to satisfy the requirements to declare the system qualified or suitable for the intended purpose. This decision is based on vendor assessments for C&Q documentation purposes (as described in Chapter 10) and the criticality of the testing. It is often desirable to minimize the amount of retesting performed.

The C&Q Plan may also address the expectations of the documentation. It should be noted that pristine documentation, i.e., documentation that has minimal errors or corrections, is not essential but the documentation needs to be easy to follow and understand. Refer to Chapter 13 for guidance on Good Documentation Practice.

6.2.3.3 Coordination with Overall Project Execution Plan

Another important aspect is working with the project manager to ensure that the planning of C&Q activities, whether a separate plan or part of another plan, fits seamlessly into the overall Project Execution Plan. C&Q activities should be properly reflected in the Project Execution Plan at an appropriate level of detail to be able to identify interdependencies between C&Q as well as to other project activities. Commissioning is normally occurring throughout construction and needs to occur when it is appropriate; e.g., commissioning the agitation system cannot be completed until it is energized.

Having these activities in the Project Execution Plan supports:

- Coordination of test activities among C&Q to prepare for FAT or SAT events
- Ability to schedule sequence of testing for multiple systems (e.g., electrical supply before energizing a system)

- Schedule review cycles for qualification documents with Quality Unit representatives

6.3 C&Q Plan

The C&Q Plan typically encompasses:

- Description of the scope of the plan (identification of the systems included)
- Description of the C&Q execution strategy
- C&Q related documentation requirements for each identified system (e.g., URS, FAT, SAT, Installation/Operational Testing, PQ, SOPs, etc.)
- Roles and responsibilities, e.g., approval matrix (see Section 6.4 for example)
- Reference necessary C&Q document templates (e.g., test instructions, test scripts, reports, discrepancy form)
- Planned inspections and tests
 - Documentation requirements for the inspection and test results
 - Reference procedures for inspections and tests to be performed (as much as possible at this early stage in the project)
 - Identification of SMEs for review of the inspection and test results
 - For tests to be used to support qualification, include the acceptance criteria to be met for all CDEs (**Note:** The plan may defer to individual test instructions)

The specific structure and content of the C&Q Plan is typically driven by organization/site requirements.

6.3.1 Scope of the Effort

The scope captures all systems that are covered within the scope of the project. This includes both direct impact and not direct impact systems (as described in Chapter 3). More details are provided below.

6.3.1.1 Additional Scope Considerations

PQ activities may be included in a C&Q Plan for pharmaceutical grade utilities (e.g., WFI, Purified Water), support systems (e.g., autoclaves, depyrogenation ovens, washers), environments (e.g., non-environmental monitoring in clean rooms), and non-product PQ (e.g., media fills for filling lines). Individual organizations/sites need to decide if these are in qualification or a separate validation program.

Cycle development for areas such as sterilization and cleaning also need to be considered. Cycle development can identify factors that require qualification or that modify the qualification. These are often executed after the equipment qualification effort. It is recommended to not perform the final qualification testing until after cycle development since changes identified by cycle development can be captured in the Engineering Change Management system (see Chapter 12). Individual organizations/sites need to decide if cycle development is part of the C&Q effort and capture the decision in the C&Q Plan.

6.3.2 Strategy and Approach

The C&Q Plan needs to define C&Q strategy and approach to aid in overall project planning. The C&Q Plan captures whether systems will be commissioned only or commissioned and qualified. The system classification (as described in Chapter 3) and System Risk Assessment (as described in Chapter 4) have identified the CPPs and CDEs that need to be supported by the C&Q effort.

The rigor of testing depends on the user requirements, CDEs, and system characteristics (e.g., packaged system, modular, or installed system) as well as experiences with the vendor.

An aspect that needs to be captured in the C&Q Plan is the identification of the documentation source that will be utilized to satisfy the C&Q requirements. Appropriate prerequisites, means, and checks should be described in the plan to ensure reliable results, e.g., the pre-approval of vendor/manufacture documents by an SME. If vendor-provided documentation or testing is to be accepted to support qualification, the criteria for determining if it can be utilized needs to be established in the Plan. Refer to Chapter 10 for details regarding vendor assessments for C&Q documentation purposes.

The C&Q Plan should also capture if individual pieces of equipment or systems will be tested separately because they are delivered and installed at different times by different vendors or if testing will be executed once all components are installed. Dependencies within the scope of work (e.g., if one system needs to be tested before another system is tested) should also be included.

6.3.3 Documentation

The C&Q Plan should capture document planning and control as well as execution of testing. The C&Q Plan should reference appropriate document control and content procedures to satisfy engineering, commissioning, qualification, operations, and maintenance requirements. Utilizing electronic storage of documents is recommended as it allows for searching and easier retrieval. If electronic storage will be utilized, ensure the vendors and contracting companies are aware and can support the delivery of their documentation in that means.

The Plan should define responsibilities for document preparation, collection, review and approval, and how the documents will be organized. This Guide recommends that a document matrix be considered as a means of planning and communicating these responsibilities. Documents also need to be tracked to ensure they are completed when they are needed.

