



GOOD PRACTICE GUIDE:

Good Engineering Practice

Second Edition

Design, Delivery, and
Operation of Engineered Systems

System Design Practices

System Lifecycle Processes

System Delivery Practices

Project Engineering
Management

System Operational Practices



GOOD PRACTICE GUIDE: **Good Engineering Practice**

Second Edition

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ISBN 978-1-946964-48-9

Preface

This ISPE Good Practice Guide aims to provide a definition and explanation of the term Good Engineering Practice (GEP). It describes the fundamental elements of GEP as it should exist in the pharmaceutical industry, encompassing core concepts and engineering practices. The concepts and practices of GEP are fundamental and applicable, to varying degree, to other regulated industries.

It brings together a wealth of information on GEP and provides tools to allow benchmarking of current company practices against what is considered industry good practice.

The Guide includes attachments which provide industry examples, currently in use, of GEP and auditing methods, together with checklists that may be of use to the reader.

Acknowledgements

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Special Thanks

The Leads would also like to thank ISPE for technical writing and editing support by Nina Wang (ISPE Guidance Documents Technical Writer/Editor) and production support by Lynda Goldbach (ISPE Publications Manager).

The Team Leads would like to express their grateful thanks to the many individuals and companies from around the world who reviewed and provided comments during the preparation of this Guide; although they are too numerous to list here, their input is greatly appreciated.

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1 Introduction

1.1 Purpose

The purpose of this Guide is to define GEP that supports and enables the design, delivery, and operation of engineered systems in regulated industry. In the context of pharmaceutical engineering and GxP guidance, GEP is frequently referred to as a prerequisite to compliance activities and may be loosely defined in documents. GEP is often used to describe an engineering management system that is expected in a regulated company, but which is not mandated by GxP regulations. For example, effective project progress monitoring and control is not a regulatory issue but is necessary for the efficient operation of a company and is part of GEP.

This Guide considers the entire range of pharmaceutical engineering activity and identifies key attributes of GEP within it, including how GEP relates to and interfaces with GxP. The scope of GEP covers the complete lifecycle of engineering projects and engineered systems from conceptual design to retirement. GEP provides a foundation required across the pharmaceutical industry that other areas, such as GxP, build upon. This Guide also defines and clarifies GEP as an enabling process for Quality Risk Management (QRM)-based integrated Commissioning and Qualification (C&Q) as described in *ISPE Baseline® Guide: Volume 5 – Commissioning and Qualification (Second Edition)* [1].

This Guide was developed through the collaboration of representative professionals from various sectors and geographic regions of the pharmaceutical industry with the intention of determining a common understanding of the concept and principles of GEP. This document identifies practices that exemplify how GEP concepts may be applied in the pharmaceutical industry. The aspects of GEP discussed in this Guide are intended to describe the minimum requirements for GEP in engineering activities.

The intended audience for this Guide includes project, process, and other engineers who are involved in the design, delivery, and lifecycle management of engineered systems in the pharmaceutical and other regulated industries. This Guide may be beneficial to other stakeholders involved with such engineered systems, including business, manufacturing/operations, and quality.

1.1.1 Scope

The scope of this Guide incorporates all aspects of engineering related to the design, delivery, and operation of facilities and engineered systems, from conceptual design to retirement, but is focused on engineering practices within the pharmaceutical and other regulated industries. The scope of this Guide includes project engineering management for projects to design and deliver systems within the scope of this Guide. However, business practices such as decision-making processes regarding “what” projects to undertake, including feasibility and other business studies, are outside the scope of this Guide. Additionally, business activities that are upstream from GEP activities (such as Research and Development (R&D), process development, and Manufacturing Science and Technology (MS&T)) that may result in a decision to perform or provide inputs to GEP activities, and that may have many characteristics to which the practices described in this Guide may apply or benefit, are outside the scope of this Guide.

This Guide is by its nature generic, and specific requirements will need to be selected and adapted to suit the individual company. Similarly, the applicability and rigor of engineering practices described in this Guide should be commensurate with the needs of the individual company and with the scale, complexity, and risk of a given engineering process or project. For example, the scope of this Guide can include engineered systems with integrated automation and controls; however, each company must determine the appropriate application of this Guide versus *ISPE GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems* [2] or other applicable guidance documents for their specific systems.

1.1.2 Benefits

Running a business efficiently requires working practices that will deliver optimum value for a given scope of work. The adoption of GEP can lead to a balance of expenditure and activity in relation to benefits. Benefit is most likely gained when finite resources are focused on identified higher risk aspects or when high risk aspects are more intensely controlled to enable reliable delivery and seamless production. Specific potential benefits include facilitation of speed-to-market of regulated products through efficient delivery of manufacturing facilities and systems and an optimized level of quality oversight, commensurate with the maturity of established GEP.

1.2 Rationale for this Second Edition

The first edition of this Guide was published in 2008. Since that first publication, the pharmaceutical industry and regulators have developed industry standards, best practices, and regulatory guidance around topics that relate to GEP, culminating in particular in *ISPE Baseline Guide: C&Q (Second Edition)* [1] which was published in 2019. The revised C&Q Guide incorporates ASTM E2500 [3], EU GMP Annex 15 [4], ICH Q8, Q9, and Q10 [5, 6, 7], and applicable regulatory guidance. This revision of the *ISPE Good Practice Guide: Good Engineering Practice* incorporates, as applicable, the revision to *C&Q Baseline Guide* [1], and defines and clarifies GEP as an enabling process for QRM-based integrated C&Q.

Additionally, the revised *C&Q Baseline Guide* [1] references an Engineering Quality Process (EQP) that aligns the application of GEP under the overall Pharmaceutical Quality System (PQS) for QRM-based integrated C&Q. This revision of the *GEP Good Practice Guide* describes the EQP, its relationship to the overall PQS, and its application to facilitate GEP as an enabling process for QRM-based integrated C&Q.

1.3 Structure of the Guide

The breadth and coverage of GEP, including how GEP relates to and interfaces with GxP, is covered in Chapter 2.

The structure of the Guide divides GEP activity into the following categories, as shown in Figure 2.1 (Chapter 2) and described in Section 1.4.2:

- Core Concepts
 - Risk Management (Chapter 3)
 - Cost Management (Chapter 4)
 - Organization and Control (Chapter 5)
 - Innovation and Continual Improvement (Chapter 6)
- Practices
 - System Lifecycle Processes (Chapter 7)
 - Project Engineering Management Practices (Chapter 8)
 - System Design Practices (Chapter 9)
 - System Delivery Practices (Chapter 10)
 - Operational Support Practices (Chapter 11)

- Ancillary Support Practices (Chapter 12)
- Enabler
 - Engineering Quality Process (Chapter 13)

This Guide includes appendices containing templates and examples for core concepts, practices, and enablers. Refer to Appendix 1 for an example GEP policy document.

1.4 Key Terms and Concepts

1.4.1 Key Terms

1.4.1.1 Good Engineering Practice

For the purposes of this Guide, GEP exists in the context of the regulated industries and for the purpose of “supporting and enabling GMP”. The ultimate purpose of GMP is to provide benefit, and to prevent harm, to the end-user (patient) of the drug product. Thus, by extension, part of the purpose of GEP is to provide benefit, and to prevent harm, to the end-user of the drug product produced with a process that uses engineered systems designed, delivered, and operating in a manner suitable for the intended purpose.

Ultimately, as with “good” regulated practice (GxP), GEP is “good” as a result of reliable, cost-effective delivery of quality of work. With Good Manufacturing Practice (GMP), manufacturing practices are “good” when they reliably result in manufacturing of drug products that meet their quality attributes, specifications, and requirements. Likewise, engineering practices are “good” when they reliably result in project deliverables that meet stakeholder requirements and engineered systems that are designed, delivered, and operate throughout their lifecycle, from conceptual design through decommissioning, in a manner suitable for the intended purpose and meeting user requirements and stakeholder expectations. Ultimately, particularly for regulated industries, engineering practices are “good” when they result in manufacturing facilities and systems that function efficiently, safely, and reliably to produce a product that meets quality specifications. However, the motives for aspiring to practice “good engineering” are wider than the need to comply with GxP regulatory expectations; they encompass productivity, safety, and other business related drivers.

Good Manufacturing Practice (GMP) is defined as:

“a system for ensuring that products are consistently produced and controlled according to quality standards. It is designed to minimize the risks involved in any pharmaceutical production that cannot be eliminated through testing the final product.” (WHO [8])

Thus, for the purposes of this Guide, an analogous definition for **Good Engineering Practice (GEP)** is:

a system for ensuring that engineered systems are consistently and reliably designed, delivered, and operate in a manner suitable for the intended purpose according to user requirements, stakeholder expectations, and quality requirements, and are maintained in a state of control throughout their lifecycle, in order to minimize risk to product quality and patient safety.

1.4.1.2 Other Key Terms

- **Commissioning versus Integrated C&Q:** As used in this Guide, the term “commissioning” refers to GEP commissioning activities rather than to the QRM-based C&Q process defined in *ISPE Baseline Guide: C&Q (Second Edition)* [1]. Refer to Section 10.4.1.

- **Continual Improvement:** The term “continual improvement” is also referred to as “continuous improvement”. For the purposes of this Guide, the term continual improvement is used in alignment with ICH Q10 [7] and ISO 9000 [9]: *“recurring activity to increase the ability to fulfill requirements.”*
- **Deviations:** As used in this Guide, the term “deviations” is limited to out-of-specification results for approved/market-distributed product. The term “Deviation Systems” refers to the Quality system to manage such deviations/out-of-specification results.
- **Direct Impact Systems:** A system that directly impacts product Critical Quality Attributes (CQAs), or directly impacts the quality of the product delivered by a critical utility system. All other systems are considered to be not direct impact. [1]
- **Engineered Systems:** For the purposes of this Guide, the term “engineered systems” includes all systems designed, delivered, and maintained throughout their lifecycle per GEP, including custom-designed, stick-built, catalog, and commercial off-the-shelf systems.
- **Good Documentation Practice (GDP):** This Guide uses the acronym “GDP” to mean Good Documentation Practice, which is sometimes abbreviated as GDocP. When used alone, “GDP” refers to GMP/GxP GDP. The term “engineering GDP” is used to refer to GDP appropriate for GEP activities.
- **Good Regulated Practice (GxP):** This Guide uses the acronym “GxP” to refer collectively to regulated good practices for manufacturing (GMP), laboratory (GLP), and other related regulated practices.
- **Quality Risk Management (QRM) versus Risk Management:** The term risk management refers to management of risk in general, including risks to product quality and patient safety, business risks, project risks, Health, Safety, and Environmental (HSE) risks, etc. Both QRM and general risk management can use the same process and tools in the management of risk. The key difference is that QRM specifically addresses the management of risks associated with process risks to product quality and patient safety.

