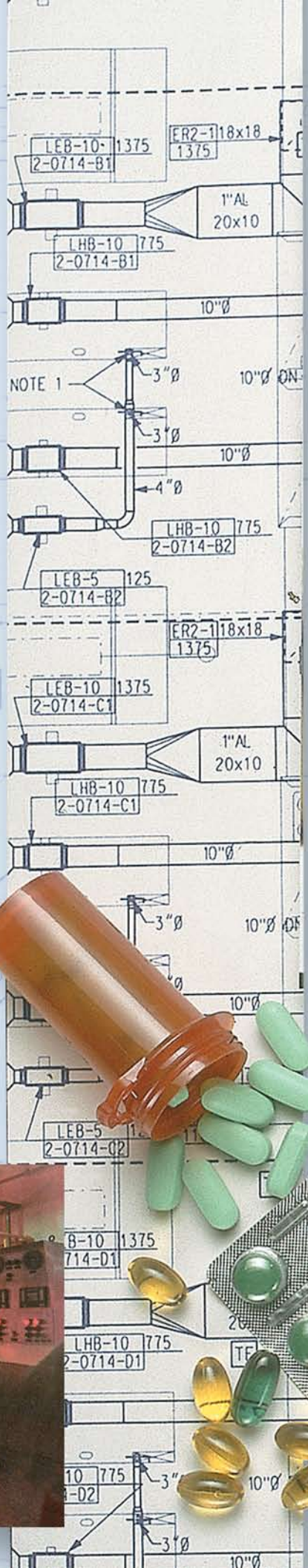
ISPE

Baseline®
PHARMACEUTICAL
ENGINEERING GUIDE

Pharmaceutical Engineering Guides for New and Renovated Facilities



Volume 5
Commissioning and Qualification

First Edition / March 2001

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

February 9, 2001

Dear Colleagues:

The Food and Drug Administration (FDA) is pleased to cooperate with the International Society for Pharmaceutical Engineering in the development of the Baseline® Pharmaceutical Engineering Guide for Commissioning and Qualification of new manufacturing facilities. This Guide is an excellent example of how FDA and industry can work in areas where both industry and the public can benefit.

This document covers engineering aspects of commissioning and qualification of new manufacturing facilities and modifications of existing facilities. FDA's written guidance in this area is limited, but we welcome cooperative efforts and the dedicated intensive work demonstrated by the engineers who voluntarily initiated the development of this Guide.

This Guide is solely created and owned by ISPE. It is not an FDA regulation, standard or guidance document and facilities built in conformance with this Guide may or may not meet FDA requirements. FDA has provided comments for ISPE's consideration in preparing this Guide. It should be helpful to the engineering profession and the industry in commissioning and qualification of manufacturing facilities

FDA is pleased with the development of this document and we look forward to a continued working relationship as future Baseline® Pharmaceutical Engineering Guides are developed.

Sincerely,

Janet Woodcock, M.D.
Director, Center for Drug Evaluation and Research

Dennis E. Baker
Associate Commissioner for Regulatory Affairs

ISPE PHARMACEUTICAL ENGINEERING GUIDE

FOREWORD

For many years, the pharmaceutical industry has experienced increases in the cost of new facilities. These increases in cost have been driven in part by uncertainty about the requirements for regulatory compliance. Some significant areas of concern are validation, particularly related to automation systems, and the trend to validate back to source utilities. The absence of a consistent and widely accepted interpretation of some regulatory requirements has led to one-upmanship. This practice of building increasingly technically advanced facilities has led to increased cost, longer lead times and, in some cases, delays in bringing new products to market.

In May 1994, engineering representatives from the pharmaceutical industry engaged in a discussion with the International Society for Pharmaceutical Engineering (ISPE) and the Food and Drug Administration (FDA). As a result of that discussion in November 1994, ISPE began work on nine facility engineering Guides, now known as the *Baseline*® Pharmaceutical Engineering Guides. The first, "Bulk Pharmaceutical Chemicals," was published in June 1996. The second, "Oral Solid Dosage Forms," was published in February 1998. The third, "Sterile Manufacturing Facilities," was published in February 1999. The fourth, "Water and Steam Systems," was published in January 2001. This is the fifth such Guide, covering "Commissioning and Qualification." Each Engineering Guide was created by, and is owned solely by ISPE. The FDA provided comments on this and previous Guides, and many of their suggestions have been incorporated.

As with the other previously published Guides, the Commissioning and Qualification Guide has been sponsored by ISPE's Pharmaceutical Advisory Council, made up of senior pharmaceutical engineering executives from owner companies, and ISPE senior management. Overall planning, direction, and technical guidance in the preparation of the Commissioning and Qualification Guide was provided by a Steering Committee most of whom were involved in the Bulk Guide. The Commissioning and Qualification Guide itself was produced by a Task Team of individuals who expended a great deal of their own time in its preparation and development.

Editors' Disclaimer:
This Guide is meant to assist pharmaceutical manufacturers in the design and construction of new and renovated facilities that are required to comply with the requirements of the Food and Drug Administration (FDA). The International Society for Pharmaceutical Engineering (ISPE) cannot ensure, and does not warrant, that a facility built in accordance with this Guide will be acceptable to the FDA.

