

Commissioning and Qualification

The image is a composite. The left side features a detailed flowchart of a medical device design and testing process. The flowchart includes boxes for 'User Requirements Specification', 'System Risk Assessment', 'Design Review/Design Qualification', 'Commissioning/Testing', 'Acceptance and Release Report', 'Next V St Op', 'Verify CAs/CDEs and Quality/Regulatory Requirements', 'Document Traceability and Acceptance Criteria', and 'Approve DQ (Summary Report)'. It also lists inputs like 'Vendor Documents', 'Good Engineering Practices', and 'Change Management'. A dashed line labeled 'Traceability' connects 'User Requirements Specification' to 'Commissioning/Testing'. A large oval encircles 'User Requirements Specification' and 'System Risk Assessment'. The right side of the image shows a photograph of a person in a light blue cleanroom suit and cap, interacting with a large industrial machine with a screen. The background is a clean, white environment.

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VOLUME 5

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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Company affiliations are as of the final draft of the Guide.

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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])

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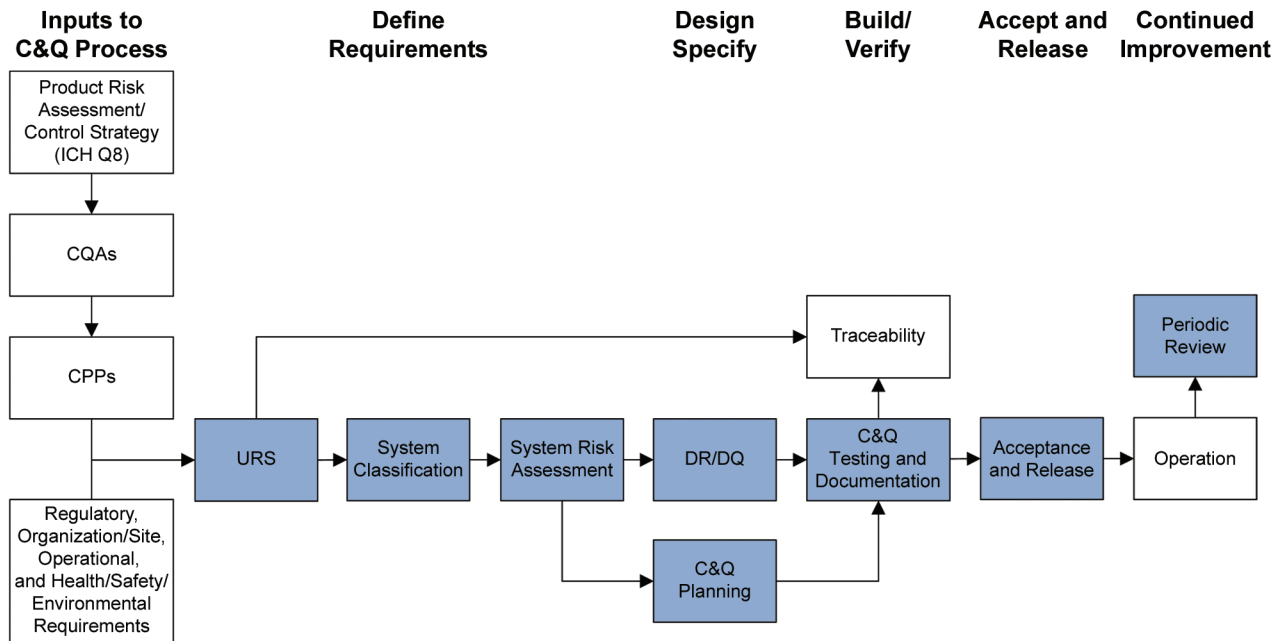
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1.4 Process Overview and Structure of the Guide

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)

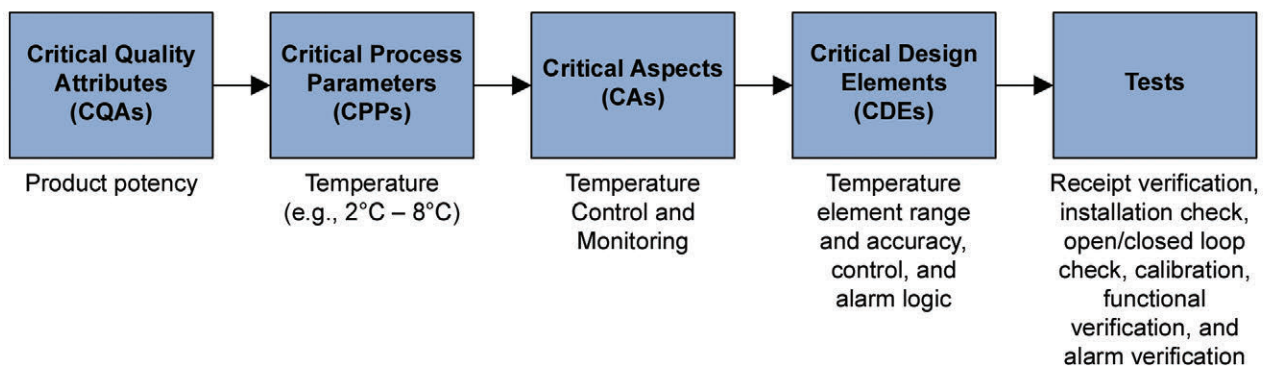
The process begins with the development of the URS (Chapter 2). This includes defining the product quality related user requirements that must be met for a system to be suitable for the intended purpose.

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.