1.4.2 Key Concepts

The typical aspects of a GEP program may be categorized into three subsections:

- Core Concepts
- Practices
- Enablers

1.4.2.1 Core Concepts

Core concepts include risk management, cost management, organization and control, and innovation and continual improvement. These core concepts are essential activities in support of the GEP activities applied in support of the product lifecycle to ensure safe and reliable operations of facilities, systems, and equipment.

- **Risk management** is the *“the systematic application of policies, procedures and practices to the activities of communicating and consulting, establishing the context and assessing, treating, monitoring, reviewing, recording and reporting risk.”* (ISO 31000 [10]) QRM is an expectation by regulatory authorities for the manufacturing and use of drug product over the product lifecycle. Risk management includes QRM, project risk management, and other aspects.
- **Cost management** should consider project constraints including budget, schedule, resources, and quality, and ensure that the cost impact of any activity is understood, assessed, and managed, in order to return the best value for the regulated company. Value is measured as a balance between cost, quality, and process durability.

- **Organization and control** refers to organizational structure and control mechanisms. Organizational structure should ensure maximum efficiency and that the overhead to output ratio is acceptable. Control mechanisms within an organization should monitor the performance and progress of assigned activities. A clear structure of organization and control is required to respond effectively to the changing demands of the business.
- **Innovation and continual improvement** support regulatory and industry objectives for encouraging new technological advances, utilizing state-of-the-art pharmaceutical science, applying risk-based approaches to focus attention on critical areas, and facilitating application of modern quality management practices and principles.

1.4.2.2 Practices

Practices include system lifecycle processes, project engineering management practices, system design practices, system delivery practices, operational support practices, and ancillary support practices.

- **System lifecycle processes** apply to engineered systems throughout their design, delivery, and operational lifecycle, including Engineering Change Management (ECM), engineering issue management, and engineering document and drawing management.
- **Project engineering management practices** support overall project engineering management, including project requirements and scope definition, project planning and organization, project value analysis, and project control and monitoring. Many of these practices are covered extensively by the *ISPE Good Practice Guide: Project Management for the Pharmaceutical Industry* [11].
- **System design practices** support engineering system design, including system boundary definition, system requirements definition, design development, and design review.
- **System delivery practices** support engineering system delivery, including vendor management, construction quality, commissioning, and turnover.
- **Operational support practices** support the operation of engineered systems throughout their operational lifecycle, including asset management, calibration, routine and breakdown maintenance, and decommissioning.
- **Ancillary support practices** support ancillary activities related to engineered systems, including engineering storage, waste management, and facility and equipment repurposing.

1.4.2.3 Enablers

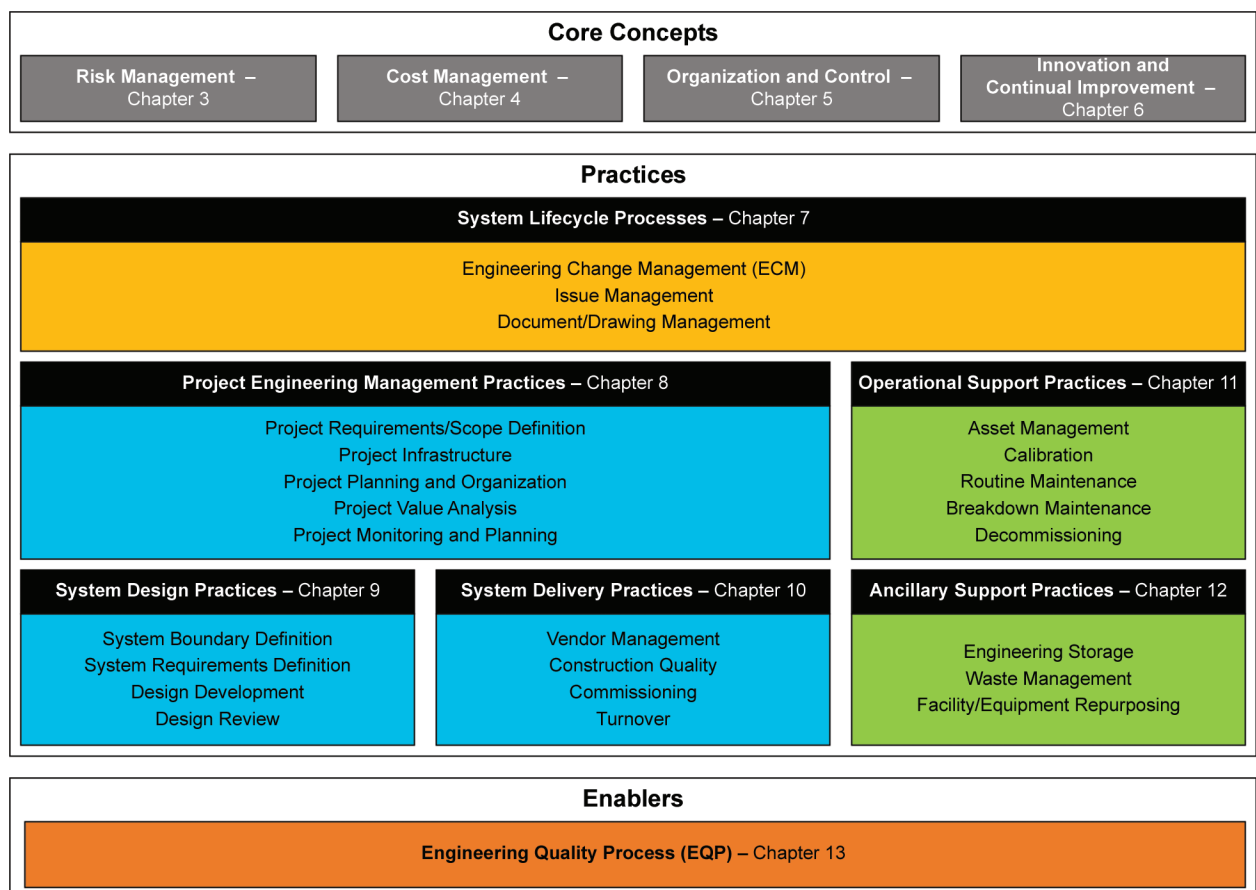
Enablers for GEP are not engineering practices themselves, but rather are external practices or processes that support and enable GEP and/or the successful application of GEP to deliver an intended outcome. Enablers include the **Engineering Quality Process (EQP)**. For the purposes of this Guide, the EQP will be addressed as the linkage between the overall PQS and established GEP and as the boundary between Quality oversight and engineering activities, particularly as applied to delivery of the QRM-based integrated C&Q process. However, the EQP may also provide a similar interface with business operations, HSE, or to other site non-quality or quality systems.

2 Breadth and Coverage of GEP

2.1 Introduction

Figure 2.1 illustrates the breadth and coverage of GEP. Core Concepts (shown at the top) underpin and permeate System Lifecycle Processes, Project Engineering Management, System Design, and System Delivery Practices, as well as Operational and Ancillary Support Practices. The Engineering Quality Process (shown at the bottom) acts as an enabler for GEP in the context of, and as the Quality link to, QRM-based integrated C&Q and other Quality practices for regulated companies. Refer to Appendix 1 for a GEP process flow diagram.

Figure 2.1: Good Engineering Practice Breadth and Coverage



2.2 GEP in Relation to GxP

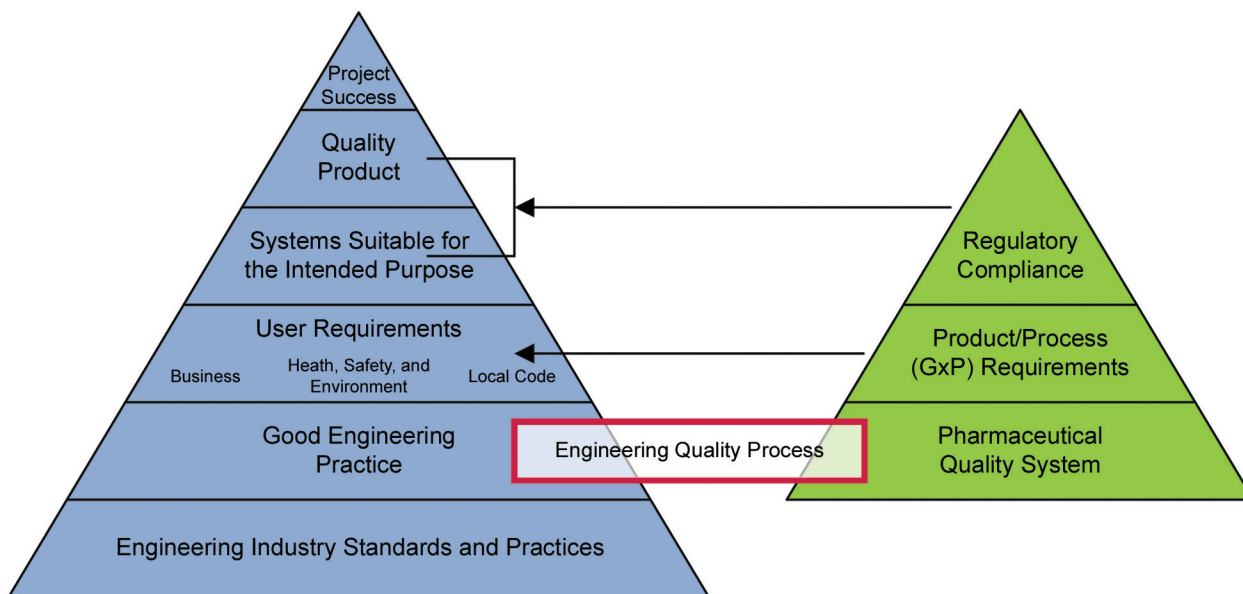
This Guide considers the entire range of pharmaceutical engineering activity and identifies key attributes of GEP within it, including how GEP relates to and interfaces with GxP. The scope of GEP covers the complete lifecycle of engineering from conceptual design to retirement. GEP provides a foundation required across the pharmaceutical industry that other areas, including regulated “good” practice or GxP, build upon.

GEP is founded on general engineering industry standards and practices, and are a subset of those practices focused on the design, delivery, and lifecycle management of engineered systems in regulated industry. GEP incorporates system requirements to design and deliver systems that are suitable for the intended purpose and meet stakeholder expectations. Systems that are designed, installed, and operate in a manner suitable for the intended purpose ultimately support processes that reliably produce product that meets quality requirements, which is the ultimate measure of success for engineered systems.

In this hierarchy, established GEP procedures represent the engineering “quality system” that meets engineering industry standards in support of ultimate project or operational success. In this regard, GEP is analogous to the PQS that meets regulatory requirements in support of the manufacture of quality products. The EQP establishes the formal linkage between GEP and the PQS. By delivering systems meeting all user requirements, GEP delivers the subset of requirements that impact product quality. By delivering systems that are installed and operate in a manner suitable for the intended purpose, GEP delivers quality impacting systems for which Critical Design Elements (CDEs) are installed and operate in a manner suitable for the intended purpose to provide Critical Aspects (CAs), thereby ensuring regulatory compliance, product quality, and patient safety.