ACKNOWLEDGEMENTS

This Guide was developed by an integrated US-European team under the co-leadership of Alan Phillips of Pfizer and Christopher Wood of GlaxoSmithKline.

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[1] With the support of John Hughes (TVS Inc.), Jon Sheh (Alza Inc.) and Gary Schoenhouse (Genentech).

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Robert Coleman (National Drug Expert, DEIO)

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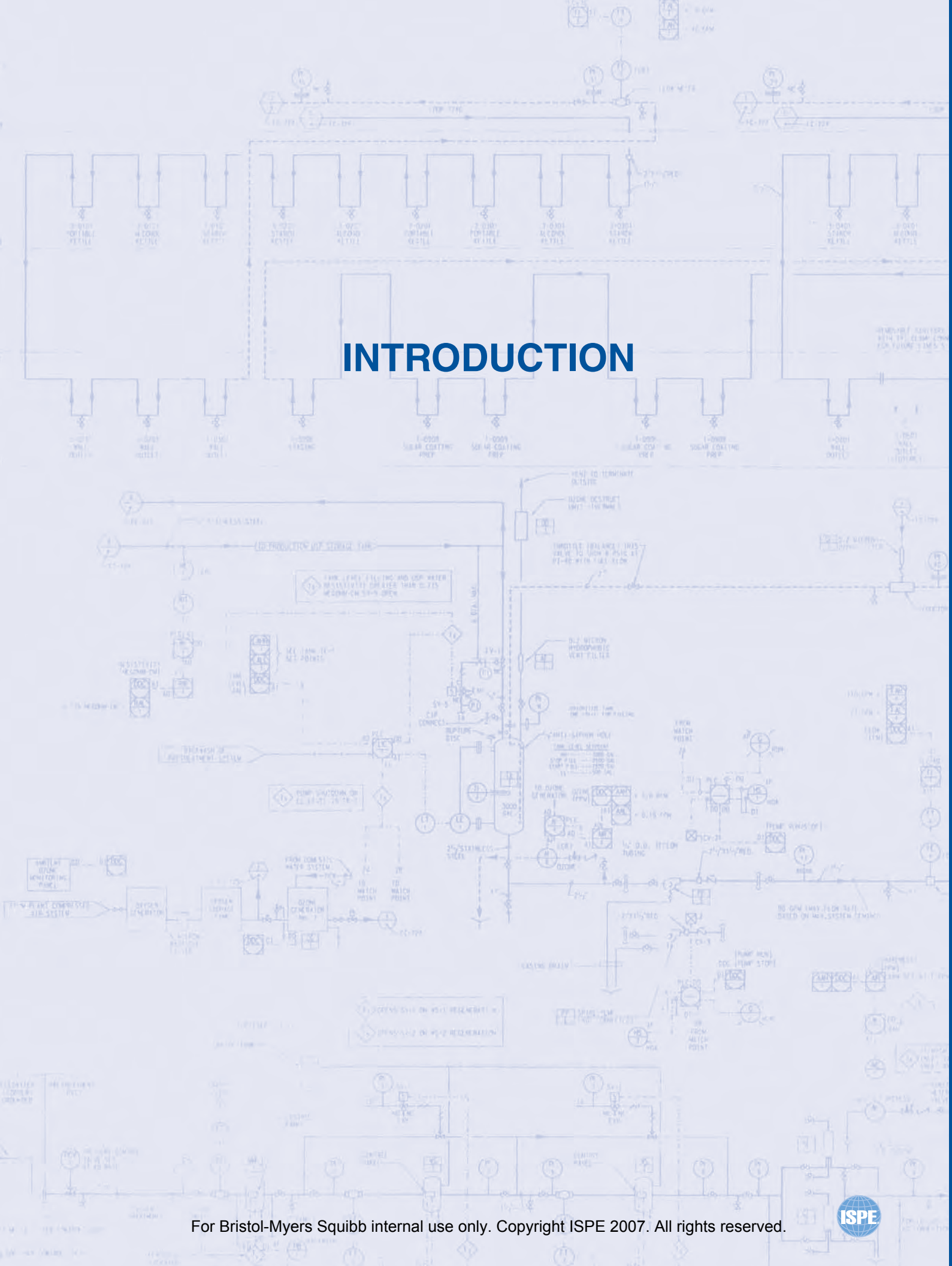


1. INTRODUCTION

1.1 BACKGROUND

The design, construction, commissioning, and qualification of manufacturing facilities regulated by the FDA or other regulatory authorities pose significant challenges to manufacturers, engineering professionals and equipment suppliers. These facilities are required to meet cGMP regulations while remaining in compliance with all other governing codes, laws, and regulations.