Documents that are typically tracked include:

- URS
- System Risk Assessments
- Drawings
- Equipment specifications including any automation specifications (e.g., functional specifications)
- Vendor correspondence and transmittals
- Requests for information
- Submittals (e.g., shop drawings, manufacturers data sheets, user manuals)
- Required procedures (e.g., equipment operating procedures, maintenance)
- Change management (see Chapter 12)

- Schedules
- Open items/punch list
- Commissioning/qualification execution documents
- Discrepancies
- Turnover packages
- Project reports

6.3.4 C&Q Plan Contents

The C&Q Plan should define the systems that will be commissioned and qualified based on the system or area boundaries. The plan should include a description of systems including their means of automation. The system overview should be a high-level process narrative, including system boundaries, based on operational/functional requirements. The C&Q team representatives should provide input in defining system boundaries (which can be in a system description, marked on P&IDs, or highlighted on system drawings) in the early project phases to develop an executable plan. It is often possible to gather much of the system overview information from other project documentation.

The C&Q Plan should address the level of testing for each system. This may range from detailed descriptions to references to standard tests. An alternative is to provide only high-level descriptions in the C&Q Plan and leave the detailed descriptions to execution documents. The selected approach should increase the level of efficiency and effectiveness. The plan should also include project schedules by system (as defined by the system boundaries) that capture the dependencies between systems (i.e., ones that need to be completed before completing others).

Commissioning is an important aspect that requires planning, documentation, and managed resources. Commissioning encompasses testing from FAT, testing during construction, SAT, installation testing, and much of the start-up activities (described in Section 7.3) of a project lifecycle including those that will be used to assess the qualification of a direct impact system. The C&Q Plan should also establish the framework necessary to ensure clear consistent communication and coordination required between predecessor and successor lifecycle activities (e.g., construction, C&Q, Process Validation, operations/maintenance).

Testing during commissioning should be used to support qualification. If commissioning documentation will be used to support qualification, it is critical to involve the leader of the qualification effort and the Quality Unit in the planning and coordination of commissioning activities and deliverables. A periodic commissioning planning and status meeting should be established to ensure appropriate planning for this stage of the project.

The C&Q Plan needs to include C&Q steps. There are two typical phases:

- Installation: Documentation supporting installation is successfully completed. This may include FAT and SAT documentation as well as site commissioning for systems built at the site.
- Operational: Documentation supporting the functionality and performance of the system after the system has been mechanically completed. This may include testing performed in FAT and SAT.

The plan should address the steps to follow when test results do not meet the expected results or acceptance criteria (discrepancy). There should be a predefined methodology for how discrepancies should be handled (see Section 7.4).

6.4 Example Approval Matrix

Table 6.1: Example Approval Matrix

Document	Pre-Approvers			Post-Approvers			Typical Document Preparation	Guide Chapter Reference
	Quality Unit	Production User	Technical	Quality Unit	Production User	Technical		
C&Q Plan	Not applicable			A	A	A ¹	Technical	Chapter 6
User Requirements Specification (URS)	Not applicable			A ²	A	A ¹	Technical	Chapter 2
System Classification	Not applicable			A	A	A ¹	Technical	Chapter 3
System Risk Assessment	Not applicable			A	A	A ¹	Quality Unit ³	Chapter 4
Design Review (DR)	Not applicable				A	A ¹	Technical	Chapter 5
Design Qualification (DQ)	Not applicable			A	A	A ¹	Quality Unit ³	Chapter 5
Commissioning inspection/testing documentation (e.g., FAT, SAT)		A	A ¹		A	A ¹	Technical	Chapter 7
Qualification testing documentation where used ⁴	A	A	A ¹	A	A	A ¹	Quality Unit ³	Chapter 7
Turnover Package	Not applicable				A	A ¹	Technical	Chapter 7
Commissioning Acceptance and Release Report	Not applicable				A	A ¹	Technical	Chapter 8
Qualification Acceptance and Release Report (including testing from commissioning)	Not applicable			A	A	A ¹	Quality Unit ³	Chapter 8
Traceability Matrix	Not applicable			Not applicable			Technical	Chapter 8
Vendor Assessment (when vendor documentation utilized for C&Q)	Not applicable			A		A ¹	Technical	Chapter 10
General Note: A = Approver								
Notes:								
1. Technical includes Engineering, Process, and SME. SME may be Engineering, Automation, Validation, Research and Development, Safety, or Manufacturing Technical Lead; therefore, a second signature is not required from the same discipline.								
2. If the Quality Unit has already approved the source documents from which the quality requirements within the URS were obtained, then the Quality Unit does not need to approve the URS. Quality approval is not required for systems that are not direct impact systems (e.g., boilers).								
3. In many cases, the responsibility for developing the document is given to Technical or Validation.								
4. If IQ and OQ test protocols are required by the organization/site policy, many organizations also require that these protocols are pre and post-approved by the Quality Unit.								

