



Good Practice Guide

Applied Risk Management for Commissioning and Qualification

Arc of Acceptable Approaches

Traditional IQ/OQ
(ISPE Baseline Guide: Volume 5)

Good Practice Guide

Risk-Based Verification
(ASTM E2500-07, ISPE FSE Guide)

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Good Practice Guide

Applied Risk Management for Commissioning and Qualification

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Preface

The global pharmaceutical industry and regulators are responding to the challenge of significantly improving the way drug development and manufacturing is managed. New concepts are being developed and applied including science- and risk-based management approaches, a focus on product and process understanding, and the application of Quality by Design concepts.

The international regulatory community has outlined their position on these new “Science- and Risk-Based Approaches” concepts in the ICH Q8, Q9, and Q10 quality guidelines, where guidance is given on applying these concepts across the entire drug life cycle.

This Good Practice Guide provides direction to industry on the practical application of these “Science- and Risk-Based Approaches” for the commissioning and qualification activities related to the manufacturing of medicinal drug products undertaken to support the process validation phase of the product life cycle. This Guide aims to provide practical guidance on how to successfully implement the principles of ICH Q8, Q9, and Q10 with respect to commissioning and qualifying GMP equipment, systems, facilities, and the manufacturing processes they support, and how to demonstrate that they are *suitable for their intended use*.

Uncertainty about the requirements for regulatory compliance may drive up costs, and discourage innovation and technological advancement. Neither of these outcomes benefits public health. ISPE Good Practice Guides describe current good practices with the aim of providing an approach that is effective, cost-efficient, and in compliance with existing regulations and related guidance.

The Guides are solely created and owned by ISPE. They are not regulations, standards, or regulatory guideline documents, and facilities built in conformance with the Guides may or may not meet FDA or other global regulatory requirements.

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1 Introduction

Pharmaceutical global regulatory agencies usually have long-standing GMP requirements which require facilities, systems, and equipment used in pharmaceutical manufacturing to be verified as **“suitable for their intended use.”** In the decade 2001-2011, the pharmaceutical industry, in conjunction with a number of global regulatory agencies, has initiated a strategy determined to focus on “risk-based” pharmaceutical manufacture.

Guidance on the Quality Risk Management principles set out in ICH Q9 (Reference 1, Appendix 5), the use of science- and risk-based approaches to establish suitability for intended use involves:

- the systematic identification of risks to product quality and patient safety
- the verified or validated control of these risks
- the application of science and engineering based control measures and strategies for conducting the verification or validation activities

This Guide is intended to facilitate the application of the science of Quality Risk Management (QRM) to the Commissioning and Qualification (C&Q) practices used within the pharmaceutical industry. It also is intended to provide the means to undertake a stepwise transition from the traditional Commissioning and Qualification (C&Q) practices to science- and risk-based approaches.

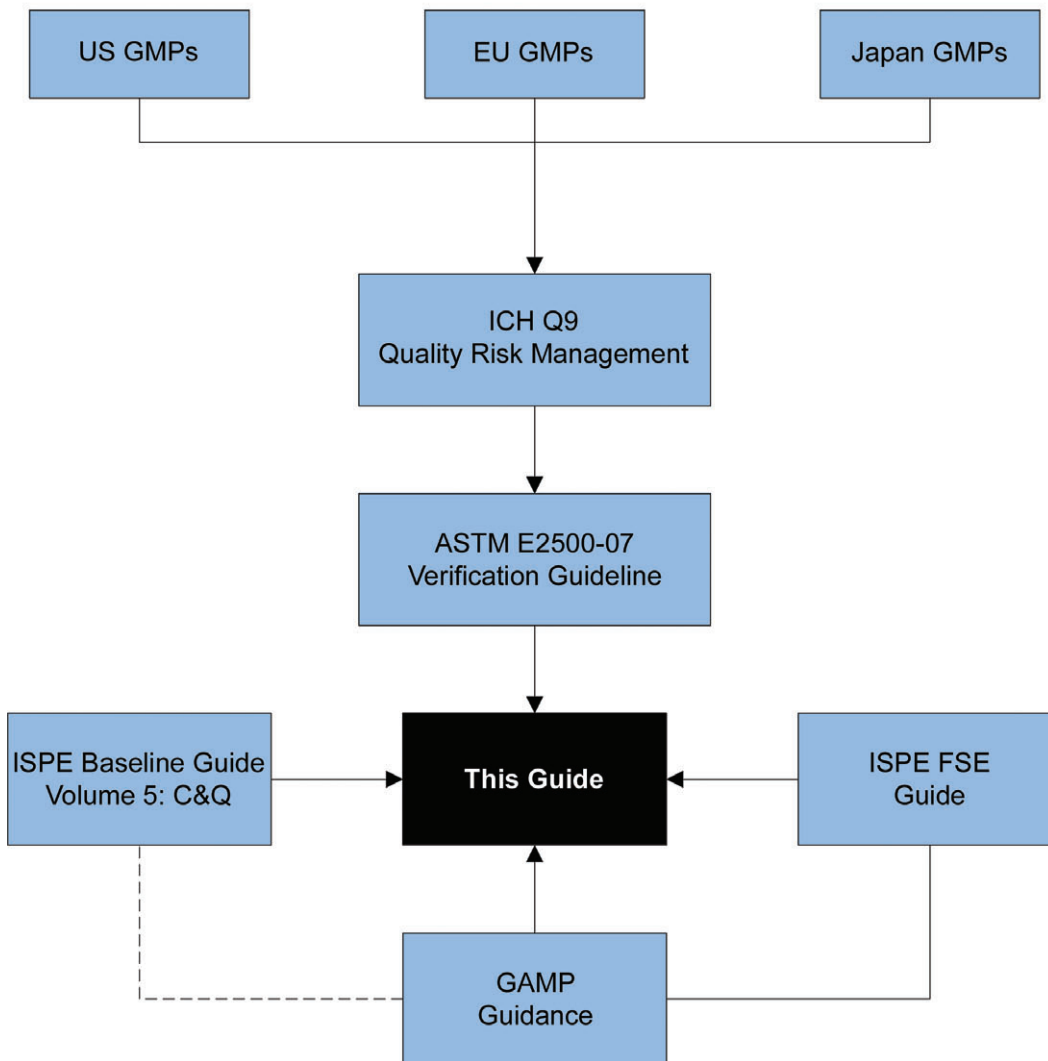
1.1 Background

A number of key publications form the basis for conducting science- and risk-based commissioning and qualification approaches and, therefore, also form the basis for this Guide. These include:

- ICH Q9, “Quality Risk Management”(2006) (Reference 1, Appendix 5)
- US FDA Guidance for Industry, “Process Validation: Principles and Practices” (2011) (Reference 2, Appendix 5)
- ASTM E2500-07 “Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Systems and Equipment” (2007) (Reference 3, Appendix 5)
- ISPE Baseline® Guide: Volume 5 – Commissioning and Qualification (2001) (Reference 4, Appendix 5)
- ISPE Guide: Science and Risk-Based Approach for the Delivery of Facilities, Systems, and Equipment (2011) (Reference 5, Appendix 5) [**Note:** The abbreviation “ISPE FSE Guide” will be used for later references to this Guide.]

This Guide builds on the concepts and principles of these documents as well as applicable GxP regulations, laws, and codes.

Figure 1.1 illustrates the relationship of this Guide to GMP regulations, ICH, and other ISPE guidance.

Figure 1.1: Relationship of This Guide to GMP, ICH, and ISPE Documents

Note: GAMP Guidance has typically been used to support the C&Q activities associated with Computerized/Automated Systems.

1.2 Purpose and Objectives

The purpose of this Guide is to facilitate the transition from traditional commissioning and qualification practices to science- and risk-based approaches, e.g., those outlined within ICH Q8(R2), Q9, and Q10 (References 1, 6, and 7, Appendix 5).

This Guide describes a number of strategies that organizations may follow in developing or revising their Quality Management Systems (QMSs) and work processes associated with commissioning and qualification of facilities, systems, and equipment to help accomplish this transition.

The primary objectives of this Guide are to:

- provide a “roadmap” for a range of transition strategies for organizations wishing to migrate from traditional practices towards science- and risk-based approaches

- link the traditional **qualification** practices and terminology (e.g., in ISPE Baseline® Guide Volume 5 (Reference 4, Appendix 5)) to the **verification** approaches and terminology, e.g., in the ISPE FSE Guide and ASTM E2500-07 (References 3 and 5, Appendix 5)
- describe practical methods for applying Quality Risk Management (QRM) to the specification, design, qualification, and life cycle management of pharmaceutical manufacturing equipment, systems, and facilities, while maintaining as much as possible an organization's existing Quality Management Systems and Qualification mechanisms in order to minimize the cost, time, and organizational impact of a transition to science- and risk-based approaches

1.3 Rationale for Transitional Strategies

There are a range of effective and compliant practices for demonstrating and documenting *suitability for intended use*. The application of **science- and risk-based approaches** is limited only by the extent of process and product knowledge within an organization and the ways in which this knowledge is utilized. It should not be limited by the document title or format used within that organization.

Traditional commissioning and qualification practices, represented for purposes of this Guide by the ISPE Baseline® Guide Volume 5 on Commissioning and Qualification (Reference 4, Appendix 5), do not incorporate Quality Risk Management principles focused on manufacturing processes and, therefore, will only be deemed acceptable when updated with science- and risk-based approaches.

Organizations may decide that the time and cost of converting Quality Systems and document architecture to adopt a pure verification approach is not justifiable. These organizations may require a transitional commissioning and qualification strategy which builds on their traditional practices and also addresses the science- and risk-based approaches. The decision will be based on a value assessment specific to each organization. The impact on life cycle costs for maintaining the qualified state (e.g., costs of maintenance, calibration, and change management) should be considered when making this decision. Figure 1.2 illustrates the intended role of this Good Practice Guide in “bridging” the transition.