The cost and time required to bring such facilities on line has been increasing, in many cases due to inconsistent interpretation of regulatory requirements. The ISPE and engineering representatives from a broad base of healthcare companies (e.g., pharmaceutical, device, biotechnology, etc.) have entered into a partnership with the FDA to enhance understanding of Baseline cGMP requirements for facilities. This Guide is intended to define key terms and offer a consistent interpretation, while still allowing a flexible and innovative approach to facility design, construction, commissioning and qualification. A fundamental goal of the Guide is to provide value added guidance to industry that will facilitate timely and cost effective commissioning and qualification of facilities.

This Guide is one in a series of Baseline® Guides being planned and produced by ISPE. The majority of these are specific to one functional area (e.g., Oral Solid Dosage Forms); however, this Guide provides advice and guidance that may be applied to all types of facilities, utilities, and equipment found in the healthcare industry.

This Guide was prepared by ISPE, and has incorporated comments from:

- industry representatives from all areas and disciplines
- FDA Field Investigators and personnel from The Center for Drug Evaluation and Research

It is recognized that industry standards evolve and this document reflects the understanding of them as of publication date.

1.2 SCOPE OF THIS GUIDE

This is a Guide to be used by industry for the design, construction, commissioning, and qualification of new or newly renovated manufacturing facilities that are regulated by the FDA or other health authorities. It is neither a standard nor a GMP. It is not intended to replace governing laws, codes, standards, or regulations that apply to facilities of this type. These are mentioned only for completeness and where their impact affects facility, equipment and utility design relative to cGMPs. The use of this document for new or existing facilities, equipment, or utilities is at the discretion of the owner or operator.

This Guide focuses on the engineering approaches and practices involved in providing cost effective manufacturing facilities in a timely manner that meet their intended purposes. Specifically, the Guide addresses the process of designing, constructing, commissioning, and qualifying the facilities, utilities, and equipment regulated by the FDA or other health authorities.

This Guide is not intended to address any aspect of process/product validation. This is a subject that has been well defined by the FDA and other authorities, and for which substantial guidance documentation exists.

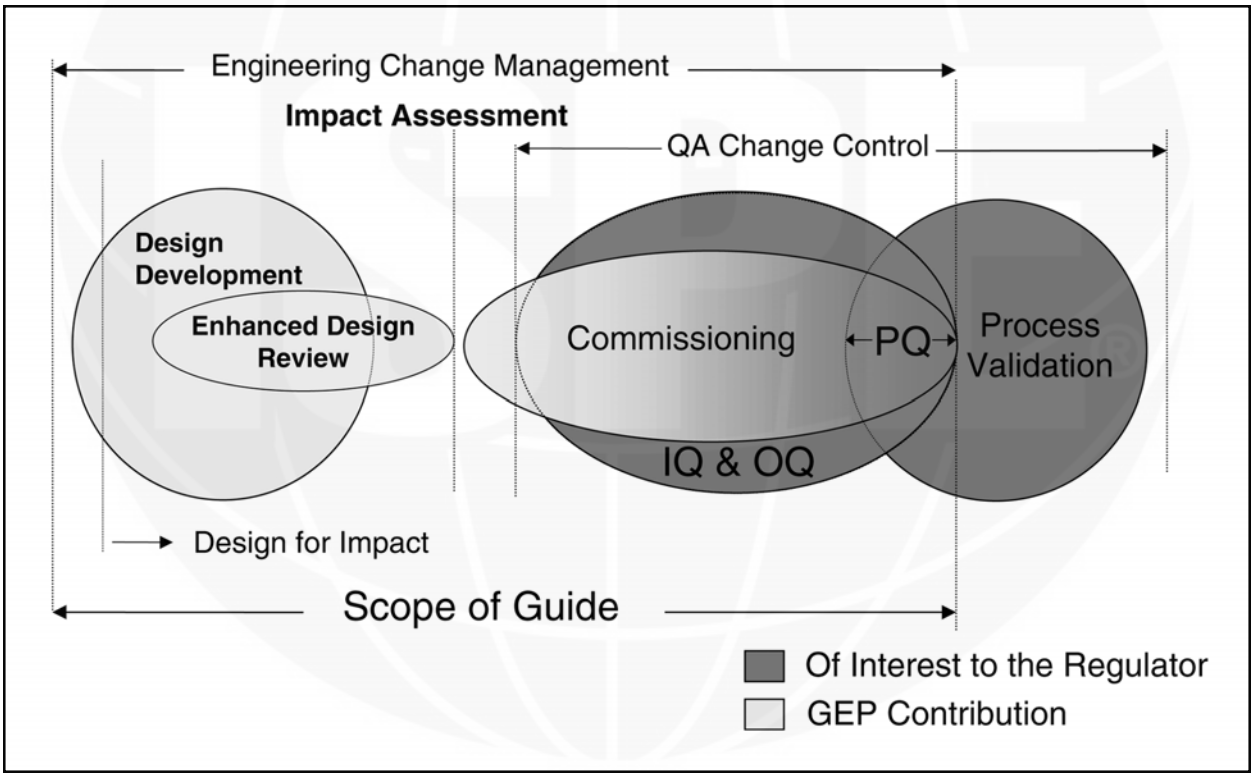
It must be recognized; however, that **Commissioning and Qualification** activities are the foundation upon which Process Validation is built. Furthermore, these activities play a crucial role in delivering operationally effective, safe and efficient facilities, utilities, and equipment. Therefore, it is important to ensure that a comprehensive approach is undertaken during the commissioning and qualification process. A well conceived and executed commissioning and qualification plan can greatly facilitate a timely and cost effective validation effort.