The positioning of GEP in relation to GxP is shown in Figure 2.2.

Figure 2.2: Positioning of GEP in Relation to GxP

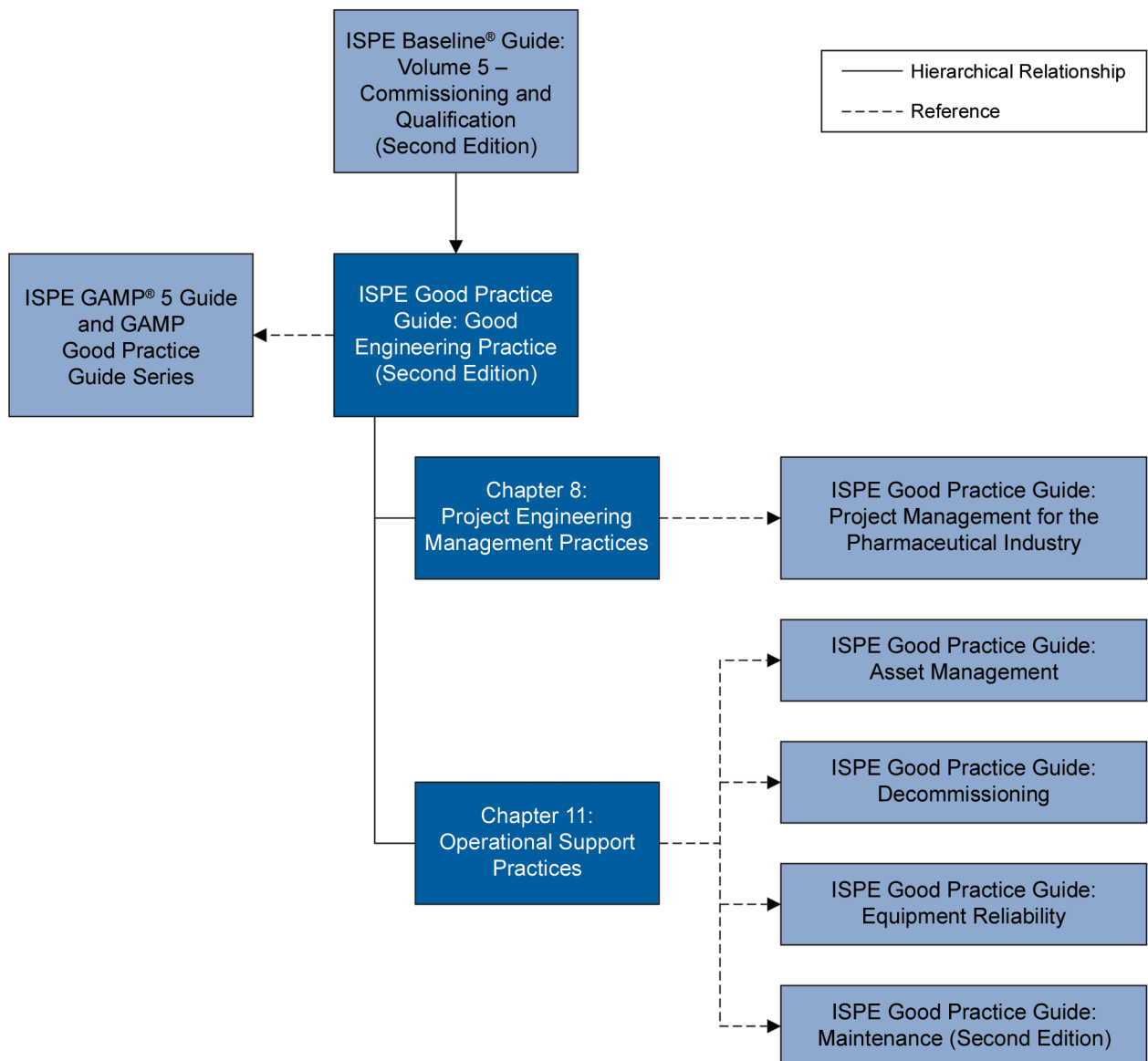


2.3 This Guide and ISPE Guidance Documents

This Guide references, links to, and supports several other ISPE Guidance Documents. This Guide formally supports the QRM-based integrated C&Q process described in *ISPE Baseline Guide: C&Q (Second Edition)* [1], for which GEP is an enabling process. The engineering concepts and practices described in this Guide, in many cases, are fully covered by other ISPE Guidance Documents. Where this applies, this Guide will summarize the processes and practices, and reference the applicable document, rather than duplicate content.

Figure 2.3 shows how this *ISPE Good Practice Guide: GEP (Second Edition)* relates to other ISPE Guidance Documents.

Figure 2.3: How This Guide Relates to Other ISPE Guidance Documents



3 Core Concept – Risk Management

3.1 Introduction

Risk management is at the core of most GEP activity such that there is a balanced evaluation of risks against benefits. Effective risk management, as a core principle, needs to address uncertainty in terms of the nature or source of the risk, its extent or degree, and how it can be addressed. Where practical, efforts should be made to mitigate risks to an acceptable level.

Risk management principles should be incorporated into the application of GEP to:

- Facilitate better and more informed decisions
- Provide greater assurance of the company's ability to deal with potential risks to product quality
- Supports the company's efforts to achieve and accomplish its business objectives and HSE requirements

Incorporation of risk management into GEP can favorably influence the following key engineering activities/functions that can provide support to practices shown in Figure 2.1:

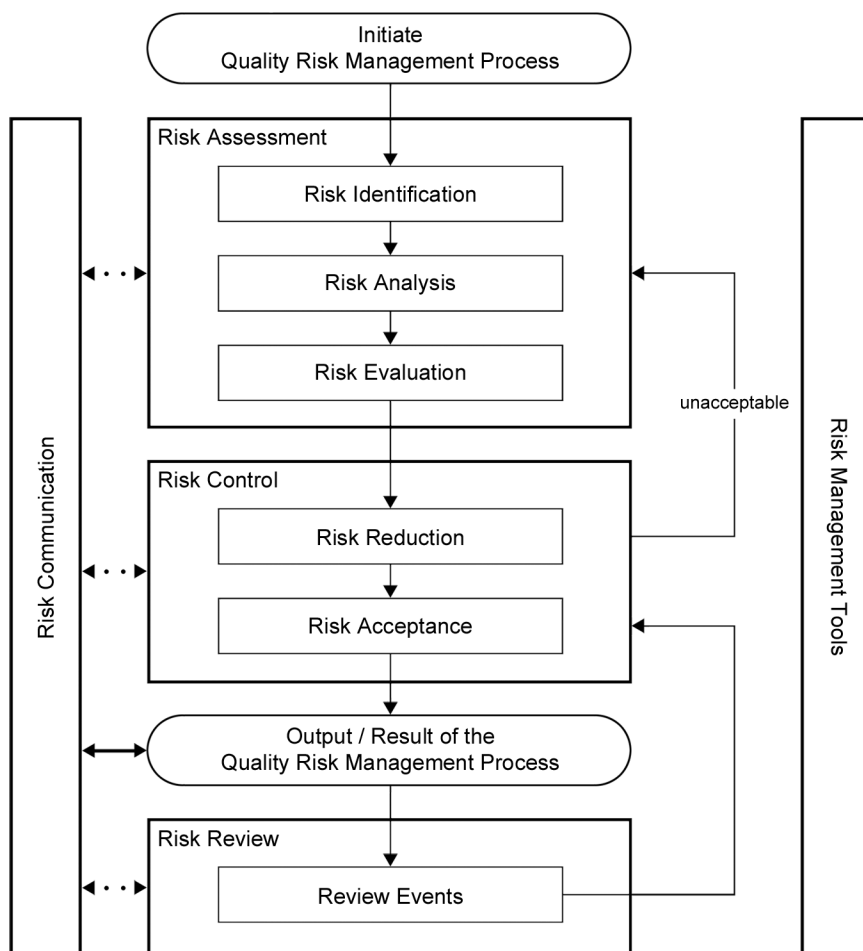
- Project Execution Plan
- Engineering Change Management (ECM)
- Engineering issue management
- Engineering document management
- Design review
- QRM-based C&Q
- Vendor assessment and management
- HSE
- Maintenance management (spare parts, maintenance, calibration, etc.)

This chapter provides a general overview of the risk management process and covers the application of risk management to key GEP-based engineering support activities. For the purposes of this Guide, application of risk management follows the overall structure of the ICH Q9 [6] process due to its overall familiarity in the pharmaceutical industry.

3.2 Risk Management Process

Application of risk management to GEP may be formal or informal; it should be commensurate with the project or system lifecycle stage, degree of risk, organizational maturity, and applicable subject matter expertise. Regardless of the approach, whether formal or informal, the results of the risk management effort should be documented for future reference or review. The general risk management process as defined in ICH Q9 [6] describes a systematic approach for the assessment/analysis, evaluation, control, communication, and review of risks, as outlined in Figure 3.1.

Figure 3.1: Overview of Risk Management Process (ICH Q9 [6])



3.2.1 Risk Assessment

Risk assessment is defined in ICH Q9 [6] as:

“A systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards [followed by] the analysis and evaluation of the risks associated with exposure to those hazards.”

In the application of risk management in the context of GEP, categories for risk consideration generally include project risks, product quality risks, business risks, environmental, health, and operator safety risks. It is a reality that risks can never be fully avoided or mitigated simply because of practical limitations. It is necessary for organizations to accept some level of residual risk. Application of risk management should include a prioritization process whereby risks with the greatest loss impact and the greatest probability of occurring are handled first.

Risk assessments should be performed by an appropriate team. This team should include a facilitator, Subject Matter Experts (SMEs) in product/process/HSE, process/system owner, manager, vendor representative, and quality representative when required. Risk assessments begin with a well-defined scope and an area of focus. Appropriate risk tools are then selected and/or adapted to support the risk assessment execution process.

3.2.1.1 Risk Identification

Risk identification is the “*systematic use of information to identify the potential sources of harms (hazards)*” [6] to provide the basis for further steps of the risk management process. Information sources can include historical data, theoretical analysis, informed options, and the concerns of the stakeholders.

3.2.1.2 Risk Analysis

Risk analysis is the “*estimation of the risk associated with the identified hazards. It is the qualitative or quantitative process of linking the likelihood of occurrence and severity of harm*” [6] to each identified hazard and estimating the associated risk.

3.2.1.3 Risk Evaluation

Risk evaluation is the use of a quantitative or qualitative scale to compare a given risk criterion to the estimated risk, to determine the significance of the risk [6].

Although detection is a common control utilized to mitigate risk, it should not be included in the initial risk evaluation in consideration of severity and occurrence for use in ranking of risk.