Figure 1.2: The C&Q Good Practice Guide “Bridge” Concept



When evaluating the “distance” across this “bridge” that an organization wishes to travel, it is important to note the difference between:

1. adopting practices which are lean and efficient – which is optional
2. ensuring practices provide verification of acceptable control of product quality and patient safety – which is compulsory

Steps taken on the way across the “bridge” could be to:

- introduce Good Engineering Practices to support verification activities
- re-focus the role and responsibilities of the Quality Unit
- establish Quality Risk Management as the basis for scope and extent of verification activities
- structure verification documentation which is sufficiently flexible to be synchronized with the project progress rather than to rigidly dictate the project execution
- establish a project change management process appropriate to the level of impact during project execution
- introduce a Subject Matter Expert (SME) concept as a role to take responsibility in the respective area of expertise
- leverage verification results from different activities such as design reviews, commissioning, start up, qualification to support the **suitable for their intended use** evaluation

These steps are dependent on each other, but can be accomplished at different times. When evaluating the “distance” across the “bridge,” an organization may choose which step to take initially based on the individual benefit to effort ratio.

1.4 Scope

This Guide addresses those aspects of planning, specification, design, and delivery of facilities, utilities equipment, and associated automation necessary to qualify them as suitable for their intended use.

It is intended to cover pharmaceutical manufacturing (including drug substance, drug product, and biopharmaceuticals). It also may be applicable to medical device or blood product manufacturing systems and equipment.

This Guide is applicable to automation elements associated with equipment and system control, and is harmonized with and should be read in conjunction with GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems and the associated GAMP® Good Practice Guide: A Risk-Based Approach to GxP Process Control Systems (References 8 and 17, Appendix 5).

The activities described in this Guide address the facilities and systems qualification portion of the overall process validation life cycle (described as Stage 2a in the current FDA Process Validation Guideline (Reference 2, Appendix 5).

The principles contained within this Guide are applicable to the delivery of new commercial manufacturing capability. They also may be used during modifications to existing regulated manufacturing facilities. The use of this Guide for new or existing systems is at the discretion of the regulated company.

This Guide is not intended to address directly the provisions of process or product validation within the life cycle. Furthermore, this Guide does not cover product development activities. It should be acknowledged and understood that a solid process knowledge base, which typically originates in development, is necessary in order for any meaningful QRM activities to take place.

Also out of scope of this Guide are all other types of risk which are the responsibility of an organization to control, e.g., environmental, safety, business, non-GMP regulatory compliance.

1.5 Benefits

Patients benefit from the application of science- and risk-based approaches through a reduction of risk and improved real-world product quality. Pharmaceutical manufacturing organizations also can benefit from such programs through the opportunity to:

- significantly reduce costs/time when compared to traditional commissioning and qualification practices
- improve process knowledge as basis for subsequent operations and life cycle maintenance
- ensure focus is on quality-critical system features rather than diluting effort across all system features
- provide clarification of roles and responsibilities, with more efficient use of SMEs
- more consistent and reliable achievement of User Requirements
- improved alignment with post-ICH Q9 regulatory expectations

1.6 Key Concepts

The following key concepts are applied throughout this Guide:

- science-based Quality Risk Management
- product and process understanding as its basis
- focus on achieving suitability for intended use
- flexible approaches to risk assessment and qualification
- including only value-added activities
- appropriate and well defined roles and responsibilities that allow each professional discipline to contribute from their area of expertise, without being expected to compensate for the real or perceived deficiencies of another discipline

1.7 About This Guide

This Guide assumes a general familiarity with the terms and conventional definitions of traditional commissioning and qualification practices; specifically the mechanisms and terms used in the ISPE Baseline® Guide Volume 5 on Commissioning and Qualification (Reference 4, Appendix 5). Readers who may lack such familiarity are urged to consult available informational sources describing pharmaceutical industry commissioning and qualification practices, e.g.:

- EU GMP Guideline Annex 15 (Reference 9, Appendix 5)
- PIC/S PI006-3 – Validation Master Plan Installation and Operational Qualification Non-Sterile Process Validation Cleaning Validation (2007) (Reference 10, Appendix 5)
- relevant ISPE Publications (see Appendix 5)

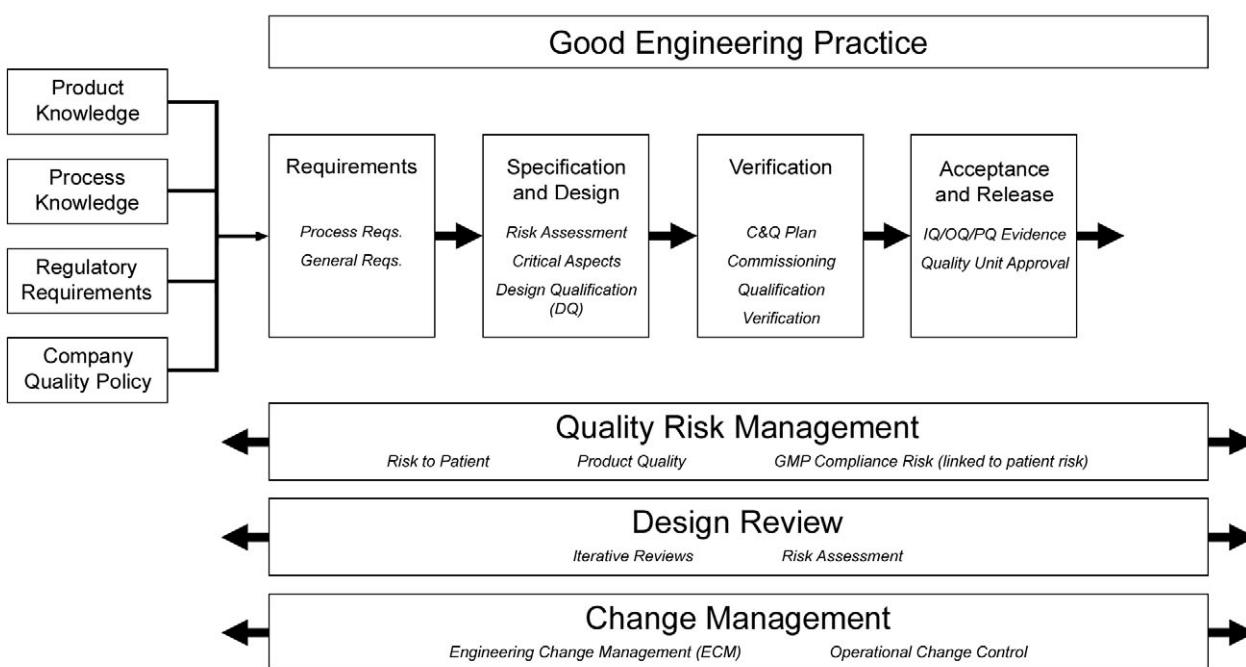
As a transitional or “bridge” document, this Guide deliberately uses the traditional terminology of commissioning and qualification, and generally retains the basic documentation mechanisms of Installation Qualification (IQ) and Operation Qualification (OQ) protocols and IQ/OQ summary reports. This Guide recommends the rigorous elimination of wasteful practices which have often surrounded development of such documentation.

2 Fundamentals of Applied Risk Management for Commissioning and Qualification

2.1 Introduction

This chapter describes the fundamental elements and requirements of applied risk management for commissioning and qualification. The key stages of such a program are depicted in Figure 2.1, referenced from the ASTM E2500-07 (Reference 3, Appendix 5) standard, supplemented with the italicized text indicating fundamental topics related to each stage which are addressed within this Guide:

Figure 2.1: ASTM E2500-07 Process Flow with Concepts from This Guide



2.2 Applied Risk Management for C&Q Process Overview and Prerequisites

The basic process for Applied Risk Management for C&Q described in this Guide can be summarized as a well managed engineering approach (run by SMEs) using Good Engineering Practice (GEP) combined with Quality Unit involvement and approval at agreed strategic points.

There are several pre-requisites necessary for an effective and efficient program for the application of QRM to C&Q, including:

1. **Process Knowledge:** Sufficient science-based understanding and knowledge of the processes to be supported by the systems in question, either through development data as described by ICH Q8 (for new products) or through documented experience regarding the manufacturing process, quality history, and respective requirements (for legacy products).
2. **Quality Risk Management Knowledge:** An experienced or preferably expert level of understanding of QRM principles and the tools to be utilized within the project team.