Where non-engineering issues are covered, (e.g., support systems, documentation, decision processes) the guidance is provided to show engineers the importance of such topics and the impact they have on the commissioning and qualification process. Consequently, non-engineering topics are not covered comprehensively. Specialist advice from QA Departments should be sought where additional information is required.

The Guide is intended primarily for facilities, equipment, and utilities required to meet regulatory requirements to supply the United States (US) market and is aligned with US standards and references. The Guide also may be helpful to manufacturers needing to meet European requirements.

The scope of this Guide is summarized in the diagram below.

Figure 1-1 Scope of the Commissioning and Qualification Guide



1.3 KEY FEATURES AND CHAPTERS OF THIS GUIDE

The following key concepts are defined and used as a basis for guidance:

- "Direct Impact" systems
- "Indirect Impact" systems

- System Impact Assessment
- Good Engineering Practice
- Commissioning
- Qualification Practices
- Enhanced Design Review
- Installation Qualification
- Operational Qualification
- Performance Qualification
- Consistent Terminology
- Documentation Requirements

SOME BRIEF EXPLANATION OF THESE IS AS FOLLOWS:

It is the function of the facility, equipment, or utility that determines what level of commissioning and qualification are needed.

- **"Direct Impact" systems** are expected to have an impact on product quality
- **"Indirect Impact" systems** are not expected to have an impact on product quality

Both types of systems will require **commissioning;** however, the "Direct Impact" systems will be subject to supplementary **qualification practices** to meet the additional regulatory requirements of the FDA and other regulatory authorities.

This differentiation between system type is important and will determine the attention and effort given to each and by whom. Therefore, the determination as to whether the system is "Direct" or "Indirect" impact is critical. System Impact Assessment provides the thought process as well as some key questions that must be asked in making the determination.

During the production of this Guide, regulatory authorities have expressed concern that designating a system "Indirect Impact" might be a means of doing less than full testing on a system that may actually require it. This is not the intention. The objective is that through a comprehensive impact assessment process, those systems presenting a risk to product quality are identified and given the attention appropriate to this level of risk, by the right people. The importance of involving QA in the impact assessment and determination process is emphasized, as the impact assessment forms the foundation upon which qualification rationales and plans are ultimately based.

For this process to work it is essential that an explicit rationale is provided for the "Indirect"/"Direct" impact assessment and that the rationales are fully understood, documented, and endorsed by QA Departments. This places a responsibility upon engineers to communicate clearly the nature of operation of engineering systems and their potential impact on product quality.

It also will be seen that throughout the Guide, the application of **Good Engineering Practice** is essential to the commissioning and qualification activities. Good Engineering Practice, commonly referred to as GEP, is proven and accepted, cost-effective, engineering methods and practices that ensure the effective satisfaction of stakeholder requirements. As such, GEP ensures that an engineering project meets the requirements of the user while being cost effective, compliant with regulations and well documented. Guidance and standards that have been defined by engineering institutes and other learned bodies support GEP. For "Direct Impact" systems, GEP is supplemented by enhanced documentation and qualification practices with the active participation of Quality Assurance personnel.