3.2.2 Risk Control

Risk control follows a thorough decision-making process in which the identified potential risks are ranked and compared against predefined thresholds to determine whether the risk is acceptable, or whether further risk reduction is necessary. Not all identified risks may require mitigation; only those that are deemed unacceptable in the course of risk evaluation need to continue into risk control. Other (acceptable) risks may also have controls applied where there is opportunity for improvement. Actions (e.g., design change, detection, procedures) undertaken to implement risk management decisions comprise the scope of risk control.

3.2.2.1 Risk Reduction

Risk reduction is “*actions taken to lessen the probability of occurrence of harm and the severity of that harm.*” [6]

3.2.2.2 Risk Acceptance

Risk acceptance is “*the decision to accept risk.*” [6] Risk acceptance decisions are the responsibility of senior management.

3.2.3 Risk Communication

An appropriate level of documentation is needed to capture the thought processes and the logic involved for communications and future reference. The significance of the risk to the business and its impact on product quality or safety should define the level of documentation involved. Established documentation processes should be used.

3.2.4 Risk Review

During implementation of the engineering function to which risk management has been incorporated into GEP, it is likely that changes will occur or that new knowledge and experience will be obtained. As appropriate, the outputs/ results of the activity being conducted should be monitored and/or reviewed to determine if there is an impact on the risk.

3.3 Application of Risk Management to GEP

This section discusses the incorporation of risk management principles into key GEP-based engineering support activities. The following descriptions do not specifically address risk review due to the generic nature of this element in all risk management applications. Refer to Appendix 2 for examples of risk application and the specific application of risk assessment to lifecycle processes and GEP practices.

3.3.1 Project Execution Plan

The primary objectives for the delivery of a capital project, as well as relative priorities, specific strategies, and action plans, are contained in the project execution plan. The project execution plan provides the foundation for the owner and the project management team to achieve the desired end results of the project and to ensure there is a consistent focus and agreement for project scope and priorities, cost, schedule, quality, and critical issues. It provides the principle means of communication to all participating parties (e.g., project team members and customer management), and provides the basis for which all subsequent plans, project specific guidelines, contractor execution plans, and process flowcharts should be prepared.

It is critical that crucial project risks be assessed throughout the project lifecycle, particularly during project execution and change management, where new sources of risk may be introduced and where there is the opportunity to apply mitigating safeguards through risk control.

Risk Assessment

The primary elements of risk associated with project execution involve cost, schedule, and quality level. An easy-to-use risk assessment matrix allows for the calculation of project risks by quickly identifying those things that can go wrong and weighing the potential impact.

Risk Control

In terms of project execution, risks include both negative risks (threats) and positive risks (opportunities). Strategies for risk control depend on the nature of the identified risk. Refer to the Project Management Institute (PMI) – A Guide to the Project Management Body of Knowledge (PMBOK® Guide) [12] for detailed descriptions on risk control strategies; these strategies are summarized as follows:

- Escalate: the risk (threat or opportunity) or its proposed response is outside the scope of the project and/or the authority of the project manager and is escalated to the program or portfolio level or other relevant part of the organization.
- Avoid (threat)/Exploit (opportunity): decision or action to eliminate the threat or avoid its impact, or to ensure that the opportunity is realized.
- Transfer (threat)/Share (opportunity): decision or action to shift ownership of the risk to a third party, to manage the risk, and to bear the impact of a threat occurrence or to benefit from the impact of an opportunity.
- Mitigate (threat)/Enhance (opportunity): decision or action to reduce the probability of occurrence and/or impact of a threat, or to increase the probability of occurrence and/or impact of an opportunity.
- Accept: decision to accept the risk (threat or opportunity) as-is, without taking proactive action, generally when the risk is low priority or where other risk control strategies are not cost-effective. Acceptance may be passive (logging in the risk register and monitoring) or active (establishing a contingency reserve).

3.3.2 Engineering Change Management

Risk-based GEP change management must be established throughout a manufacturing system's lifecycle. Refer to Chapter 7, Section 7.2.

3.3.3 Design Review

Risk management is an integral part of design review. Refer to Chapter 9, Section 9.5.

3.3.4 QRM-Based C&Q

As described in *ISPE Baseline Guide: C&Q (Second Edition)* [1], the robust application of GEP during project implementation results in facilities, systems, and equipment capable of efficiently manufacturing products meeting predefined user requirements. The incorporation of QRM into the C&Q process provides the focus for those product quality impacting elements resulting in documented qualification (established suitability for the intended purpose) in support of Performance Qualification and Process Performance Qualification/Process Validation. As presented in the Baseline Guide, QRM is applied to the described C&Q process to identify and document the CAs and CDEs that provide the focus for the GEP-based verification to support GMP qualification. Additionally, risk management principles apply to other GEP activities as part of the system QRM C&Q process, including periodic review and decommissioning.

The remainder of this section provides a brief overview. Refer to *ISPE Baseline Guide: C&Q (Second Edition)* [1] for the details of the integrated QRM-based C&Q process.

Risk Assessment

As per regulatory requirements, “*decisions on the scope and extent of qualification and validation should be based on a justified and documented risk assessment of the facilities, equipment, utilities and processes.*” [4, 13] The C&Q System Risk Assessment (SRA) serves this purpose by focusing the verification effort on direct impact systems, while ensuring product quality and patient safety.

While the use of FMEA or FMECA (Failure Modes and Effects Analysis, Failure Mode, Effects, and Criticality Analysis) tools are widespread in the pharmaceutical and biotechnology industries, these tools are not always well suited for C&Q. The SRA tool described in *ISPE Baseline Guide: C&Q (Second Edition)* [1] may be more efficient and can be scaled to include individual equipment, systems, or areas of manufacturing.

A multidisciplinary team should be appointed to identify and assess risks that have or might have an impact on Critical Process Parameters (CPPs) and their related product CQAs.

Risk Control

After identifying, assessing, and recording risks related to product quality and patient safety, care should be given to the classification of the risks (low, medium, high).

Actions applied to accept or mitigate risks are either built into the system design (CA/CDE), and therefore must be included in the system User Requirement Specification (URS) or integrated into a procedure. Both of these mitigation types must be integrated in the C&Q plan and their implementation verified during the C&Q program.

From a Quality by Design (QbD) point of view, it is highly recommended to build mitigation actions into a system's design to enhance its capability and robustness. Procedural controls might be applied where design control implementation is not reasonable from a cost or feasibility standpoint.

3.3.5 Vendor Assessment and Management

Throughout the manufacturing lifecycle, in applying GEP and meeting various other regulatory or corporate requirements, vendor selection and related risk assessment are essential to the business. When it is intended to use vendor testing and documentation in support of QRM-based C&Q, refer to Chapter 10 of *ISPE Baseline Guide: C&Q (Second Edition)* [1] for conducting vendor audits.

Risk Assessment

Vendor risk assessment is the process of identifying and evaluating potential hazards/harms related to the risks associated with a vendor's operations, products, and services delivered as well as its potential impact on projects, outsourcing, and supporting ongoing operations. When performing third-party vendor risk assessment, a determination of the most likely effects (including vendor approach to GEP application and oversight, uncertain events and subsequent identification, measuring and prioritization) is considered an essential part of GEP.

The risk assessment can be approached in either qualitative or quantitative ways. The focus is to identify vendor deficiencies early to establish controls and additional resources needed as early as possible. The identified vendor risks should be assessed in order to evaluate:

- Potential impact on business and project success
- Residual acceptable risk level
- Mitigation plan including time and responsibilities

Risk Control

Common control measures to address vendor deficiencies may include:

- Providing training and guidance to the vendor
- Adding auditing and review and approval provisions
- Witnessing critical lifecycle design phases and testing on-site
- Using third-party service providers for support

A mitigation action plan with roles and responsibilities should be clearly identified and implemented.

3.3.6 Health, Safety, and Environment

The health and safety of personnel and members of the public, as well as the protection of the environment, are a key part of risk management. Management of these risks through the lifecycle of a product, project, operations, and decommissioning are integral to ensuring HSE requirements and demonstrating compliance with the relevant global, regional, corporate, and site legislation, standards, and policies.

Risk Assessment

Throughout the product manufacturing lifecycle, in meeting GEP, and the various other regulatory or corporate requirements, Safety Assessments are essential to business. These assessments form part of risk management and include areas such as Process Safety and Occupational Health and Safety. When process safety incidents occur frequently, they typically correlate with a commensurate increase in significant harm and loss of life, potentially exposing civilians to risk.

It is critical that key safety risks be assessed throughout the product lifecycle, particularly during project execution and change management, where the root cause of risks is usually introduced, and where there is the opportunity to apply mitigating safeguards through risk control.

Risk Control

In accordance with GEP, those safety risks evaluated through risk management as unacceptable are then subject to risk reduction methods, such as hierarchical safety measures (refer to OSHA 3885 [14]), to ensure that the residual risks become acceptable.

3.3.7 Maintenance Management (Spare Parts, Maintenance, Calibration)

This section provides an introduction on the application of risk management for maintenance management, which includes spare parts management, maintenance, calibration, and related practices. For further detail, refer to the following guides:

- *ISPE Good Practice Guide: Maintenance (Second Edition)* [15]
- *ISPE Good Practice Guide: Equipment Reliability* [16]
- *ISPE GAMP Good Practice Guide: A Risk-Based Approach to Calibration Management (Second Edition)* [17]
- *ISPE Good Practice Guide: Asset Management* [18]

Implementing good risk management in maintenance management and taking a risk-based approach is key to ensuring that manufacturing is performed according to:

- High quality standards (patient safety and drug efficacy)
- Minimized business losses (e.g., time, rejects)
- Minimized impact to HSE

Application of risk management to maintenance management involves two areas of focus:

- Quality impact, referencing CAs, CDEs, and CPPs
- Business and HSE impact, referencing impact to operator health and safety, environment, and business objectives

Risk Assessment

The key difference between the approach for QRM (Quality) and risk management for business/HSE is that QRM for maintenance management should focus on the risk to patient safety, i.e., where product CQAs are not met, potentially due to deficiencies in the control of CPPs as a result of failed CDEs. An example of this risk may be a temperature measurement instrument used in product sterilization that fails or goes out of calibration. QRM activities should include assessing the risk presented by the failure to control the CPPs and implementing appropriate risk mitigation.

For business impact, risks may be identified and assessed in terms of system operational efficiency/uptime, reliability, or variability. In general, systems that are not operational by definition cannot produce poor quality product, because such systems produce no product at all. Thus, product quality is not impacted, but business objectives (output, yield, etc.) are.

For HSE impact, each system should be assessed at the design stage to determine components critical to safety (e.g., pressure relief devices, safety instrumented systems). This includes critical Personal Protective Equipment, such as respiratory protective equipment. The risk identified as deficiencies in these components should be evaluated and appropriate risk control implemented.