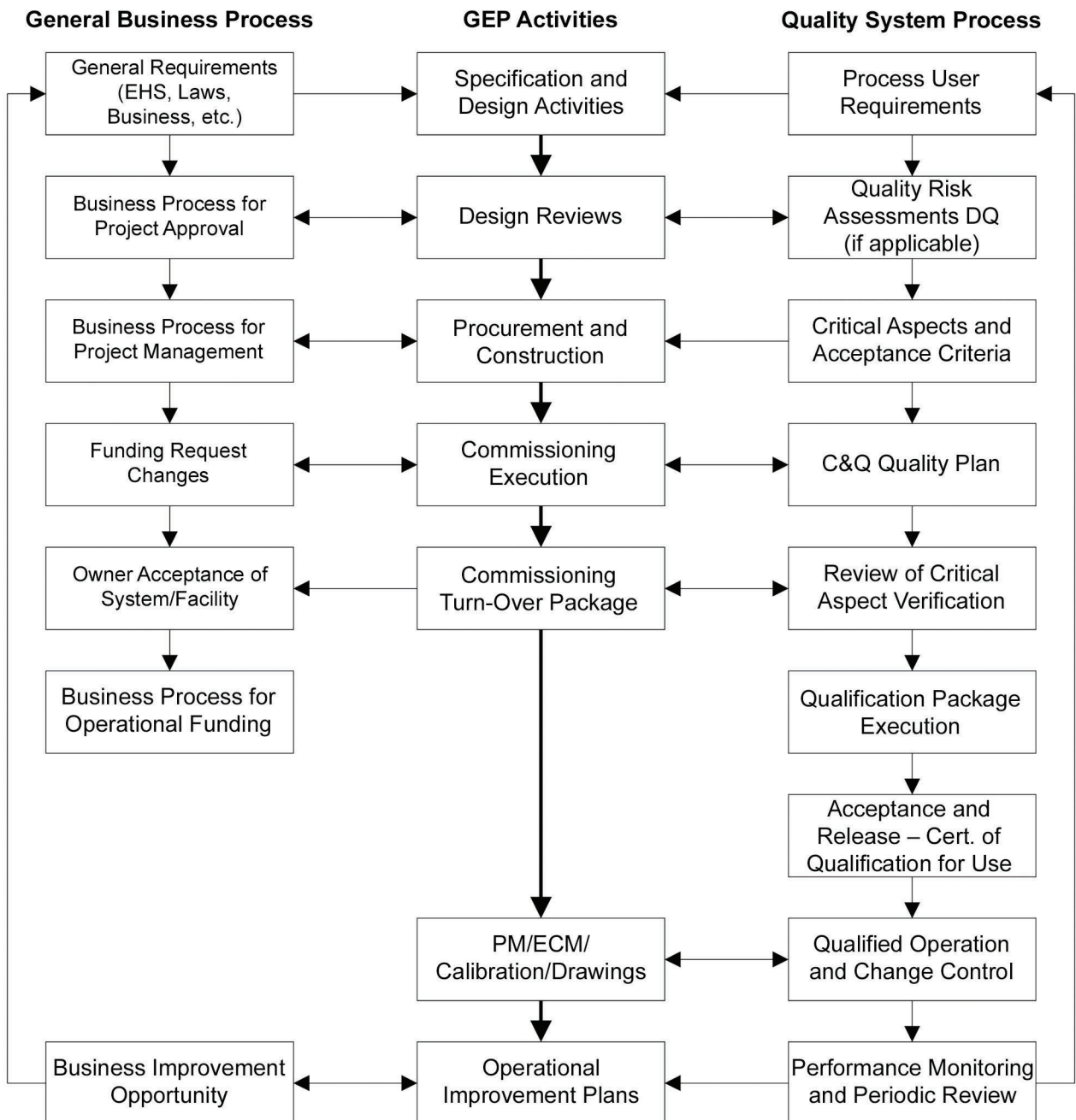
3. **Good Engineering Practices and Engineering Quality Systems:** An Engineering unit or function capable of and committed to following GEPs as described in this and other GPGs, as well as adequate standards and supporting systems (e.g., third party management procedures, Engineering Change Management (ECM), calibration, engineering documentation control).
4. **Quality Unit Understanding:** A Quality Unit with appropriate and well defined roles that understands and accepts the contribution of and necessity for GEP based documentation and practices, and is committed to both risk-based and value-added approaches.
5. **Management Support and Direction:** Funding and management commitment to provide adequate project resources, including approving project schedules which allow for the execution of critical activities and promote the participation and commitment of necessary SMEs.
6. **Documentation Concept:** The final outputs of verification (commissioning, qualification, etc.) are the evaluation of the testing results for a system confirming the “qualified state.” This includes the documentation which provides insight into test planning, execution, reporting, and as-built conditions. The level of documentation varies with the verification approach applied and should be commensurate with the level of impact on product quality and patient safety. The documentation concept should allow for flexibility in the verification process so that it can be synchronized with the project progress and should not delay the project due to unnecessary procedural requirements.

A key premise of this Guide is that there is a business case as well as a quality case for implementing these approaches. Implementation, however, is neither fast nor easy, especially when involving transition from traditional systems and cultures. Management should be prepared to stay the course.

2.3 C&Q Process Flow

Figure 2.2 depicts the general C&Q process flow.

Figure 2.2: C&Q Process Flow Detail per This Guide



Note: DQ = Design Qualification
ECM = Engineering Change Management

EHS = Environment, Health, and Safety
PM = Preventive Maintenance

2.4 Quality Unit Approval

The first element necessary for a GMP-relevant project is to establish the required points of Quality Unit involvement, and specifically Quality Unit approval appropriate for each organization. This is a regulatory responsibility of the Quality Unit. The earlier these points are identified, the greater the likelihood of a successful GMP project outcome will be. There are six points of Quality Unit approval defined by this Guide:

1. Process User Requirements
2. Quality Risk Assessments
3. Critical Aspects and Acceptance Criteria
4. Commissioning and Qualification Plan
5. Qualification Summary Reports
6. Acceptance and Release of System

In addition, for any document that has already been approved by the Quality Unit and which requires a change due to design development, additional Process User Requirements (PURs), or correction of a non-conformance condition will need to be reapproved by the Quality Unit upon revision.

The roles of Quality Unit and SME are described in the context of the scope of activities covered by this Guide.

The Quality Unit has a key role within the quality management system governing facilities, systems, and equipment. In addition to acting as a SME, the Quality Unit is responsible for overseeing quality and compliance.

A key focus of the Quality Unit is identifying and approving those aspects that are required to:

- manufacture a quality product
- ensure that appropriate procedures are followed
- ensure that risks to the patient in the manufacturing systems are adequately controlled

The approach presented recognizes that the GMP regulations give the Quality Unit the responsibility for assuring drug product quality. The approach outlined by this Guide recommends that the actual performance of activities that contribute to that quality assurance may be performed by other qualified departments or units, so long as this is agreed by the Quality Unit and the final Quality Unit review is preserved in the design of the verification/validation program. The Quality Unit is expected to identify, approve, and verify those aspects that are necessary to manufacture a quality product, and to ensure that appropriate procedures are followed to ensure that risks to the patient in the manufacturing systems are adequately controlled.

In this Guide, the term Quality Unit is used as an encompassing term that includes many quality-related roles, including those responsibilities covered by the role of Qualified Person (as defined in Article 51 of EU Directive 2001/83/EC (Reference 11, Appendix 5)).

GMP regulations require that persons of appropriate education, training, and experience are used to perform a given task.

2.5 Qualification – Demonstrating Suitability for Intended Use

The Applied Risk Management for Commissioning and Qualification (C&Q) process described in this Guide is intended to meet the intent of what regulators have referred to as “qualification.”

Global regulation, guidance documents, and industry literature make extensive use of the term “qualification,” defining it in terms of the demonstration of evidence of suitability for intended use. The FDA’s January 2011 Process Validation Guideline (Reference 2, Appendix 5) states that:

“... qualification refers to activities undertaken to demonstrate that utilities and equipment are suitable for their intended use and perform properly.” (Underline added by Guide authors.)

The same document also includes an important reference to “commissioning” in which it states:

“It is essential that activities performed to assure proper facility design and commissioning precede PPQ [Process Performance Qualification].” (Underline added by Guide authors.)

Conversely, ASTM E 2500-07 (Reference 3, Appendix 5) does not use either of the terms “commissioning” or “qualification,” except to include them under an umbrella term of “verification” which it represents as:

“... all types of approaches to assuring systems are fit for use such as qualification, commissioning and qualification, verification, system validation, or other.”

Whether an organization prefers to use the traditional “qualification” terminology per the ISPE Baseline® Guide Volume 5 (Reference 4, Appendix 5) or the “verification” terminology per ASTM E2500-07 (Reference 3, Appendix 5), the concepts in this Guide can be used equally, as described, to meet the GMP requirement for documented evidence of suitability for intended use.

Regardless of the way in which an organization chooses to describe these activities, risks to product quality and patient safety should be addressed through appropriate facility or system design and specification processes, and the functionality of the associated risk control design elements should be demonstrated, confirmed, and documented in the as-built facility or system.

In the context of this Guide the following definitions apply:

- “Qualification¹” is the demonstration of suitability for intended use which has been formally documented and approved.
- “Commissioning” is a well planned, documented, and managed engineering approach to the start-up and turnover of facilities, systems, and equipment to the end user, that results in a safe and functional environment and that meets established design requirements and stakeholder expectations.

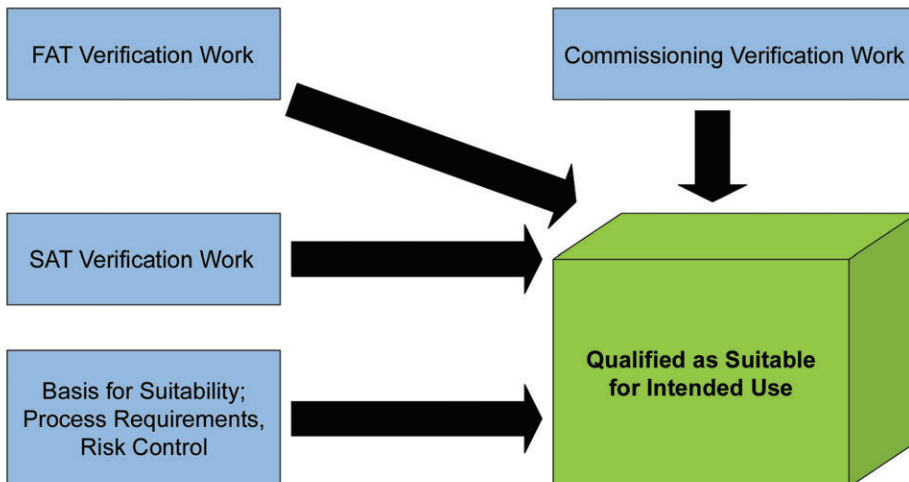
Commissioning is, therefore, one of the primary activities, alongside the design and specification process, which generate the documented evidence used to demonstrate suitability for intended use and support the achievement of the approved “qualified state.” Activities such as Factory Acceptance Testing (FAT) and Site Acceptance Testing (SAT) are an inherent part of the commissioning objective.

The inclusion of both commissioning and qualification terminology in the C&Q process described by this Guide is **not** intended to require or imply the necessity for additional testing to take place, which may be redundant to commissioning or lead to duplication, for the singular purpose of achieving “qualification” or obtaining error free documents.

¹ The ISO definition for qualification describes it as “the process to demonstrate the ability to fulfill specified requirements.” The key to using this ISO definition is to ensure that those specified requirements adequately described the “intended use” of the equipment, system, or facility.

Figure 2.3 from “Solving the Terminology Conundrum,” *Pharmaceutical Engineering*, July/August 2008 (Reference 12, Appendix 5) illustrates this central concept.