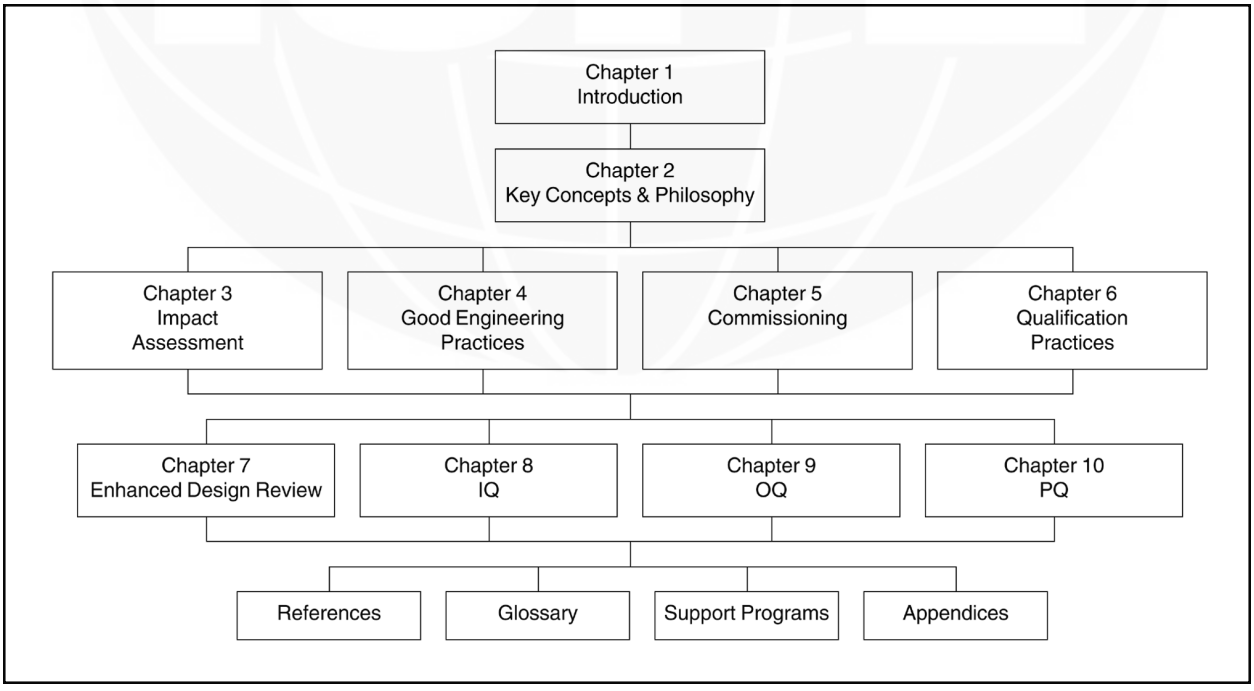
The Guide also attempts to clarify some misconceptions about how activities are defined, which activities are the subject of regulatory oversight and the sequence, if any, of these activities. For example, the Guide discusses **"Enhanced Design Review"** (EDR) and the components and criteria of this activity. The intent is to identify design aspects that are key to manufacturing facilities regulated by the FDA or other health authorities. How this enhanced design review is accomplished, either with a formal or informal process, is at the discretion of the individual company. The intent is not to establish new administrative requirements, especially for those activities not regulated by the FDA or other regulatory authorities. Enhanced Design Review is not essential for compliance of manufacturing facilities regulated by the FDA. EDR is not referenced in any regulatory publication as regulation, rules, or guidelines; however, design is well referenced in current Good Manufacturing Practice, e.g.:

The Code of Federal Regulations (CFR) title 21 Part 211 Subpart C - Buildings and Facilities and Subpart D - Equipment.

Installation Qualification (IQ), Operational Qualification (OQ), and Performance Qualification (PQ) are activities that the FDA may have an interest in, since these are the final activities before Process Validation can begin. IQ/OQ in many instances is done concurrently with commissioning and requires the enhanced documentation, QA involvement, and additional tests and checks known as **Qualification Practices.**

An overview of the Chapter structure is given in Figure 1-2.