Risk Control

Risk control for Quality, business needs, and HSE is based on decision-making to reduce or accept the assessed level of risk. This decision is based on whether the risk exceeds a specified (acceptable) level. The amount of effort applied to risk control should be proportional to the significance (likelihood and severity) of the risk. Procedural and technical controls available to reduce risks to an acceptable level include establishing maintenance management that includes, for example:

- System and component inventory controls
- Identification and inventory volume of spare parts (including classification of critical spare parts)
- Risk-based Preventive Maintenance (PM) plans with tasks and frequency based on severity and probability of occurrence of system or component failure
- Risk-based calibration plans with frequency based on instrument criticality and probability of occurrence of instrument failure
- Training of facilities, metrology, and maintenance personnel in maintenance management procedures

3.3.8 Additional Risk Management/GEP Engineering Applications

There are additional engineering support functions where risk management can have a direct influence on GEP application, such as engineering issue management and engineering document management. The risk management concepts described in Section 3.2 can be applied to these functions and any additional engineering activities that are based on the application of GEP. Robust application of risk management to GEP lifecycle elements and practices can help to ensure that engineering support systems are more robust, manufacturing operates in a state of control, safe and environmentally sustainable environments are maintained, and product quality standards are met.

4 Core Concept – Cost Management

4.1 Introduction

Cost management is a core concept of GEP, as shown in Figure 2.1. Cost management is a feature of GEP to keep related budgets under surveillance. The purpose of cost management is to manage engineering projects and operational costs through the processes of planning, estimating, budgeting, monitoring, reporting, forecasting, and closeout.

Key aspects of cost management include:

- Cost management planning by establishing policies, procedures, and documentation
- Allocating respective resources for cost management
- Estimating costs by providing estimation and benchmarking tools and using Work Breakdown Structure (WBS) or operational work packages/tasks as the basis
- Determining the budget by providing processes to aggregate the cost of activities or work packages
- Monitoring, reporting, and forecasting by establishing strategies to record project and operational expenditures, and reporting them to stakeholders
- Establishing policies and procedures for procurement and managing contracts and invoices
- Setting strategies for project closeout and benchmarking budgets for standardization, continual improvement, and contingencies for emergencies

Key deliverables of cost management may include:

- Cost Management Plan
- Funding estimates
 - Detailed cash flow forecast
 - Project risk analysis
 - Detailed staffing level estimate
- Cost reports – content may include:
 - Latest estimate
 - Scope changes
 - Risk assessment and mitigation measures to reduce risks
 - Current costs against schedule and deliverables
 - Labor changes and/or restrictions
 - Performance against budgets

- Earned value calculation

The Cost Management Plan would typically be part of the project execution plan and is further detailed in Chapter 8, Section 8.4.3.

This chapter covers the following aspects of cost management: cost estimation, cost structures, cost evaluation and benchmarking, and cost monitoring, control, and reporting.

4.2 Cost Estimation

Effective cost estimation requires adhering to a structured approach that provides simple, consistent information and numbers to stakeholders, as well as managing the expectations of those stakeholders. Often, the first budget number that is shared will continue to be referenced by the stakeholders until the closeout of the project or the budget period.

Cost estimation needs to be based on a clearly defined scope of work, agreed-upon construction and contract philosophy, WBS, and support from all stakeholders involved. The basis for a cost estimation should be documented for later reference.

Cost estimation needs to consider various aspects related to the scope, including for example:

- Environment (brownfield, greenfield)
- Site development master plan
- Utilities infrastructure and capacities
- Electrical and automation setup, infrastructure, and capacities
- HSE requirements
- GMP requirements, including costs for C&Q preparation, execution (with test material), and reporting
- Local market situation regarding availability of materials and services
- Local availability of skilled personnel, contractors, and service providers

Cost estimates should be calculated using an agreed-on methodology, especially regarding the level of detail and expected accuracy, when calculating the total cost of an investment project. The approach should consider the major elements of construction and provide a cost estimate based on work packages with the following expenditures per package, as relevant:

- Civil, Structural, Architectural (CSA)
- Mechanical, Electrical, Plumbing (MEP)
- Equipment and machinery
- Construction, support work/demolition
- Engineering (including C&Q and internal and external engineering)
- Contingency

For larger projects or projects that require a greater level of detail, each of the expenditures above can be further detailed out into cost elements. For example, the detailed elements for CSA could include, but are not limited to the following:

- Excavation
- Foundations
- External/internal walls
- Floors and ceilings
- Roofs
- Structural fitments
- Furniture and installation
- External works
- Other construction-related activities
- Location factor
- Contractor premium for special conditions
- Allowance for permits/insurances (typically 2%)
- Inflation

For more detail, refer to Appendix 3 for a cost estimation worksheet template.

Some of the cost elements may be estimated using the analogous estimating method (i.e., based on numbers from recent projects) or the bottom-up estimating method (utilizing current Requests for Information/Proposal/Quotation or benchmarks), as applicable. Uncertainties for a cost element would be covered by an additional allowance, either based on a percentage rate or a specific calculation.

For engineering and contingency, a percentage of the Total Investment Costs would typically work in early project stages but needs to be further detailed for later project stages.

Any change in scope should be addressed through a respective change management process to ensure that a proposal is properly evaluated and includes a realistic cost estimate reflecting major construction aspects and to determine whether it is acceptable. Even with a clearly defined scope of work, cost estimation often involves ambiguity and managing risks and uncertainties. Experience is valuable in this regard, and it may help to review cost estimates with senior management or a cost estimation expert. Typically, the initial cost estimate will have a broad range—plus or minus 25% with the range reducing as the project becomes better defined.

In addition to the cost estimate, the predicted spending plan is also of interest to better understand the impact of project execution on cash flow and depreciation aspects.

In scenarios where the budget is not initially approved, value engineering is an approach that can be used to refine the scope of work to a reasonable level and update related budgets to meet stakeholder expectations without compromising engineering, product, or process quality.

4.2.1 Project Cost Estimation

Prior to creating a project budget, the scope of work should be clearly defined, the concept for implementation agreed, and the basic design developed. The WBS should be established. The PMI PMBOK® Guide [12] defines WBS as a:

“hierarchical decomposition of the total scope of work to be carried out by the project team to accomplish the project objectives and create the required deliverables.”

The WBS organizes the project scope by deliverables, activities, processes, systems, or other logical groupings. This breakdown facilitates the definition of durations for defined tasks, the order of execution of tasks, and the identification of predecessor-successor dependencies for related tasks. Thus, the WBS is a useful tool for defining the scope of project deliverables, creating the project schedule, resource loading, and estimating project cost.

For a project budget to be effective, SMEs need to be involved in developing budgets covering respective work packages. Where internal SMEs are not available, estimate offers (Request for Information, Request for Proposal) from contractors should be obtained for guidance.

The cost estimate should already reflect the cost structures to be applied throughout the project for cost management and control. This also includes provision for contingencies and reserves for both known and unknown risks, based on the range of budget and nature of the project. Cost structure is discussed further in Section 4.3.

The accuracy of cost estimation for an investment project should advance following a stage gated process. The project team should report a cost estimate at set stage gates of the project and obtain approval by a steering committee. Proposed stage gates could be a post-feasibility study, post-conceptual design, and post-preliminary design.

For larger projects, it may be advantageous to seek the help of professional cost estimators to verify the estimate. Scaling budget items with benchmarks can also help to verify the budget. Finally, the cost estimate needs to be of sufficient detail, transparency, and consistency for discussions with the stakeholders in order to receive approval.

4.2.2 Operational Engineering Cost Estimation

The operational engineering budget typically covers costs for:

- The engineering function itself (overhead, headcount related costs, office rentals, admin services and support, travel, training etc.)
- External services
- Maintenance and repair
- Spare parts
- Equipment replacements planned for the budget period

In some cases, external services, spare parts, and equipment replacements planned for the budget period are allocated at a different cost center from the engineering function, but are still planned with input from operational engineering as the SME.

To develop such an annual budget, consideration of historical data is crucial. The historical data should cover the costs for maintenance and repair activities (including the costs for consumables and spare parts replacement) as well as efforts for recalibration and requalification during recent years.

This data can be supplemented by information about replacement needs and other upcoming topics such as upgrading a software package, implementing measures to meet updated regulatory requirements, transferring new equipment from a capital investment into operations, etc.

The budget should also account for unforeseen incidents, repairs, external services, etc. Based on local cost structures, the costs for pest control, access control, energy consumption, waste disposal, and IT services and infrastructure may need to be considered.

As a starting point, the maintenance and repair budget could be developed based on a percentage of the total replacement value of the installations, while also taking into consideration the appropriate training of the personnel working in this function, especially if new systems are implemented.

4.3 Cost Structures

Costs should be structured in a way to support the planning, management, and controlling of budgets. This approach applies to budgets whether based on operational work package items or WBS as well as the development and forecasting of such costs over time.

Cost structures need to reflect the company's current policy and comply with tax regulations, to distinguish between capital and expense (e.g., lease contracts) and provide transparency regarding internal versus external costs to allow for cash flow calculations.

The costs being reported should include the following:

- Total approved budget
- Allocated amount
- Amount spent and paid
- Current forecast split up into work packages or WBS

The use of standardized cost structures can be beneficial, for the following reasons:

- To avoid overlooking certain cost items during the planning phase
- To simplify and standardize regular reporting for a project or function and to allow for easy aggregation of costs for multiple projects or functions
- To identify opportunities for improvement and synergies by comparing costs of different projects or functions with each other
- To establish and update benchmarks to improve future cost estimation

Cost structures for a project should be established in an early phase of the project and maintained throughout the project. The cost center for an operational function should be established or updated in line with the planning schedule for the upcoming (annual) cost planning cycle, considering whether any exceptional activities are foreseen for this planning period.

4.4 Cost Evaluation and Benchmarking

After the cost structures have been established, mapping the scope of work, and the respective packages have been estimated and summed up to a proposed budget, the budget number may end up being higher than expected. Gaining approval for this proposed budget number requires sufficient rationales and supporting assessments.

At this point, cost evaluation and benchmarking may help provide the rationale needed to gain approval, even for a higher budget number. Being able to demonstrate the following aspects can be helpful:

- The cost structures are transparent, and numbers are consistent.
- The Total Cost of Ownership (TCO) is predicted to be lower than expected because of robust design solutions and good procurement practices.
- The numbers align well with available benchmark values from comparable projects which went well, or perhaps the respective benchmarks are significantly lower than the ones from projects that did not go as well.
- The Return on Investment (ROI) time is low.
- The maintenance budget is appropriate and relates to Replacement Asset Value (RAV).
- The Discounted Cash Flow (DCF) outcome is beneficial.
- The Net Present Value (NPV) calculation shows the economic benefit of the project.

To support such an approach, it is beneficial to evaluate executed projects, perform lessons learned sessions to identify strengths and areas of improvement. The results from this exercise can help to establish and justify budgets for new investment projects.

As sustainable solutions become increasingly in focus, the TCO is also getting more attention. A higher investment may easily pay back if it results in longer time to run, higher efficiency, or fewer emissions of, e.g., carbon dioxide (allowing for less effort later to reduce the carbon footprint of the company). For more details, refer to *ISPE Handbook: Sustainability* [19].