Figure 2.3: Solving the Terminology Conundrum



2.6 Process User Requirements

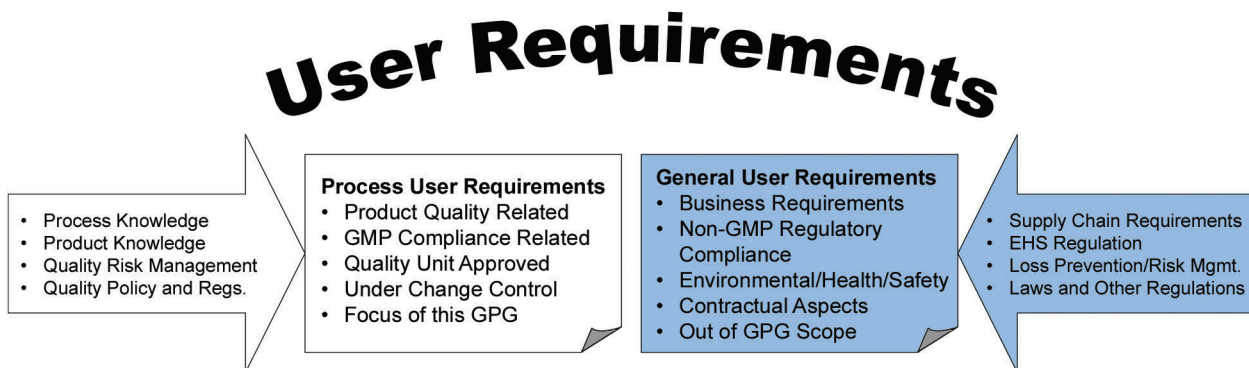
The fundamental starting document for a project is a set of clearly defined Process User Requirements (PURs). These requirements should be based on scientific process knowledge and Quality Risk Management (QRM). They are the basis for design and become the primary definition of a system being “suitable for intended use.” Put another way, for a facility or system to be suitable for its intended use, it must meet its Process User Requirements.

PURs are typically documented as part of a set of “User Requirements.” For the purposes of this Guide, two types of User Requirements are defined, which may be derived from several sources:

1. Process User Requirements
2. General User Requirements

Figure 2.4 depicts User Requirements and some of their sources.

Figure 2.4: Types and Sources of User Requirements



2.6.1 **Basis for Process User Requirements (PURs)**

PURs should include the Critical Process Parameters (CPPs) and other process conditions needed to reliably manufacture a product which consistently meets its Critical Quality Attributes (CQAs).

Knowledge of these requirements is normally based on scientific principles and process understanding acquired from development studies and pilot/clinical scale manufacturing. Another source of data may come from an organization's historical manufacturing experience and batch quality data for existing ("legacy") processes and products. For such legacy processes which predate the expectations of ICH Q8, scientific review of the manufacturing instruction parameters combined with operational experience and batch quality history may provide a strong basis for establishing PURs. Empirically-based knowledge may be better than that which an initial development effort can produce.

For some types of projects, the PURs may not be known, either completely or partially. This situation can occur for projects:

- where product or process development work is on-going
- where the product to be manufactured has not yet been identified, e.g., multi-product facilities or contract manufacturing facilities
- research and development facilities
- clinical manufacturing facilities

There should be a basis for design. End users are usually able to define as a minimum a generic set of PURs and/or performance capabilities that the equipment, systems, or facilities should meet. These requirements should be formally documented and placed under change control to become the basis for design, and can serve as the PURs. As more information or process data becomes available, these generic PURs should be updated and reviewed for impact on design suitability.

See Appendix 1 for additional information on developing appropriate PURs.

2.6.2 **GMP Compliance**

Facilities may have GMP compliance requirements that are derived from regulatory expectations which must be included, e.g., the expectation that aseptic filling will occur under ISO14644-1 Class 5 (Reference 13, Appendix 5) conditions with unidirectional airflow.

Historically, some non-value-added and non-risk-based practices found in traditional pharmaceutical C&Q programs evolved over time and were not actually required by regulation or "cGMP," and did not contribute to increasing assurance of product quality or to reducing patient risk.

The primary objective or purpose for GMP regulation is the manufacture of product that is safe and efficacious for patients. GMP compliance and product quality are logically linked. GMP compliance could be considered a PUR for GMP-relevant systems and facilities with potential for product quality impact. Expert knowledge of the relevant cGMP regulations is critical to preparing a comprehensive listing of PURs. Failure to adequately address and include the relevant cGMP requirements could be a direct risk to patient safety due to a potential loss of product availability as a result of regulatory action.

2.6.3 **Process User Requirements versus Critical Aspects**

Process User Requirements are **not** Critical Aspects (the design solutions implemented to assure that the PURs are met). ASTM E2500-07 (Reference 3, Appendix 5) defines Critical Aspects as:

“... functions, features, abilities, and performance or characteristics necessary for the manufacturing process and systems to ensure consistent product quality and patient safety.” (Underline added by Guide authors.)

- PURs are **what** the process requires to manufacture quality product.
- Critical Aspects are **how** the facility or system must deliver those quality requirements.

For further information on Critical Aspects and their determination, see Appendix 1.

2.6.4 Approval of Process and General User Requirements

There are six formal Quality Unit Approval points (QUAs) in the risk-based C&Q. The number of QUAs is determined by the organization's C&Q procedure(s) and may be reduced when transitioning to a risk-based approach, depending on the maturity of C&Q processes.

The approval of PURs represents the first QUA. Approval of PURs should be given by the Quality Unit and other relevant Subject Matter Experts (SMEs). Process scientists, manufacturing experts, engineers, and regulatory specialists may also have value-added roles in assuring adequate PURs.

Approval of PURs is an important preliminary milestone for any GMP project. It should precede final funding requests, manufacturing risk assessments, and occur soon after the completion of basic and/ or preliminary design.

Once PURs are approved, changes to these requirements will require a Quality Unit approval.

General User Requirements should be approved by the relevant SME's but may not need to be approved by the Quality Unit. Once approved, the general user requirements should be kept under Engineering Change Management (ECM).

2.7 Specification and Design

At the start of the project, the user should provide the engineering/project/design team with sufficient information to establish a basis for design. This information should include the relevant input variables to the process and related process auxiliary systems that may impact the design outcome (e.g., installation requirements, operational and functional requirements, cleaning, environmental, ergonomic, and personnel/material/waste movement).

Throughout design development, Good Engineering Practices (GEP) should be applied to evaluate design alternatives and to review design specifications and submittals. These evaluations should ensure that product, process, compliance, and general user requirements have been incorporated into the design.

In addition, a review of the risk assessment results should be performed and enhancements made to the design as required until patient risks have been adequately controlled within the design.

Design reviews should be documented, e.g., using meeting minutes or memorandum, indicating which design document aspects were reviewed and by whom. Open issues should be recorded to ensure traceability of design impacts and to ensure that the issues identified have been adequately addressed in the design.

2.7.1 Quality Risk Assessments

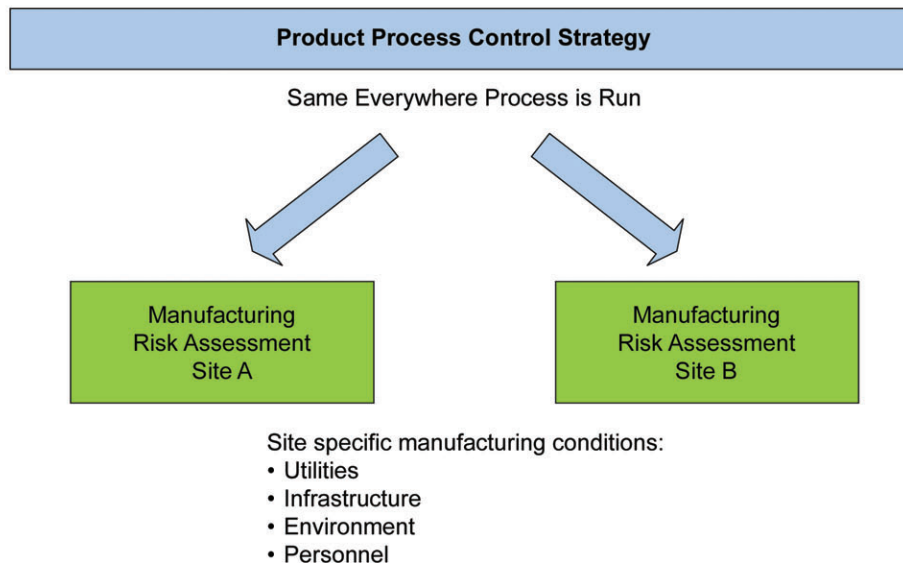
A quality risk assessment of the manufacturing process is a significant activity and can influence the early phase of design or procurement.

Design stage quality risk assessments normally use knowledge from product process risk assessments (and other process knowledge) to evaluate system design. They are an integral part of a science- and risk-based C&Q approach.

Design stage quality risk assessments should be performed as an iterative process, linked to the design development of the process system.

Figure 2.5 illustrates this two-tiered risk assessment concept.

Figure 2.5: Process Control Strategy and Manufacturing Risk Assessments



2.7.2 Identification of Critical Aspects

The key C&Q output of the design stage quality risk assessments is the identification of Critical Aspects that serve to:

1. control product quality risks to the patient
2. meet product/process user requirements

These Critical Aspects may be considered as the critical components, features, or functions of the system and will require qualification.

Systems found to include no Critical Aspects may be deemed to be non critical, and therefore be managed through GEP, commissioning, and engineering change management alone. There should be no need to include Quality Unit approval of non-critical systems.

For further information on identifying and documenting Critical Aspects, see Appendix 1.

2.7.3 Timing of Quality Risk Assessments

Design stage quality risk assessments should be performed as an iterative process, linked to the design development of the process system.

An iterative approach should identify risks, determine how to control them, and improve the design necessary to control the risks to the patient to an acceptable level. Table 2.1 provides an overview of the relationship between risk assessment and design phases within a project.

Table 2.1: Steps and Project Stages for Risk Assessments

Step	Early Start	Finish By
Prepare Inputs (based on science and process knowledge)	Concept Stage/Project Scoping Document	Start of Preliminary Design
Process focused Quality Risk Assessment	Start of Preliminary Design	End of Preliminary Design
Design Stage Quality Risk Assessment	End of Final Design	Construction Documents Approval
Risk Review (DQ)	After Completion of Design Stage Risk Assessment	Prior to IQ/OQ/PQ Preparation

2.7.4 Approval of Quality Risk Assessments and Critical Aspects

The approval of quality risk assessments represents the second QUA. Approval of quality risk assessments should be given by the Quality Unit and other relevant Subject Matter Experts (SMEs).

Critical Aspects, which derive from the approved quality risk assessments, including their associated acceptance criteria, represent the third QUA. Approval of the Critical Aspects should be given by the Quality Unit.

Other SMEs such as process scientists, manufacturing experts, engineers, and regulatory specialists should also review and approve appropriate designs and the respective Critical Aspects.