Figure 1-2 Chapter Structure

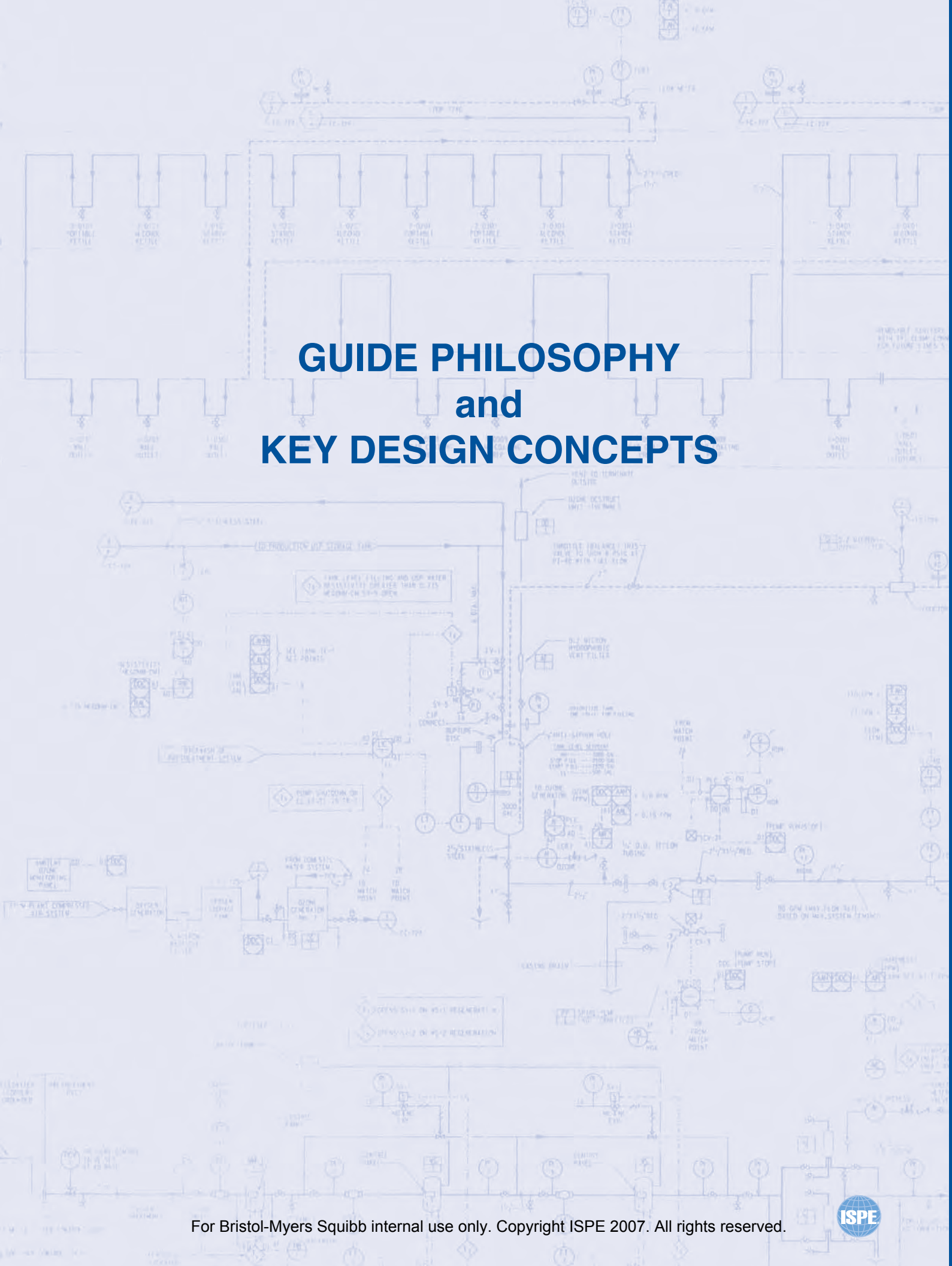


1.4 GOALS OF THIS GUIDE

There are two primary goals of the Commissioning and Qualification Baseline® Guide. The first is to bring a common terminology and methodology to the commissioning and qualification process that can be used by manufacturers, facility designers, contractors, and equipment suppliers. The second is to provide a System Impact Assessment process to bring structure and consistency to determining a "Direct Impact" system and "Indirect Impact" system.

An important secondary goal is to foster an interdisciplinary team approach to commissioning and qualification. Such an approach will help establish an effective basis for master planning and execution of facility projects. Specifically, the Guide is focused upon value added approaches that will eliminate duplication of effort and the costly practices of:

- Repeating qualification steps during process validation
- Qualifying systems that only require commissioning
- Generating insufficient or excessive documentation
- Excessively long project schedules
- Delays which can result in product supply interruptions or delayed product launches



GUIDE PHILOSOPHY and KEY DESIGN CONCEPTS

2. GUIDE PHILOSOPHY AND KEY CONCEPTS

2.1 INTRODUCTION

The purpose of this Guide is to define the Baseline® approach for the Commissioning and Qualification of facilities, utilities, and equipment regulated by the FDA. The differences between the commissioning and qualification processes, the key terms used, and the extent of regulation of the qualification process will be defined and clarified in the Guide. This will assist in optimizing the commissioning and qualification processes at regulated facilities. It is important to understand and apply the approaches outlined in this Baseline® Guide in a sound and well-reasoned manner, since every facility and project is different.

2.2 PHILOSOPHY AND KEY DEFINITIONS

2.2.1 Philosophy

The basic philosophy promoted by this Guide is as follows:

1) **Good Engineering Practice** (GEP) makes a significant contribution to meeting the regulatory demands of the pharmaceutical industry.

2) Where engineering systems may have a **Direct Impact** on product quality, supplementary **Qualification Practices** (in addition to GEP and Commissioning) are required to fully address pharmaceutical industry demands.

3) The **baseline** approach is to restrict the application of Qualification Practices to "Direct Impact" systems and build on the contribution of GEP and Commissioning.

4) Good Engineering Practice is a satisfactory approach for "Indirect" or "No Impact" Systems.

2.2.2 Key Definitions

The key definitions are discussed below and the philosophy is illustrated in Figure 2-1.

2.2.3 Direct Impact System

A "Direct Impact" system is expected to have a direct impact on product quality. These systems are designed and commissioned in line with Good Engineering Practice *and* in addition, are subject to Qualification Practices that incorporate the enhanced review, control, and testing against specifications or other requirements necessary for cGMP compliance.

In some instances, "Direct Impact" systems will depend on "Indirect Impact" systems for effective operation and therefore, any interfaces need to be carefully assessed.

2.2.4 Indirect Impact System

An "Indirect Impact" system' is not expected to have a direct impact on product quality, but typically will support a "Direct Impact" system. These systems are designed and commissioned following Good Engineering Practice only. "Indirect Impact" systems can affect the performance or operation of a "Direct Impact" system and therefore:

- Any interfaces need to be carefully assessed

- It should be ensured that "Direct Impact" systems could detect or prevent a product quality-threatening problem with an "Indirect Impact" system linked to it

In the instance when a system can be used as both a direct and "Indirect Impact" system, the requirements of the "Direct Impact" system must take precedence to ensure compliance to cGMPs.

2.2.5 No Impact System

A "No Impact" system will not have any impact, either directly or indirectly, on product quality. These systems are designed and commissioned following Good Engineering Practice only.

The design and the scope of the application of a system can determine whether or not it will have a direct impact, therefore it should be realized that there is a choice with such systems. "Design for Impact" should be considered early in the development of the design.