Introducing digital solutions, such as Building Information Modeling, to a project will initially add to the engineering budget, but in the long run could reduce the risk of failure and reduce the duration of, project execution. In addition, this technology typically provides a much better basis for project turnover to the end-user organization.

The TCO, including operating, decommissioning, and disposal costs, should be considered in investment decisions. Determination of TCO should include consideration of the following aspects:

- Impact of the investment on other systems (interconnected, side effects on other systems, data communication)
- Impact of the running costs (depreciation, maintenance and repair, spare parts management, energy consumption, emissions, and waste, required head count for operation, etc.) on the Cost of Goods Sold
- Start-up and training
- Costs for integrating new types of components and instrumentation and using new equipment manufacturers
- Divestment costs for other systems to be demolished to free up space for installation as well as divestment costs for the investment itself (at the end of system lifecycle)

Benchmarks, if not available in-house, can be sourced from professional project estimation companies. The ROI typically would be applied to evaluate a project budget, calculate the expected payback period, and compared with alternative investment opportunities.

The RAV, expressed as a percentage, is calculated by taking the annual cost of maintaining the asset and dividing it by the total replacement value of the asset. RAV is typically in the range of 2% to 5%. This calculation requires defining how the total RAV has been calculated, e.g., whether or not the asset running costs are included.

DCF is a valuation method used to estimate the value of an investment based on its expected future cash flows. DCF analysis attempts to figure out the value of an investment today, based on projections of how much money the investment will generate in the future. This method is also used to compare competing projects.

In some cases, the developed budget will not receive the approval by management because, for example, the calculation method used (RAV, DCF, etc.) does not show the expected result, e.g., does not fit with the available resources. In this scenario, the budget may need to be revised. Cost reduction typically falls into three categories:

- Scope reduction
- Scope deferment
- Value engineering

Value engineering is a methodology to systematically investigate different value-for-money scenarios based on adjusted project requirements to ensure that adequate quality is delivered at optimum cost. It can be applied when companies are seeking opportunities for budget reduction without impacting project scope or quality. To cut the budget without adjusting the project requirements accordingly is typically not a good solution. Also, the impact on TCO of any proposed solution should be considered in this review.

4.5 Cost Monitoring, Control, and Reporting

Cost monitoring and control is the process of evaluating the status of the project/activity to update the overall costs and managing or preventing changes to an approved baseline and budget. This process should be performed continually throughout the project/activity in order to be effective.

Cost monitoring and control usually include, at a minimum, processes for the following:

- Providing an overview of costs budgeted, allocated, spent and paid for (capital and expense, internal versus external costs)
- Identifying and, where possible, influencing the factors that cause changes to the authorized cost baseline
- Ensuring that all change requests are acted on in a timely manner and within the predicted budget
- Ensuring that cost expenditures do not exceed the authorized funding by period, by WBS component, by activity, and in total for the project
- Monitoring cost performance to isolate and understand variances from the approved cost baseline
- Monitoring work performance against funds expended
- Tracking the amount of change orders required, as this shows how accurately the project was defined in the first place

Cost monitoring and control enables the prevention of changes and helps to keep expected cost overruns within acceptable limits. Monitoring and controlling the project/activity cost requires knowledge of the actual costs spent to date. Any increase to the authorized budget can only be approved through an integrated and approved process of change control. Monitoring the expenditure of funds without regard to the value of work being accomplished for such expenditures has little value to the project/activity, other than to track the outflow of funds.

Much of the effort of cost monitoring and control involves analyzing the relationship between the consumption of funds and the work being accomplished for such expenditures. In order to do that, work performance data is gathered in a continuous manner from the field. Work performance data should contain data on project/activity status, such as which costs have been authorized, incurred, invoiced, and paid.

The work performance data is usually generated by the use of certain metrics to predict trends, allowing the team to effectively identify the necessary corrective actions. Accurate data is essential in order for the evaluations to effectively denote corrective actions. Work performance data is then completed with information on how the project work is performing compared to the cost baseline.

Typical techniques to monitor and control costs are:

- Variance analysis
- Earned value analysis

These techniques are also necessary for forecasting needs and, at a later stage, financial analysis. Variances in the work performed and the cost of the work are evaluated at the work package level and control account level. For projects using earned value analysis, Cost Variance (CV), Cost Performance Index (CPI), Estimate at Completion (EAC), Variance at Completion (VAC), and To Complete Performance Index (TCPI) are documented for inclusion in the status reports.

Analysis of project performance may result in a change request to the cost and schedule baselines or other components of the plan. Change requests are processed for review and disposition through an integrated change management process.

Lastly, cost reporting is necessary to inform all appropriate stakeholders of potential, approved, or declined changes to the baseline or project/activity budget and the general associated cost performance. This data should be collected periodically into a Cost Control Report, which can even be incorporated into a broader project/activity control report. The Cost Control Report typically contains the following components:

- Approved budget
- Current activities
- Cost expended to date
- Percentage of work completed
- Estimated final cost or forecast: Estimate to Completion (ETC) and EAC
- Variation + or -

The organizational procedures that can influence and be leveraged for the correct execution of cost monitoring and control include:

- Formal and informal cost control-related policies and guidelines
- Cost control tools
- Monitoring and reporting methods to be used
- Expert judgment engagement

5 Core Concept – Organization and Control

5.1 Introduction

Organization and control is a core concept of GEP, as shown in Figure 2.1. Organizational structure should ensure maximum efficiency and that the overhead remains commensurate for the respective output. Control mechanisms, including monitoring, within an organization should monitor the performance and progress of assigned activities and apply corrective measures when the performance is not met. A clear structure of organization and control is essential for effectively responding to the changing demands of the business.

The organizational setup should ensure that the degree of control is commensurate with the level of maturity of processes over time and with the demonstrated performance level of those responsible for carrying out those processes. This setup includes the organization of teams, interfaces, scope of work definition, as well as the stakeholders of an operational engineering function or of a project. Appropriate management support is crucial for success in the respective scope of work.

Companies should have a long-term business strategy, which may include formal site/organization plans (e.g., Site Development Plans).

5.2 Supporting Engineering Practice Capabilities

Companies should develop and establish GEP capabilities, for example:

- Management support for the establishment of and adherence to GEP for design, delivery, and operation of engineered systems
- Definition of good documentation practices appropriate for GEP processes (engineering GDP) with rigor commensurate with risk
- Established processes for auditing GEP to ensure established written procedures are appropriate for engineering processes and are followed
- Good understanding of the GEP requirements, purpose, and success factors that cultivate a culture of GEP throughout the organization
- Reproducible and predictable engineering delivery system for operational and project engineering
- Continual improvement process to incorporate lessons learned from past projects into corporate engineering guidelines or standards
- Enabling the stakeholders to understand the interdependencies, roles and responsibilities, and complexities of GEP in the operational and project environments

The organizational structure should be appropriate for this purpose. Well organized operational engineering functions and projects need to be aware of relevant regulations, business needs, HSE, and the GMP/Quality perspective. Practices need to be established to properly implement respective requirements into design, planning, execution, and documentation.

5.2.1 **Management Support**

Management needs to be structured to sufficiently support and serve operational engineering and project engineering, based on trust and collaboration. Management should lead by example and share decision-making with the employees. Decisions need to be taken at the right level, and people need to be empowered to execute as appropriate for their area of expertise and level of responsibility.

This approach also applies to operators and involving them during project phases such as concept, design, and C&Q. Performing Gemba walks¹ with the operators is also a good practice. Operators are key players in design enhancement and continual improvement. See Chapter 6, Section 6.2.2 for more information on continual improvement.

Management also needs to ensure proper time management of team members considering their work life balance.

Establishing interdisciplinary teams helps to avoid silos in the organization and extends the knowledge basis for decisions. Operational excellence initiatives help to improve workflows and create a better working environment.

5.2.2 **Established GEP Procedures**

Companies should have defined procedures to cover the anticipated range of projects as well as operational engineering support. This includes appropriate governance procedures, either on a general basis or for an individual project or function. These procedures should be approved, managed, and controlled through the EQP when supporting GMP activities. These procedures should reflect the project group or function structure and the respective reporting structure, and a documentation strategy, describing:

- Retention and storage criteria
- Planning, progress, and cost reporting
- Change management (appropriate to each stage and activity)
- Design reviews
- Quality control, including punch list management to capture discrepancies, incidents or other unexpected situations and field findings

Companies should organize their project and operational engineering activities according to defined procedures and processes. There should be a formal method of developing a project plan to achieve the defined objectives, reviewing them against the organization strategies/plans with a means of monitoring project progress against the project plan. There should also be a formal method of developing the objectives for the operational engineering function to optimally support and contribute to business success, including performing reviews against the company strategies/plans.

5.2.3 **Engineering Good Documentation Practice**

GEP documentation should adequately support several processes such as ECM, design review, maintenance, and the integrated C&Q process, as based on the appropriateness of that rigor for the given GEP activity and may determine the extent of Quality unit approvals. Therefore, engineering GDP should be established to provide the appropriate data quality.

¹ Gemba (going to where the work is) is an element of Lean principles. Gemba walks enhance the culture of excellence of a site by creating visible management commitment and engaging employees at all levels of the organization. (ISPE Cultural Excellence Report (201))

Engineering GDP standards should consider the principles of ALCOA. Data should be:

- **Attributable:** Identify who performed a recorded task and when it was performed.
- **Legible:** Information should be readable and unambiguous.
- **Contemporaneous:** Recorded or observed at the time of activity.
- **Original:** Original data is the first recording of data, or a “true copy” which preserves content or meaning.
- **Accurate:** Free from error. No editing performed without documented amendments.

These and other principles should be applied in a manner that is appropriate for the GEP activity being performed and commensurate with the risk-based rigor of the activity and its related documentation. Documentation should establish evidence of who has done what, when, and why. Documentation should be well maintained to ensure data completeness, accuracy, and consistency. Documentation standards should be defined for data lifecycle management.

What is appropriate for GEP activities is not the same as what is appropriate for GMP activities, and should not be expected to be. For the purposes of this Guide, the additional data integrity principles of ALCOA+ (Attributable, Legible, Contemporaneous, Original, Accurate, Complete, Consistent, Enduring, Available), as defined in the Pharmaceutical Inspection Co-operation Scheme (PIC/S) Guidance on Data Integrity [21] and elsewhere, generally apply to data that support product quality within the PQS, and are therefore considered to be outside of the scope of GEP. The definition of appropriate engineering GDP in support of the integrated C&Q process or other Quality activities should be determined based on risk assessment and defined in the EQP (see Chapter 13).

5.2.4 GEP Auditing

Internal audits and reviews help to verify proper execution and progress to support the project teams and operational functions in meeting their objectives and achieving business success. Such audits could either be performed on a regular basis or could be driven by incident or risk, size of a project, or impact of a site function. The auditing function does not necessarily need to be a Quality function; it could rather be an SME with auditing skills from a peer engineering function, e.g., from another site. The purpose of such audits should be a collaborative approach to evaluate the maturity of established GEP procedures and to support improvement of the inspected function where appropriate. The more mature the company's GEP capabilities are, the less Quality unit involvement and oversight (approvals) may be required to ensure appropriate outcomes. Refer to Appendix 4 for a GEP inspection checklist template.