Approval of Critical Aspects and associated acceptance criteria should precede:

- procurement or construction activities
- C&Q planning
- commissioning or verification activities (e.g., FAT/SAT)

Once the acceptance criteria for the Critical Aspects are approved, subsequent changes to these criteria should require a Quality Unit approval.

2.7.5 Design Reviews and Design Qualification

Design reviews are planned, systematic reviews to evaluate design deliverables against requirements and specifications, identify issues, and propose corrective actions. They are performed throughout the specification and design phase by the appropriate SMEs.

The effort, formality, and documentation of these reviews should follow the ICH Q9 principle of being commensurate with the level of risk. Design review documentation may take the form of engineering meeting minutes or notes. For highly critical, novel systems, design review and stage approvals may be extensive and generate significant project documentation. This Guide does not prescribe methods for normal engineering review of these design deliverables.

Design Qualification (DQ) may be an expectation in the form of a qualification document by regulatory agencies. It may also be required by the local organization's procedures.

A simple document format for documenting the output of design reviews which typically meets cGMP expectations for DQ (where applicable) is a simple "traceability matrix" comparing the PURs to the supporting Critical Aspects captured in design specifications. An example of a simplified and hypothetical DQ traceability matrix is shown in Table 2.2.

Table 2.2: Example of a Simplified and Hypothetical DQ Traceability Matrix

PUR	Corresponding Design Specifications
Utility system must provide Purified Water USP.	System material of construction will be 316L SS as per Vendor Eng. Spec. XX-YY
	Water purification to be provided through vapor compression distillation Vendor Eng. Spec. XX-ZZ

DQ may be the design approval review reflecting the proposed installed facility or system (as designs and design reviews may be iterative and develop throughout the project). Design changes affecting Critical Aspects should require the approval of the Quality Unit, while all others may be managed under Engineering Change Management (ECM).

The design approval review or DQ Report could consist of or refer to:

- the final quality risk assessment that documents the satisfactory design control of all identified hazards to the patient
- identification of each critical aspect of the physical and functional design that serves to control identified risks to the patient
- description of each critical aspect in terms that are verifiable through inspections or testing (acceptance criteria)
- physical and functional aspects of the design that serve to meet a product or process user requirement in terms that are verifiable (mainly through performance testing)

It should also state whether the design is fit for its intended use.

The general user requirements may also be reviewed to confirm the design incorporates each requirement.

The Design Review (or Design Qualification) report should be approved by the Quality Unit and other relevant SMEs. This represents the fourth QUA.

2.8 C&Q Planning

A C&Q Plan should be developed to focus verification efforts on Critical Aspects. This plan can provide both general and project-specific directions for how a C&Q project is to proceed.

2.8.1 Alternative Names for the C&Q Plan

This Guide refers to a “C&Q Plan.” Other titles given to this plan are based on an organization’s preferences and policies, e.g.:

- Verification Plan
- Validation Plan
- Project Quality Plan

Teams may also choose to segregate these subjects into separate plans, e.g., a Commissioning Plan and a Qualification Plan.

GEP, GMP, and QRM principles should be included the C&Q Plan.

For purposes of this Guide, consistent with the transitional theme of connecting traditional language to science- and risk-based approaches, the term “C&Q Plan” will be used to represent such project documents, while the approach used for planning will incorporate the science- and risk-based activities.

2.8.2 **Elements of C&Q Plans**

ASTM E2500-07 (Reference 3, Appendix 5) states:

“The verification plan should define what constitutes acceptable documentation of subsequent verification activities.”

Typically, C&Q Plans include or reference:

- project scope definition and/or system boundaries
- strategy/studies or tests to use/timing or sequence/scheduling
- definition of acceptable documentation of detailed activities
- roles and responsibilities for SMEs and participating organizations
- acceptance criteria for project and/or project components
- incorporation of risk management to prioritize activities and determine level of formality, effort, and documentation
- definition and requirements for project change management
- provisions, if any, for the use of supplier qualification documents
- validation policy, and reference to existing documents
- Quality Unit and relevant SME approval (for systems with Critical Aspects)

For further information on the contents of a C&Q Plan, see Appendix 2.

2.8.3 **Timing of C&Q Plans**

Plans should be developed and approved before the activities they govern are scheduled to occur. The act of developing a plan causes issues to be discussed and resolved, responsibilities to be defined, and may illuminate problems while they are easier to solve. This can maximize the benefit of the C&Q Plan.

The content decisions also may affect C&Q Plan timing requirements. For example, if Critical Aspects and acceptance criteria are to be defined in the C&Q Plan, timing related to the approval of Critical Aspects applies (see Appendix 1).

2.8.4 **Quality Unit Approval of C&Q Plans**

Quality Unit approval of the C&Q Plan for applicable facilities and systems represents the fifth QUA. This should usually precede the approval of:

- protocols

- execution of tests/inspections
- collection of data to be used to demonstrate evidence for qualification

It also should precede any “approval to build” instruction to suppliers, in order to avoid introduction of additional costs through project change management.

Approval should also be given by other SMEs. The SME approvers may include project management, process support, engineering, verification SMEs, process owner, operations or other end user, and maintenance.

Subordinate plans may or may not be approved by the Quality Unit and other relevant SMEs depending on local procedures and practices.

2.8.5 C&Q Plan Change Control

The approved C&Q Plan should be maintained throughout the project. Changes to the C&Q Plan should be controlled. Responsibility for maintenance and control of the C&Q Plan typically lies with the project owner or project manager. All affected groups should be notified by the C&Q Plan owner of necessary changes; this helps to promote coordination and efficiency. The C&Q Plan should be structured and managed so that it can be easily updated (e.g., use of an attachment for list of systems that can be revised without significant effort or time) and changes should be listed in a change history. A project change management procedure should be established to manage changes to the C&Q Plan and other project documents.

Changes to the C&Q Plan that affect Critical Aspects should require Quality Unit approval.

2.9 Commissioning

At time of publication, the ISPE definition of commissioning is:

“A well planned, documented, and managed engineering approach to the start-up and turnover of facilities, equipment, facilities, and associated automation (collectively, ‘manufacturing systems’) to the end user that results in a safe and functional environment that meets established design requirements and stakeholder expectations.”

ASTM E2500-07 (Reference 3, Appendix 5) uses “verification” as an umbrella term to include:

“... all types of approaches to assuring systems are fit for use such as qualification, commissioning and qualification, verification, system validation, or other.”

By both of these definitions, the traditional engineering-based (and managed) GEP practices of commissioning facilities and systems are included in the types of evidence used for demonstrating and documenting suitability for intended use – or for qualification (see Figure 2.1).

This Guide discusses **the use** of commissioning and its associated documentation for the qualification of applicable systems as one step on the transition from traditional C&Q practices to science- and risk-based approaches.

Procedures for commissioning testing, inspection, and other verification activities, and their respective acceptance criteria should be determined and approved by appropriate technical SMEs, including the Quality Unit where appropriate. (i.e., for systems which include Critical Aspects).

For further information on commissioning, see Appendix 4 (taken from the ISPE FSE Guide (Reference 5, Appendix 5)).

2.9.1 *Scope of Commissioning*

The ISPE definition of commissioning as applied by this Guide has a wide scope. All activities intended to verify that a given facility or system meets its user requirements – both process and general – are included as “commissioning.” The scope of commissioning, therefore, can be from FAT to SAT to any and all testing, inspection, etc., that has potential for use in documenting the state of suitability for intended use.

This holistic view of commissioning scope means encompassing both verification-type activities (inspections and tests) and other necessary engineering activities, such as start-up and setting to work. To meet established design requirements and to make use of supplier and construction quality control documents means that commissioning begins as soon as the design has been approved, and does not end until the final hand-over to the end user following successful completion of any identified open issues.

2.9.2 *Utilization of Commissioning Data as Qualification Evidence*

Commissioning activities may provide all of the verification activities and testing/inspection documentation required prior to performance testing; in traditional protocol terms, all of the IQ and OQ testing, documentation, and associated activities. Given the scope of commissioning and that some activities, such as FAT, may occur earlier than the traditional points of IQ and OQ, there are several conditions which should be considered in order to utilize commissioning data for subsequent qualification purposes:

- Critical Aspects and acceptance criteria should have been approved previously, by appropriate SMEs including the Quality Unit.
- A commissioning change management procedure should be established, typically Engineering Change Management, not requiring Quality Unit involvement except for changes to pre-approved Critical Aspects or acceptance criteria.
- Pre-installation testing or inspection (such as FAT) can only be the final verification of characteristics and items that will not be affected by disassembly, transport, and reassembly at the installation site, such as materials of construction or internal controller software logic.
- The documentation standards to be applied during commissioning should be established in advance of any commissioning execution activities. Training on these standards should take place for all relevant internal and external personnel. A review and/or an audit of the executed test documents should be undertaken to ensure that the required standards were successfully achieved. (See Chapter 4 of this Guide.)

It is usually desirable to have an independent third party (end user or end user-representative) witness verification of Critical Aspects, although the decision to do so is up to the owner organization.

2.10 *Guidelines for Turn-Over Packages (TOPs)*

The content and the quality of the turn-over package (TOP) are fundamental to the successful execution of projects. In terms of risk management, the TOP provides information to support proper operation, maintenance, and change control, thus reducing operational risks.

The purpose of the TOP is to provide complete documentation on system components, equipment, and set-up. This documentation may be used for the complete system life cycle, including ongoing maintenance, system change management, and retirement. This would also include as-built documentation (agreed upon data, drawings, software, etc.) turned over to end user. The turn-over package should be accepted and approved.

2.10.1 Contents of TOPs

The content of TOPs is usually determined by organizational procedure, end user preference, GEP, system complexity, and agreements with suppliers. There should not be “must have” items in a TOP. Information included in a TOP should ensure controlled operation, maintenance, and change. A complex, novel piece of equipment, therefore, would require more types of information than a simple off-the-shelf pump, which may only need a spare parts list and Installation/Operation/Maintenance (IOM) manual.

A typical TOP may include life cycle related documents including:

- SOPs
- spare parts lists
- maintenance records
- as-built drawings
- material of constructions
- loop calibration documentation
- material safety data sheets
- system start-up and shutdown information

The TOP contents should be clearly set out and agreed upon by all parties prior to placement of orders. The delivery of the documentation requirements should **not** present a risk to the project at a later stage, from either content or timing aspects.