2.2.6 Design for Impact

"Design for Impact" is used to describe the practice of making conscious design decisions with respect to the impact of the system in operation **at the beginning of design development.** As suggested by Figure 2-1, the impact of many systems will be determined by their design and application. By careful design, the number of systems having a direct impact can be reduced. The direct impact **functions** remain, but the systems with which they are associated are chosen by the designer.

Where possible, the impact of systems should be set as design objectives. This will avoid the formal "Impact Assessment" presenting any major surprises with respect to system impact, and thus prevent either a redesign, or a wider scope of systems being subject to Qualification Practices. Neither of these scenarios presents a threat to product quality; however, an opportunity to reduce costs will have been missed.

2.3 GOOD ENGINEERING PRACTICE (GEP)

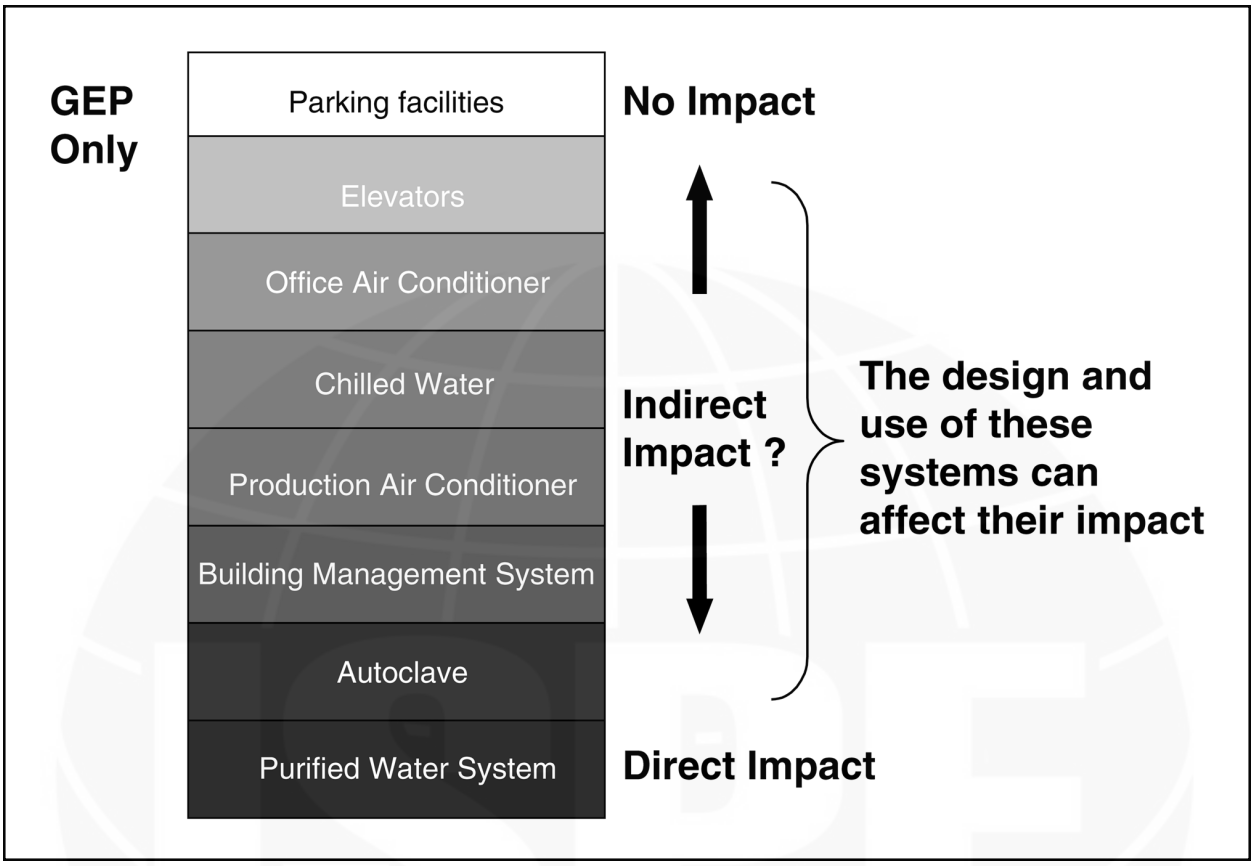
GEP is defined as:

"Established engineering methods and standards that are applied throughout the project lifecycle to deliver appropriate, cost-effective solutions."

Good Engineering Practice, related to facilities, utilities, and equipment regulated by the FDA encompasses the following:

- Design and installation that takes full account of cGMP, safety, health, environmental, ergonomic, operational, maintenance, recognised industry guidance, and statutory requirements
- Professional and competent project management, engineering design, procurement, construction, installation, and commissioning
- Appropriate documentation including design concepts, design schematics drawings, as installed drawings, test records, maintenance and operation manuals, statutory inspection certificates, etc.

Figure 2-1 The Impact Spectrum



2.3.1 Enhanced Design Review

Enhanced Design Review[2] may be defined as:

"A documented review of the design, at an appropriate stage in a project, for conformance to operational and regulatory expectations."