From a project perspective, an audit process can cover the following aspects:

- Proper setup of the project organization
- Whether sufficient resources are allocated to the project
- Identification and consideration of interfaces to the site organization and existing installations
- Training and application of relevant procedures and best practices
- Application of engineering GDP
- Budget established according to local requirements, regarding allocation to cost centers, separation of capital and expense, investment in tangible and intangible items, etc.

- Appropriate change management system established to manage scope changes and the related impact on cost, quality, resources, and schedule
- Project controls and reporting

From an operations perspective, the audit can cover the following aspects:

- Whether the organization mirrors the scope of work and the resources are sufficient
- Proper allocation of the budget to cost centers, whether the budget is sufficient
- Establishment of regular cost reporting
- Application of engineering GDP
- Adherence to procedures and availability of records and engineering documentation, including certificates for inspections required by internal and external regulations
- Adherence to maintenance and calibration schedules, including both GMP and HSE relevant activities

5.3 Organization

Operational engineering is a crucial function in every regulated company organization, being involved in the execution of capital projects and supporting operational functions (e.g., manufacturing) in routine activities and interventions. Operational engineering plays a critical role in responding to the needs of operations, which can impact ongoing activities as well as company strategic plan implementation. For this purpose, there needs to be suitably skilled and experienced staff to perform and support the systems under GEP and keep the systems up to date.

5.3.1 Scope of Engineering Organization

The scope of work of the organization should be clearly defined, in order to identify the applicable areas of responsibility for each function contributing to the overall objectives as well as interfaces to peer functions and external parties (i.e., service providers, contractors, or external partnership involvement). Typically, an organization chart and description should clearly reflect these aspects. A responsibility matrix such as the RACI (Responsible, Accountable, Consulted, Informed) matrix is commonly used.

Functions related to engineering cover the areas of capital project engineering and operational engineering, with the local organization being structured, trained, developed, and continually assessed in a way to best achieve its objectives. Standard Operating Procedures (SOPs) act as a common basis for both internal and external staff.

5.3.2 Capital Project Engineering

Capital project engineering deals with structured development, execution, and implementation of capital investments, supporting the business strategy of the company. See Chapter 8.

5.3.3 Operational Engineering

Operational engineering organization should be considered as another key factor to support the company in reaching business goals and ensuring continuity and sustainability. Each company should have a dedicated organization to ensure that manufacturing plants and supporting equipment and facilities operate and are maintained at an appropriate level of efficiency and reliability. This needs to be based on a clear allocation of the CAs/CDEs of the equipment related to quality (GMP), safety (HSE), and business. See Chapter 11.

5.3.4 Engineering Design Standards and Specifications

Operational engineering within a regulated company is responsible for building a rigorous, disciplined, and sustainable framework for operational and project engineering to apply to projects and activities on-site. The organization should have a defined approach to specifications and engineering design standards. These specifications and design standards may be generated internally and/or reference ISO [22], ASTM [23], or other industry standards, and should be kept current by leveraging lessons learned through past projects and activities. Maintaining these specifications and design standards in a current state can be costly, but beneficial over time, because they drive consistency across the organization utilizing GEP and guide the development of projects toward the best value for the company.

5.4 Monitoring and Control

Monitoring is part of control. It is a mechanism of tracking and measuring the progress of a project against predefined performance criteria. It is used to determine the effectiveness and efficiency of engineering functions on-site with respect to contributions to manufacturing. It serves to provide the team and stakeholders with a clear vision on the current status and opportunities for improvement.

Data should be collected continually and reported on a regular basis throughout a project and for the engineering function. Monitoring requires transparency and data accuracy to enable effective corrective actions to take place.

Companies should have systems for identifying and collecting the most appropriate means of monitoring data related to project constraints, including budget, schedule, and quality.

The types of data that are commonly monitored include:

- Risks list (e.g., project risk register, system risk profile)
- Current project activities
- Approved budget (project/engineering function)
- Budget expended to date (combined with earned value calculation for a project)
- Cost forecast
- Spent resources/hours
- Percentage of work completed
- Schedule forecast
- Variation
- Project and engineering changes
- Punch list, discrepancies list
- Safety incidents

In keeping effort commensurate with the level of benefit, the team should agree on the critical data that should be monitored as well as the monitoring frequency, as aligned with the requirements set by the company. Reporting of data should be limited to what is reasonable and adds value, while providing comprehensive information at the appropriate level of detail and as an appropriate basis for decision-making. This approach minimizes extraneous workload. Moreover, monitored variables might change from a project to another and from a project phase to another.

Once collected, the data should be assessed in order to identify and predict trends that allow the team to apply improvements in risky areas where discrepancies to the original plan are observed.

Control is meant to overcome these observed issues by implementing preventive and corrective actions. Control actions are closely aligned with change management. The tools used to operate control actions include, but are not limited to:

- Risk management (Chapter 3)
- ECM or project change management (Chapter 7)
- Issue management (Chapter 7)
- Document and drawing management (Chapter 7)
- Vendor management (Chapter 10)
- Auditing

Based on the experience of the authors, these tools have been effective in monitoring and controlling capital investment projects and system operational lifecycle.

Monitoring and control mechanisms are beneficial during and after a project as well as for engineering functions. The key benefits include:

- Providing a clear and transparent status to both the team and the stakeholders
- Supporting decision-making to stay within a budget while delivering the required quality in a timely manner
- Forecasting trends and anticipating future issues
- Predicting final cost as well as date of completion and adherence to schedule
- Providing valuable benchmarking data that can be useful for similar projects or the next budget period for the engineering function

6 Core Concept – Innovation and Continual Improvement

6.1 Introduction

Innovation and continual improvement are an important element of the EQP with the goal of optimizing a process/system to improve product quality, better meet business needs, and reduce HSE impacts.

6.1.1 Scope

Improvement approaches can generally be distinguished into three categories:

- Corrective action
- Continual improvement
- Innovation

Implementation of Corrective Actions and Preventive Actions (CAPAs) can be part of GEP. However, CAPA programs are generally considered to be a GMP activity and therefore out of scope for this Guide, except for as applicable to demand/breakdown maintenance and routine maintenance (see Chapter 11, Section 11.4). The implementation of CAPAs should follow the ECM process as outlined in Chapter 7.

6.1.2 Objectives and Guiding Principles

Innovation and continual improvement are core concepts for GEP. Innovation and continual improvement support industry objectives for encouraging new technological advances, utilizing state-of-the-art pharmaceutical science, applying risk-based approaches to focus attention on critical areas, improving patient outcomes and reducing environmental impacts.

Innovation is defined as:

“The introduction of new technologies or methodologies.” (ICH Q10 [7])

Continual improvement is defined as:

“Recurring activity to increase the ability to fulfil requirements.” (ICH Q10 [7] and ISO 9000 [9])

In the context of GEP, innovation and continual improvement serve to reduce waste, provide better occupational conditions for the operator, and support the development, implementation, and operation of processes that are more efficient (and therefore less costly). Risk management is a critical component of this process.

6.1.3 Enablers

A key enabler of innovation and continual improvement is product and process knowledge—an understanding of the process and of the quality attributes of the product. A process can be considered well understood when all critical sources of variability are identified and explained, variability can be managed by the process, and product CQAs and related CPPs are clearly defined. Data and measurements are key elements to understanding a process. At a minimum, there should be a constant analysis of data collected and cost incurred in past projects or activities, as well as the update of the lessons learned register.

A second enabler for innovation and continual improvement relates to culture. It involves overcoming risk aversion related to the adoption of new technologies, developing confidence in risk communication, and the willingness to engage in research, development, and capital investment required to apply new technologies and state-of-the-art science.

6.2 Improvement Approaches

The characteristics and objectives of innovation and continual improvement as follows:

- Innovation
 - *“Revolutionary, to be a leader*
 - *Focused applications – project based*
 - *Significant capital expenditure, ROI, Top-down*
 - *Strong research component*
 - *Technical experts involved*
 - *New findings and improved knowledge”*
- Continual improvement
 - *“Product is in specification*
 - *Acceptance criteria – variable/continuous data*
 - *Evolutionary, incremental process optimization, continuous, daily activity*
 - *Carried out by plant and quality staff”*

(US FDA White Paper: Innovation and Continuous Improvement in Pharmaceutical Manufacturing [24])

6.2.1 Innovation

Innovation is different from continual improvement; it is not part of the day-to-day operations and may require additional resources to support changes in production design and operation. Innovation represents revolutionary changes, state-of-the-art science, and new approaches. Innovation can be challenging in a regulated industry, but can be facilitated through application of QbD principles and risk-based approaches. An impact assessment may be required to ensure that there is no impact to the regulatory filings.

6.2.2 Continual Improvement

Continual improvement focuses on the incremental optimization of current processes and evolutionary improvement of product quality and performance with respect to business needs, based on refinement of existing product and process knowledge. A key focus of continual improvement is the reduction of variability and elimination of process waste, which improves both the quality output and overall efficiency of the process.

In order to improve the process of cost monitoring and control, as well as the reporting, data gathering, change implementation, and lessons learned sharing, a continual improvement mindset is highly desirable so that new, robust tools are used for future projects and activities. In this sense, continual improvement should become a part of the organization's culture.

6.2.2.1 Continual Improvement Methodologies

There are numerous methodologies that can be utilized for continual improvement, including for example:

- Plan-Do-Check-Act (PDCA) Cycle
 - *"A four-step process for quality improvement. In the first step (plan), a way to effect improvement is developed. In the second step (do), the plan is carried out. In the third step (check), a study takes place between what was predicted and what was observed in the previous step. In the last step (act), action should be taken to correct or improve the process."* [25]
- Six Sigma/Lean
 - Six Sigma is a structured approach to reduce process variability and to increase process control through a process of Define, Measure, Analyze, Improve, and Control (DMAIC). Lean is a structured approach to improve process effectiveness and efficiency by reducing process waste.
 - These approaches are often merged as Lean Six Sigma, *"a fact-based, data-driven philosophy of improvement that values defect prevention over defect detection. It drives customer satisfaction and bottom-line results by reducing variation, waste, and cycle time, while promoting the use of work standardization and flow, thereby creating a competitive advantage. It applies anywhere variation and waste exist."* [25]
- Gemba Walks
 - A practice in Lean management involving going to "the actual place" or "the place where value is created." Gemba walks represent management commitment by going to the shop floor, observing the process as it is performed, and talking to the operators who perform the process.

6.2.2.2 Process Analytical Technology

Process Analytical Technology (PAT) can help deliver continual improvement by making data collection and analysis efficient, as well as simplifying real-time monitoring and the ability to predict outcomes. The end results of utilizing these tools are insights into process variability, correlation with critical design aspects, real-time statistical analysis, and the potential to utilize machine learning to handle the large amounts of data that are generated by modern processes.