2.10.2 TOP Formats

Typically, equipment suppliers have their own format for TOPs, but the client (system or facility owner) organization should clearly define a standardized format that would be accepted for TOPs. This can help to ensure consistency between various TOPs that are submitted. The client organization can propose a standard format or accept the supplier format if it meets its quality requirements. The format might be system based or equipment based. The format of TOPs should ensure that they are user friendly with tabulated sections. TOPs should be obtained for all operating systems.

Suppliers may submit a generic manual for the TOP documentation. Depending on agreements with the client, a standard TOP format may be edited so that non-pertinent information is either deleted or clearly identified as being not applicable. A complete review of included documentation should be performed by suppliers prior to submission of the TOP. This review should identify and include any missing documentation and ensure that the TOP is in an “as-built” state:

- “As-built” state is defined as documenting the final configuration of the system, including automation and its components.

The owner engineering, facilities, or maintenance organizations should maintain and keep updated the parts or information sections (including all Critical Aspects) from the TOP, as a minimum. Updates to the TOP should be included in the change management of the systems or equipment. Documentation control should meet GMP requirements.

Once the TOP is confirmed to be in an “as built” state, it should be verified and formally approved by the end user organization’s engineering SMEs.

2.11 Qualification

This Guide defines the “Qualified State” as being a state of documented and approved suitability for intended use. In an ASTM E2500-07 verification scheme, there are no IQ or OQ protocols (nor the term “Qualification”).

The FDA’s January 2011 Process Validation Guideline (Reference 2, Appendix 5), in describing part 1 of stage 2, “*Design of a Facility and Qualification of Utilities and Equipment*,” describes a path from commissioning to “Process Performance Qualification” (PPQ), stating:

“It is essential that activities performed to assure proper facility design and commissioning precede PPQ.” (Underline added by Guide authors.)

and:

“... the term qualification refers to activities undertaken to demonstrate that utilities and equipment are suitable for their intended use and perform properly.” (Underline added by Guide authors.)

Specific activities of IQ and OQ are not mentioned here or in any part of 21 CFR Part 210, 211 (Reference 14, Appendix 5). Nevertheless, several FDA “Guidance for Industry” documents, the EU GMP Guide Annex 15, ICH Q7A (References 9 and 15, Appendix 5) and several PIC/S documents (Reference 10, Appendix 5) mention IQ and OQ as verification process steps.

As this Guide aims to provide transitional strategies from traditional approaches to Applied Risk Management in C&Q, this section discusses the efficient and value-added use of qualification documentation mechanisms. These aim to avoid adding unnecessary cost and time to applicable projects, while providing a strong base for ongoing facility and system life cycle maintenance and GMP regulatory compliance.

2.11.1 “Pre-Approval” of IQ and OQ Protocols

Practices considered inefficient and wasteful in traditional IQ and OQ protocols included disqualifying verification (typically commissioning) activities and documents, which had technical merit based only on the fact that their generation occurred **prior** to Quality Unit pre-execution approval (“pre-approval”) of an IQ or OQ protocol.

Example

An engineer may install a motor, verifying and documenting in commissioning the direction of rotation (as complying with design) as part of initial installation, yet have to **repeat** that observation (already knowing the “answer”) once a Quality Unit “pre-approved” protocol with documented “Acceptance Criteria” for that motor rotation test was available.

In many cases, even a visual observation “test” such as this one would have had a protocol test record form including a detailed test description – providing the opportunity for “deviations” to minor, inconsequential, or erroneous test description language (organizations may have produced CAPAs for such minor “exceptions”) and required re-execution of the entire protocol after corrections have been implemented.

The above example helps illustrate several points regarding the effectiveness of pre-approved IQ and OQ protocols. It should, therefore, be noted that IQ and OQ activities are essentially engineering (SME) activities and can be addressed primarily, if not exclusively, though SME-generated documentation

The approved “acceptance criteria” for such tests are based entirely on a system’s approved design and intended application, which is established through scientific and engineering principles. IQ and OQ “acceptance criteria” therefore represent detailed design criteria – and as such, should be derived by technical SMEs (engineers and scientists) during the process and engineering design phase:

If an organization desires to achieve “right-first-time” and “one-time” verification, without unnecessary redundancy, it is impractical to require that all applicable verification activities only occur against an already pre-approved protocol.

Many activities happen too early in the design/build/verify sequence for the protocol generation process and may even predate any specific client or project-specific documentation, e.g.:

- materials of construction verification or supplier schematics
- software specifications
- manuals
- product information

A stated expectation for what constitutes acceptable results should be determined before confirmation or verification testing is performed.

Documents such as the Quality Risk Assessment, Design Qualifications, or C&Q Plan are document options for documenting Critical Aspects. These documents should be developed earlier in the overall project life cycle than traditional development and approval of IQs and OQs.

Organizations may consider using protocols that explicitly allow the utilization of appropriately documented supplier and/or C&Q team verification documents even if generated prior to protocol pre-approval. For further information on using commissioning and supplier documentation, see Chapter 4 of this Guide.

2.11.2 Execution of Qualification

Execution of the verification activities associated with traditional IQs and OQs may be accomplished during appropriately executed and well documented commissioning. Further review of these execution activities may be required to designate a facility or system as “qualified” and suitable for its intended use. A report of this review process might take the form of an IQ/OQ Summary Report.

There may be occurrences where IQ and OQ protocols are the simplest, most efficient, and most sensible documentation mechanism to capture both the execution and review of the required verification activities.

There is no definition of which activity is included during “IQ,” or which should only be included during “OQ.” The logical sequence of testing is more important than which activity is included during “IQ,” or which should only be included during “OQ,” e.g., the calibration of measuring loops needs to be performed successfully before functional tests are executed utilizing the measured results.

Traditional protocol types may be consolidated. The ASTM-model utilizes a single SME and Quality Unit approved summary (that the system is suitable for its intended use) for approval and release. Where verification that all Critical Aspects meet their acceptance criteria has been adequately documented and reviewed as accurate and complete, the Quality Unit should be able to approve the facility or system as suitable for intended use – or “qualified.”

2.11.3 Qualification Strategies

Three possible execution strategies are:

1. Executing qualification as an audit of GEP or commissioning work
2. Executing qualification as combination review and field testing
3. Executing qualification of simple systems with protocols

Executing Qualification as an Audit of GEP or Commissioning Work

In this approach, the pre-protocol is executed as a “desk exercise” where the protocol serves as a checklist of the Critical Aspects, and the GEP documentation (FAT, SAT, commissioning, TOP, etc.) is reviewed to confirm that each critical aspect has been verified (tested) by adequate means to meet the approved acceptance criteria. The evidence gathered during execution of GEP documentation is reviewed. If a “Critical Aspect” was already successfully tested during commissioning and documented information is sufficient, this test result is referenced instead of being repeated. If the data gathered are insufficient, additional tests should be planned and executed, and results reported.

A final summary report can be developed providing a summary of the GEP work. The report should discuss deviations discovered during GEP work and critical deviations reviewed by the Quality Unit and appropriate SMEs. It should also contain a conclusion as to the suitability of the facility or system for its intended use.

Executing Qualification as Combination Review and Field Testing

In this approach, the protocol is executed by utilizing specific GEP documentation, supplemented by additional field testing. For example, FAT, SAT and commissioning documents could be reviewed with respect to structural testing and start-up functional testing, and supplemented by a final equipment operational run-through (typically normal operating mode only), to include any other testing that could not be satisfied by a review of GEP documentation. The FAT, SAT, and commissioning work may have been performed while a number of automation software testing and changes were occurring, and a final operational test of the equipment should be performed once the start-up team has turned over the system following the commissioning phase.

Executing Qualification of Simple Systems with Protocols

For simple, off-the-shelf systems risk assessments, Critical Aspect lists, acceptance criteria, and C&Q Plans can all be combined into one or more qualification protocol documents. Examples for application of this approach include new, simple, “out-of-the-box” table-top systems that have very little “engineering” support and very little commissioning execution requirements.

2.11.4 C&Q Non-Conformances

There can be situations where the field conditions (result of inspection or test) do not match the acceptance criteria. A risk-based approach should be followed in response to such circumstances.

Non-conformances involving Critical Aspects should be resolved in order to qualify the system or facility. Four resolution pathways are possible:

1. If the resolution involves modification of the approved design, the Quality Unit should approve the change including necessary re-tests. Impact on Design Qualification documentation (if any) and possible revision of that documentation, as well as update of as-built documentation, should be considered.

2. If a fix or repair can be made while not changing the approved design, the non-conforming incident should be logged along with how it was resolved, retested, and a consideration of potential of the fix or repair to invalidate any previous verification work already accomplished (similar to the principle of regression testing in software – looking at what else the change or repair might have affected).
3. Revise the process design, such that the item in question is no longer a Critical Aspect. The system or facility may be rendered non-critical through a modification of the Process Control Strategy (as in adding an additional downstream control point). Revision to the overall process control strategy, which may have its origins in the product development phase, is unusual during C&Q following a discovery that something is not working as intended.
4. The degree of criticality for a specific design feature previously identified as a Critical Aspect may be subject to review and possible change. “Use-as-is” decisions, and/or the modifications which over-ride the SME judgment, should be low-frequency outcomes.

Non-conformances **not** related to Critical Aspects should be evaluated by appropriate SMEs who should approve the departure from specification. Corrective actions/work-arounds should be indicated. Documentation should include rationale for the non-critical nature of the acceptance criteria. It should be clarified whether a test needs to be repeated.

2.11.5 Records of Non-Conformances

There may be business reasons to retain records of failed inspections or tests, such as to enforce contract provisions or allocate costs of poor quality. There may be an engineering interest in failed test results to support troubleshooting or reliability analysis.

From a quality and compliance perspective of confirming equipment is suitable for its intended use, failed testing that relates to equipment reliability should be retained and presented as part of the final acceptance and release package approval. This would usually be limited to failed performance testing, although select failed operational testing may also relate to reliability of the equipment or system.

Documentation of non-conformances that do not relate to performance reliability (such as an I/O connection error) normally does not need to be retained from a quality/compliance perspective.

2.12 Process Performance Qualification (PQ or PPQ)

The “Process Performance Qualification” stage of the process validation life cycle is referred to by the FDA as the stage after which the facilities and systems have been successfully qualified. In traditional C&Q terminology, Process Qualification, or Performance Qualification (both PQ) were the labels assigned for testing usually conducted with product, or placebo product, involving operating personnel, final procedures, quality controls, etc. This PQ stage was intended to assure that the manufacturing process in question would consistently produce an output meeting all its quality attributes, i.e., process validation on a unit operation scale.

Within this Guide, this stage is simply termed Process Qualification or “PQ.”

2.12.1 PQ Objectives

PQ activities have a different, process-based focus than the engineering-based focus of IQ and OQ. The primary objectives of PQ resemble that of process validation:

- Demonstrates evidence that the system, equipment, or process is capable of consistently performing to meet the PURs defined early in the project

- Confirms the procedures used to operate and verifies the specific capabilities of a given process equipment system
- Demonstrates that the Critical Process Parameters (CPPs) (if any) are under control and that product output meets any applicable Critical Quality Attributes (CQAs)

2.12.2 Pre-Approval of PQs

The key to an organization's PQ pre-approval approach is whether it is considered a "qualification" or "validation" activity. In scenarios where it is considered a validation document, pre-approval of PQ protocols by the Quality Unit and other appropriate SMEs, such as process support or Manufacturing Science and Technology (MS&T), is a general expectation. If the PQ is deemed to be part of the qualification phase, **which will be followed by subsequent validation activities**, the quality pre-approval of PQs can follow the guidance already given in this Guide for approval of IQs and OQs. In this case, PQ will be executed before the acceptance and release of the facility, system, or equipment.

Execution of PQs

As part of the objective of PQ is to confirm procedures and controls, the operation of equipment, etc, should be performed by operational personnel using actual procedures. In cases where new procedures have not been finalized or issued, drafts and redlines may be used, but should be retained for comparison to the procedures eventually issued, and include any required adjustments to procedure discovered during PQ.

FDA's January 2011 Process Validation (Reference 2, Appendix 5) guidance states the following for testing of equipment and systems:

"... utility systems and equipment operate in accordance with the Process User Requirements in all anticipated operating ranges. This should include challenging the equipment or system functions while under load comparable to that expected routine production."

and:

"Operating ranges should be shown capable of being held as long as would be necessary during routine production."

Hopefully, well rationalized and risk-based approaches will continue to be acceptable in determining test durations and repetitions.

From a science and engineering perspective, equipment testing schemes should be intended to fully capture inherent process variability and any other sources of product quality variation, related to the operation of the system and process in question.

2.13 Acceptance and Release

Once the IQ, OQ, and PQ are successfully executed and the documentation completed, the system would be considered ready for acceptance and release for use by the Quality Unit. Typically, a team of SMEs including the Quality Unit reviews all documentation prior to final release. These documents may include:

- IQ
- OQ
- PQ

- commissioning
- raw testing data (or selectively reviewed by performing audit)
- all pertinent SOPs
- calibration and maintenance procedures and records

All critical deviations should be recorded, addressed, retested where necessary, and successfully completed.

Where non-critical deviations arise, it may be acceptable for open issues to remain open if not affecting product quality; this should be indicated in the report and manufacturing planning implications should be considered. Non-critical deviation open issues should be addressed to a responsible person with a specific timeline by which they should be resolved.

The acceptance and release phase is that point at which a formal review of all the verification work should be performed. The systems and process equipment should be deemed to be suitable for their intended use), the systems and process equipment should be approved before release to begin manufacturing operations, and Quality Unit pre-approved change control according to local/site procedures should begin.

This review should include the appropriate SMEs including a representative from the department that will accept care, custody, and control of the item. If a system or piece of equipment includes Critical Aspects, then the Quality Unit should be part of the acceptance and release formal review, focusing on Critical Aspects.

The acceptance and release phase should occur as a cooperative review between the Quality Unit and the C&Q team. The C&Q team should review the results of verification work from an overall technical perspective. The Quality Unit should review the results from the perspective of adequate control of product risk and patient safety and demonstrated capability to meet the PURs.

The Quality Unit should approve the acceptance and release certification document, which should address each item described in this section of the Guide. Other approvers could include the end user. Note that this acceptance and release “document” is a certification that the equipment or system is suitable for its intended use.

The final approval and release occurs when the Quality Unit completes their review and accepts the system by signing the acceptance and release summary report and/or change control document. This approval usually releases the system for use by the manufacturing operations unit. This is the sixth QUA.

In general, items that should be in place prior to acceptance and release include:

- change control system
- calibration/maintenance system
- SOPs available
- operator training
- system log book available (paper/electronically)

Project teams may choose to manage these aspects of the manufacturing quality system separately from the turn-over of qualified systems, provided these aspects are entirely in place prior to product manufacturing operations.

The Quality Unit should also verify that all requirements to add the systems into the operating facility have been met.

If a change control is issued to add new equipment or a system to an existing operation, then all requirements should be met.

In some exceptions, there may be non-critical punch list items that may still require closure.

Acceptance of the system with open items should be a Quality Unit decision. Typically, all critical and key items have to be addressed and a few minor non-critical items may remain open for a short period of time.

Quality Unit acceptance and release represents the initiation of the “Qualified State” and the beginning of operational change control (Quality Unit pre-approved), continuous performance monitoring, and periodic review.

3 Operation and Continual Improvement

This chapter addresses the transition to, and practical application of, science- and risk-based approaches to the ongoing operation and “life cycle management” of existing (or “legacy”) systems and facilities.

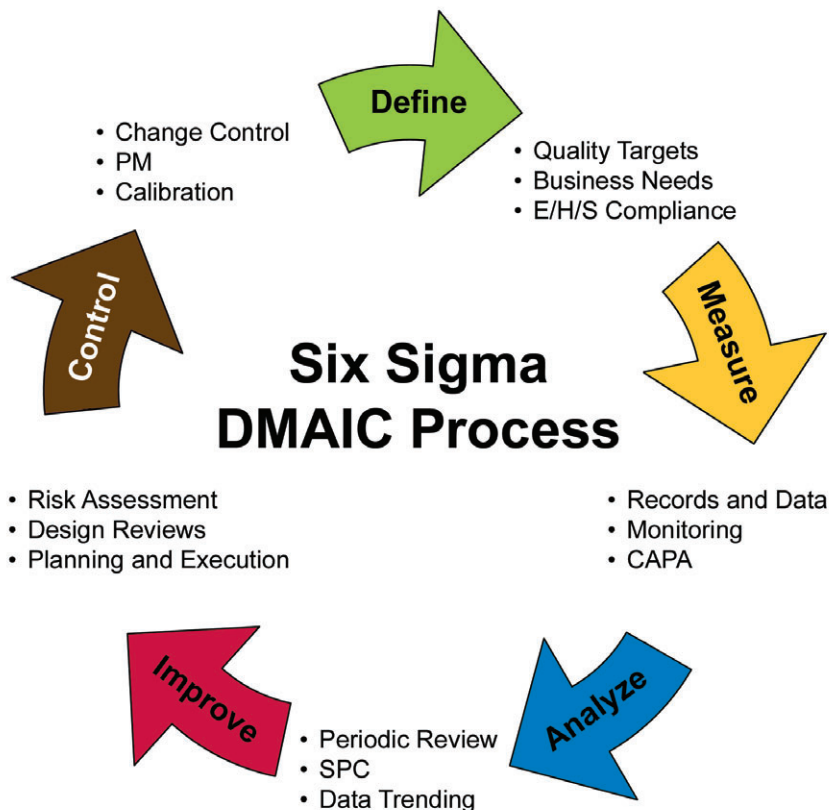
“Life cycle management” is the term used in this Guide to refer to all aspects of post-acceptance ongoing operations, including:

- change control
- maintenance
- calibration
- ongoing monitoring and review
- continual improvement
- decommissioning

“Life cycle management” includes activities and documentation necessary to assure that applicable systems and facilities remain in a “qualified state.”

A six sigma “DMAIC” diagram as shown in Figure 3.1 is an example of the continuous process of monitoring, identifying, and implementing improvements discussed in this Guide.