6.2.2.3 Benchmarking

Benchmarking is another tool for innovation and continual improvement. Benchmarking improves organizational understanding by providing a basis to compare performance against internal organizations, direct competition, and "best-in-class". Benchmarking can be done at the strategic level, the project level, and the process level.

Benchmarking in the context of GEP typically covers the following areas:

- Commissioning costs
- Calibration and maintenance practices

- Reliability
- Building costs
- Project timelines
- Equipment utilization
- Manpower and staffing levels
- HSE issues

Benchmarking can be an internal effort or can be sourced out to external parties that provide benchmarking services.

7 System Lifecycle Processes

7.1 Introduction

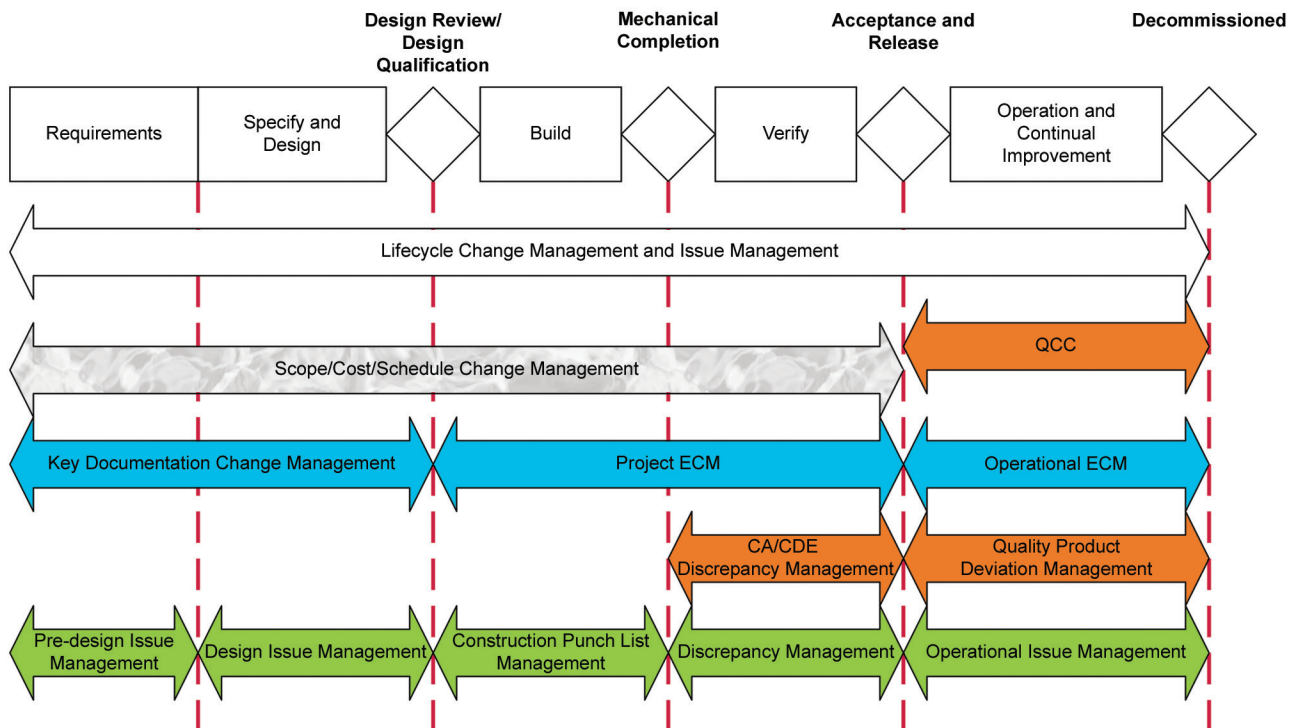
System lifecycle processes are the established engineering methods that ensure engineered systems are:

- Consistently and reliably designed, delivered, and operate in a manner suitable for the intended purpose according to user requirements, stakeholder expectations, and quality requirements
- Maintained in a state of control throughout their lifecycle, in order to minimize risk to product quality and patient safety

This chapter presents an approach to key system lifecycle processes:

- **Change management** during the requirements, specify and design, build, verify, operations and continual improvement phases of the lifecycle, with particular focus on GEP and integration with QRM (where applicable).
 - This chapter identifies the interfaces to change management processes outside the scope of this chapter, such as project ECM [1], operational ECM (during the system operational lifecycle), and Quality Change Control (QCC).
- **Issue management** includes the management of engineering issues, punch lists, and discrepancies. It is an important tool to help manage systems at each system lifecycle stage, including system design, delivery, operation, and decommissioning.
- **Document and drawing management** includes defining processes to manage the records to support all engineering/project/operations activities during all stages of the lifecycle. This is a process for generation, review, approval, retrieval, and archiving of written standards, procedures, and records, whether paper-based or electronic, while maintaining document security and integrity and adhering to engineering GDP principles.

Figure 7.1 provides an overview of the lifecycle change management and issue management processes. These processes are discussed in more detail in Sections 7.2 and 7.3.

Figure 7.1: Overview of the Lifecycle Change Management and Issue Management Processes

7.2 Change Management

Change management is critical to GEP. Processes should be defined for change management that are scaled to the risk, complexity, and system lifecycle stage. ECM can be applied during routine operations as part of, or in tandem with, a QCC Process and/or applied as a standalone process in projects.

7.2.1 Purpose and Scope of Change Management

GEP-based change management must be established throughout a manufacturing system's lifecycle. A major challenge faced by industry relates to the implementation of risk-based SME-led change management. Change management is considered the first point of control to assess the risk of a change on the accepted/fit for the intended purpose status of a system/equipment.

Change management is the process of:

- Establishing and maintaining a baseline on which the need for change can be evaluated
- Assessing impact, as appropriate to the lifecycle stage, to the budget, schedule, safety, GMP compliance, etc.
- Communicating impact to stake holders for approval
- Providing an avenue to document and complete the change
- Providing accurate records to support the change history for the different types of changes

Change management applies to systems throughout system design and delivery, beginning with requirements definition that includes all product quality impacting (CQAs/CPs) and non-product impacting (HSE, operational/business), and continuing through system acceptance and release until decommissioning. Regulated companies should have systems for recognizing the need for change across design, build, verify, and lifecycle maintenance. Change management activities should be scaled to the risk, complexity, and stage in the system lifecycle.

In the pharmaceutical industry, there are typically five categories of change management as listed below and previously shown in Figure 7.1:

- Scope/cost/schedule change management (part of Engineering Project Management as covered in Chapter 8)
- Key documentation change management
- Project ECM
- Operational ECM
- QCC (covered in detail in *ISPE Baseline Guide: C&Q (Second Edition)* [1] and is out of the scope of this Guide)

Note: Depending on the size and scale of the project, the ECM process used for the project can be the same system as the ECM process used for operations.

As stated in the *ISPE Baseline Guide: C&Q (Second Edition)* [1]:

“A key consideration for successful implementation of a change management system is to apply a flexible approach. No one change management system will fit all situations. The change management system should be able to adapt to fit all stages of the lifecycle.”

For additional information on ECM, refer to Chapter 12 of *ISPE Baseline Guide: C&Q (Second Edition)* [1].

The prospective process of risk management/QRM to identify CAs/CDEs in systems provides the basis for the use of ECM or QCC in the operations phase.

7.2.1.1 Risk Assessment

By incorporating risk assessment, proposed changes should be assessed for potential impact, as appropriate, on scope, cost, schedule, safety, C&Q, compliance, operation, maintenance, reliability etc. Selection of the risk assessment tool is based on factors such as scope of the change, point of time in the lifecycle, system/equipment complexity, and quality or non-quality impact of the change.

For changes to CAs/CDEs, risk assessment as part of the change assessment will review the impact of the change on the initially documented risk profile of the system or process to product quality or patient safety.

For risks that are not related to CAs/CDEs, risk assessment as part of the change assessment is used to determine any impact on the overall quality-related output of a system, the inherent safety of the system, or any business or reliability aspects.

7.2.1.2 Risk Control

Risk control should be commensurate with the associated risk. System testing (C&Q) is the verification that the risk controls have achieved the desired goal. The change management system should give guidance whether this testing is undertaken with an engineering or quality focus. The change management system should also facilitate a method to record the history of risk control.

7.2.2 Lifecycle Change Management

7.2.2.1 Key Documentation Change Management

Prior to design review/design qualification, in lieu of a formal system for change management, a project design issue management system can be used along with control of key project documentation. During the requirements and specification/design phases, the main responsibility for the management of changes (depending on the scale of the project) can reside with a design or engineering service provider. The system should align with the owner organization procedures/standards and there should be suitable oversight from the owner or owner representatives. The owner organization must have controls in place, such as iterative design reviews, for design and punch list activities during construction, to ensure the original design intent is maintained, as documented by the user requirements.

For GMP systems, any changes identified in the project issue management system must consider the potential impact to system CAs and CDEs. Where the QRM risk control strategy for the system is approved by Quality, changes that potentially impact CAs or CDEs must be communicated to Quality. This communication is usually in the form of review and approval of key project documents; this can include documents such as the URS, SRA, Piping and Instrumentation Diagrams (P&IDs) and design review/design qualification.

7.2.2.2 Project Engineering Change Management

Before new systems are used for commercial or clinical operations, there is no risk to the patient associated with changes to design or function during the project lifecycle, and therefore QCC is not applicable. ECM should be applied to manage system changes once the final design is approved. ECM change impact assessment must include an assessment of the impact of the change to the application of QRM to the system.

Further, the change impact assessment must consider the potential impact to the successful delivery of product and process user requirements and/or the ability of the system performance with respect to CPPs or the successful delivery of CQAs. Where CQAs and CPPs have already been approved by Quality, changes to specifications or acceptance criteria for CQAs or CPPs must be approved by Quality.

In all cases, changes managed through ECM are the responsibility of appropriate SMEs to assess, plan, implement, test, and verify implementation following GEP. As part of the lifecycle ECM process, ECM hands off to operational ECM and QCC (if applicable) at system acceptance and release.

7.2.2.3 Operational Engineering Change Management

Operational ECM applies to all systems throughout the system operational lifecycle, from acceptance and release through decommissioning.

Changes that may be managed through operational ECM rather than through QCC include, for example:

- Changes to non-GMP systems
- Changes to installation or operation non-CAs and/or non-CDEs of GMP systems (as documented in the SRA)
- Changes to system performance with respect to non-CPPs or system delivery of non-CQAs
- Certain categories of changes, such as like-for-like, as documented in the completed verification and approved acceptance and release documentation
- Disposal of decommissioned systems

Where operational ECM operates in parallel with QCC, a QRM-based impact assessment of the proposed change should determine whether a proposed change is managed through ECM or QCC. Refer to Section 7.2.2.4 for QRM-based impact assessment.