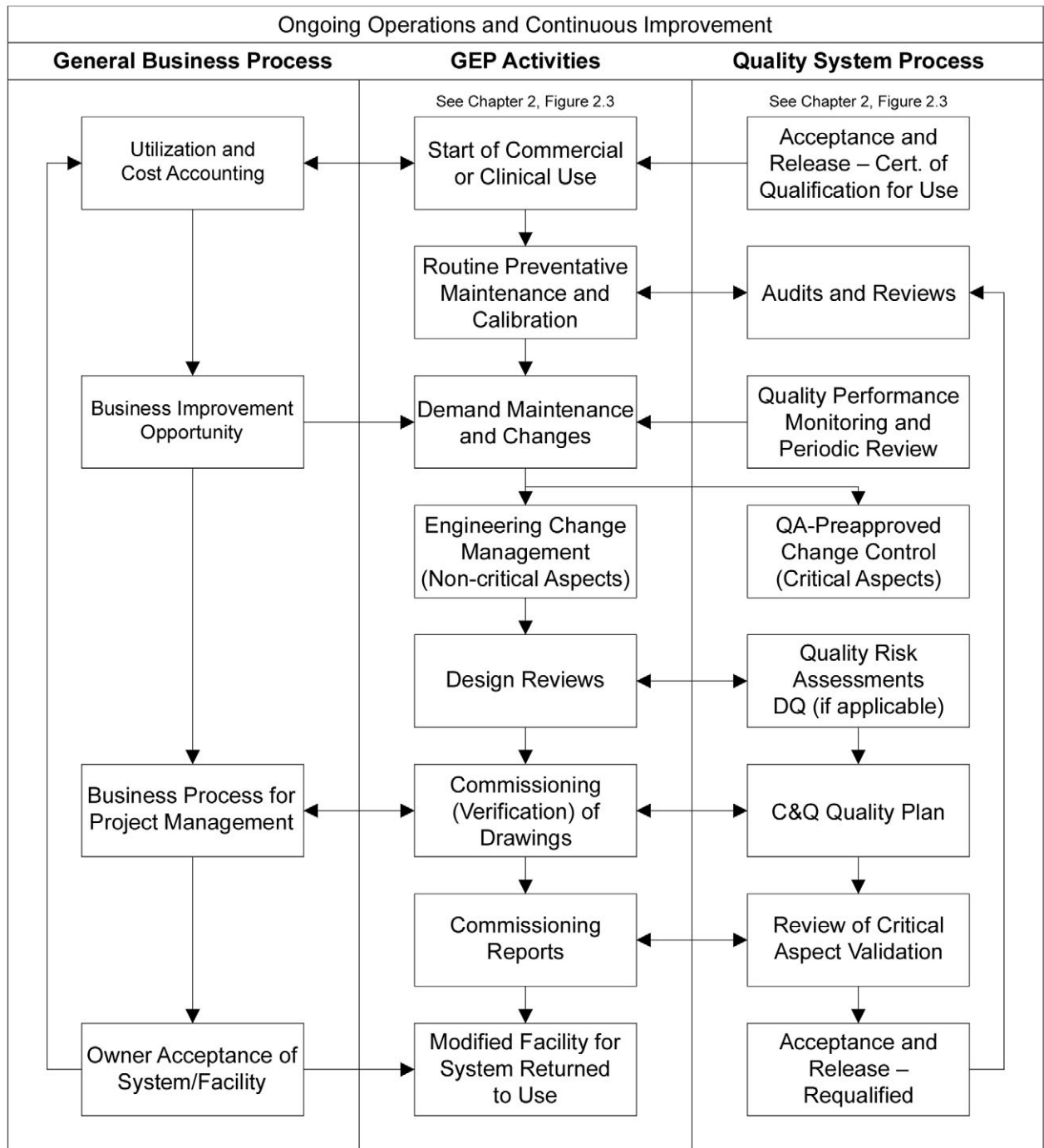
Figure 3.1: Six Sigma DMAIC Circle



3.1 Legacy System Life Cycle Flow

The process flow diagram shown in Figure 3.2 is intended to depict the science- and risk-based C&Q life cycle management of qualified systems and facilities.

Figure 3.2: Legacy System Life Cycle



3.2 Objectives of Science- and Risk-Based System Life Cycle Management

Risk-based strategies for legacy system life cycle management should account for three primary objectives as a minimum:

1. Assuring that the level of effort, formality, and documentation of the life cycle management program for each system or facility is commensurate with the level of product quality and patient risk associated with its specific use. This objective requires a focus on systems or facilities which are critical to quality and specifically on any quality related Critical Aspects of those assets.
2. Maintaining a “qualified state” of operation for those systems and facilities that directly impact product quality. This objective requires change management, ongoing performance monitoring (as appropriate to level of risk), and periodic evaluation or review, such as maintenance and calibration.
3. Facilitating innovation and continual improvement by reducing unnecessary obstacles to change, fostering a culture of Quality by Design (QbD), and providing adequate mechanisms for control of the identification, design, review, implementation and verification of changes, improvements, and new risk control strategies.

3.3 Maintenance, Calibration, and Continued Suitability for Intended Use

Maintenance and continued suitability for intended use is the phase of the system life cycle that supports operation of the system and production of the drug product or intermediate. During this phase the main focus should be on:

- periodic maintenance and inspection
- adjustment
- calibration
- repair
- incremental modifications or changes
- maintenance of the data and documentation that support the system

3.3.1 Initial Conditions

Following completion of verification, acceptance, and release, there should be a high level of confidence that the initial conditions of the system reflect desired functions, meet user requirements, and that the filed data and documentation are accurate and complete. These initial conditions represent the baseline qualified operating condition of the system or facility.

3.3.2 Maintenance

The purpose of maintenance is to keep facilities, equipment, and utilities operating in accordance with their design specifications.

For systems and facilities with Critical Aspects, maintenance of the performance of such aspects should assure that quality risks remain under control and PURs continue to be satisfied. Such activities may be performed during maintenance execution or during preparation of manufacturing systems for production (e.g., filled volume check at a filling line).

The goal of maintaining the PURs for each asset should be the standard for designing and executing the maintenance program both during the project and over the life cycle of the asset.

For further details on GEP based maintenance programs see, the ISPE Good Practice Guide on Maintenance (Reference 16, Appendix 5). Items discussed in this section may provide some additional insight into maintenance considerations.

3.3.2.1 *Planning the Maintenance Program*

The maintenance staff and end user should develop the guiding principles for the maintenance program for a given site and the products being manufactured. Documented procedures and schedules should be developed and approved by appropriate SMEs. The Quality Unit role for this activity is to assure that it occurs and that maintenance procedures and schedules are in place. Unless the Quality Unit has SME knowledge of a particular maintenance activity, it is usually not considered value-added to have a requirement for Quality Unit approval of technical maintenance or engineering procedures.

Maintenance programs should consider the maintenance of Critical Aspects and respective acceptance criteria and should ensure that there is adequate documentation to demonstrate that systems remain suitable for their intended use throughout the life cycle. Quality related considerations for such a program could include:

- Spare Parts and Parts Control: Critical spare parts should be identified as part of original qualification documentation. Parts with direct product contact are particularly important to document and control. Parts stocking strategies should include:
 - consideration of the risks of using replacement parts from alternative suppliers
 - the likely urgency for replacements when needed
 - how use of spares will be authorized and controlled
- Establishment of “Functionally Equivalent” or “Like-for-Like” Replacement Rules: Acknowledging that it is a practical impossibility that every part be replaced with an exactly identical spare if needed, defining what represents a “like-for-like” replacement must be established and agreed to by SMEs including the Quality Unit. Change control requirements around like-for-like replacements may be less rigorous than for modified part replacements. These designations should be based on quality risk and carefully considered. For further information on change control practices, see Section 3.5 of this Guide.
- Critical and Non-Critical Preventive Maintenance: Preventive Maintenance jobs should be performed in a timely and correct manner and product and quality impact should be considered. The Preventive Maintenance program should establish criteria for critical and non-critical Preventive Maintenance and provide for differentiated levels of control and response. Critical Preventive Maintenance not performed on time or correctly should be investigated for both cause and potential quality impact.

Note: The criticality of a Preventive Maintenance may not be related to the operational criticality of the item. For example, a non-critical storage vessel may have a gasket or seal that, if not changed on a defined schedule, has been shown to contribute to extraneous matter events and product complaints. Risk assessment by system SMEs is the recommended method to determine Preventive Maintenance criticality.

3.3.2.2 *Demand Maintenance*

Equipment breakdowns, malfunctions, etc., are usually an everyday occurrence during operation. The organizational response and procedures should be planned. In general, demand maintenance and repairs can be divided into two categories:

1. Non-emergency changes that can and should be handled through routine change control processes described in Section 3.5 of this Guide
2. Emergency situations that represent an immediate risk to product, personnel, or the environment, etc., and which should be corrected without delay

3.3.2.3 *Emergency Changes*

Procedures for handling emergency changes should be developed by SMEs and approved by the Quality Unit. These procedures should describe:

- The conditions that constitute an “emergency” (including the fact that emergencies cannot be planned or scheduled) – any change that can be planned is **not** an emergency
- Quality Unit approval requirements when Critical Aspects are affected by an emergency change. Even when Quality Unit pre-approval is not possible in an emergency situation, the requirement that the Quality Unit approve all changes to Critical Aspects is not waived.
- Expeditious time frames and documentation requirements for SME review of the change(s) and determination of re-verification and any requalification requirements

Examples of possible procedural mechanisms to cover emergency changes include:

- An “emergency” is an immediate and inadequately controlled hazard affecting product quality, personnel and/or community safety, environmental control, business continuity, or physical assets.
- A Quality Unit representative should be verbally notified (as a minimum) of the situation and proposed remediation, and should agree that the scenario meets the criteria for an emergency and that any proposed actions are necessary and appropriate, along with any restrictions or limitations that may apply.
- That within a reasonable and defined period of time (e.g.: 72 hours or three calendar days) a full SME review of the change and potential verification and/or requalification requirements be documented. This documentation should include a verified (by Quality signature) account of the original Quality Unit approval given at the time of the incident.

3.3.3 *Calibration*

Calibration establishes and verifies the reliability and performance of an instrument. All instrumentation used for pharmaceutical manufacturing, whether directly or indirectly involved with the process, should be individually assessed against their specific use to establish their criticality to the process and, therefore, determine the precise calibration requirements.

A calibration criticality assessment should be performed as part of the introduction of new instruments and measurement equipment. The outcome of the assessment will be the calibration requirements for the individual instruments such as the range, tolerance, and calibration method and frequency. This information can be used to populate the calibration register and calibration methodology. The calibration criticality may be evaluated as part of the Risk Assessments described in Chapter 2 of this Guide, or may be conducted as a separate activity that is informed by the general findings of the Risk Assessments.

The criticality assessment should consider the impact of the instrumentation on:

- product safety
- identity

- strength
- purity or quality
- facility/environmental safety or business efficiencies

The assessment should be performed by a multidisciplinary SME team including (but not limited to) representatives from the production unit (process owner or SME) and engineering, including automation and Quality Unit. Process limits and tolerances should be correctly defined in relation to the process or task in which the instrument will perform. This information is needed to determine calibration specifications.

Instrument criticality categories may include:

- product critical instruments
- process/system critical instruments
- safety/environmental critical instruments
- non-critical instruments
- non-calibrated instruments

Calibration program requirements, such as investigation of out of tolerance calibrations, change control requirements, and documentation approvers, may vary depending on the criticality classification. For example, instruments that are not associated with a Critical Aspect may not require Quality Unit approvals during the change control process. The calibration of instruments associated with a Critical Aspect and the calibration test instruments should be verified during C&Q. An organization may decide whether to cover critical and non-critical instruments with one calibration program or to distinguish between critical and non-critical instruments and cover non-critical instruments with engineering procedures under governance of calibration SMEs.

For more information on calibration, refer to the ISPE GAMP® Good Practice Guide on Calibration Management (Reference 17, Appendix 5).

3.4 Continued Verification

Continued verification is the third stage of the FDA's process validation life cycle, and applies to qualified systems and facilities, as well as processes. This stage also aligns with the measure/analyze phases of the DMAIC circle in Figure 3.1.

A program for the collection and evaluation of data relevant to the performance of the system or facility should be used as the basis for the ongoing and continuous verification that systems and facilities remain suitable for their intended use.

3.4.1 Quality Data

A number of different sources of quality-relevant data can be used in the evaluation of continued suitability for use, including:

- change control history
- process parameters and recorded data