This is discussed further in Section 2.4.2.

2.3.2 Commissioning

Commissioning may be defined as:

"A well planned, documented, and managed engineering approach to the start-up and turnover of facilities, systems, and equipment to the End-User that results in a safe and functional environment that meets established design requirements and stakeholder[3] expectations."

[2] The term "DQ" has not been used to avoid any confusion between the regulatory interest in the design of medical devices and that of facilities, utilities, and equipment.
[3] The stakeholders will vary depending on the impact of the system.

The term ”commissioning” typically encompasses the following tasks:

- Physical Completion[4] and Inspection
- Setting to Work
- Regulation and Adjustment
- Testing and Performance Testing
- Planning and preparation associated with managing the above activities

These terms and their associated tasks, described within Codes of Practice etc., define GEP for commissioning and should form the foundations for Installation and Operational Qualification. The full definition of these terms may be found in Chapter 5.

2.4 QUALIFICATION PRACTICES

2.4.1 Overview

For “Direct Impact” systems, Good Engineering Practice should be enhanced and supported by Qualification Practices to meet the compliance needs of businesses regulated by the FDA and other regulatory authorities.

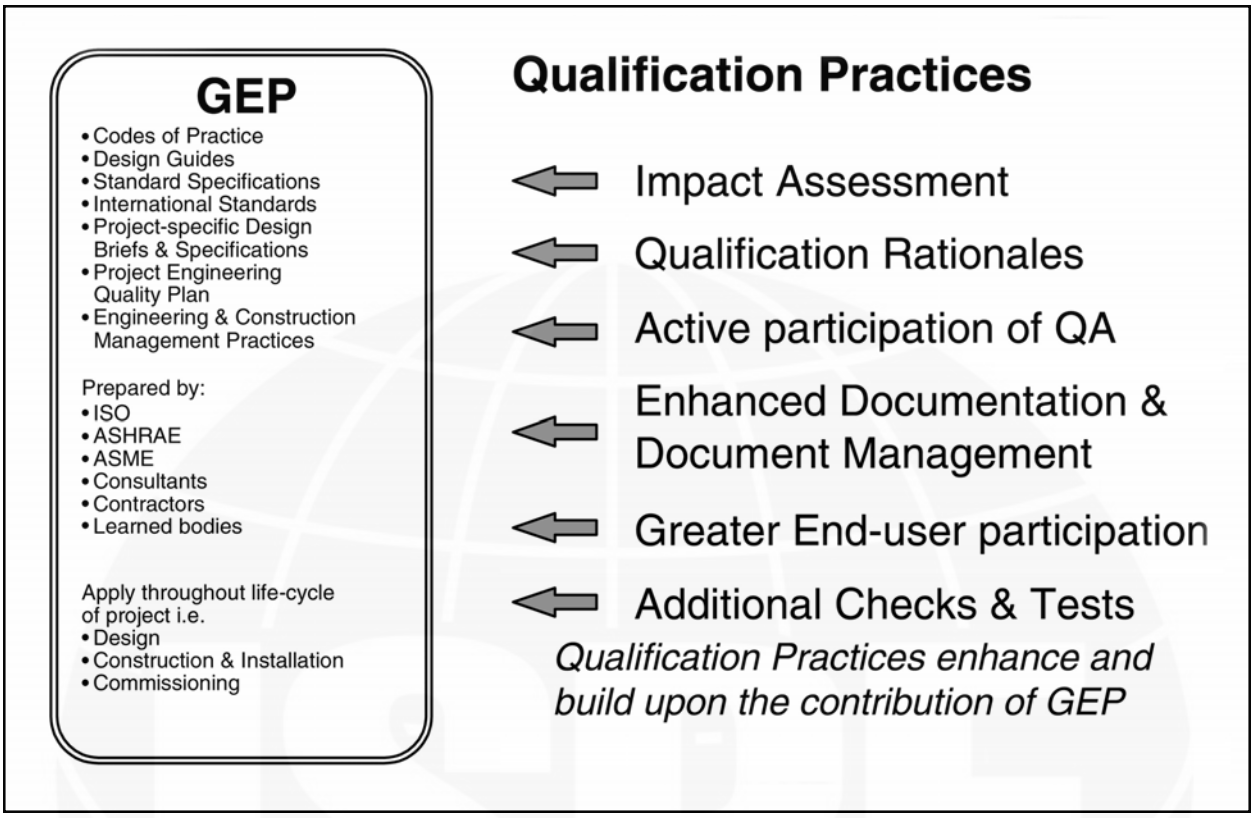
Qualification Practices include:

- System Impact Assessment
- Active Participation of the Quality Assurance department
- Enhanced documentation, document management, and a structured approval process
- QA Change control
- Greater end user participation
- Training
- Use of Qualification Rationales to identify what should be checked, how, to what extent, why, and by whom
- Deciding what **not** to check and why

These Qualification Practices should be applied to “Direct Impact” systems throughout the project lifecycle.

[4] **Physical Completion** is a project milestone where the installation of a system, or clearly demarcated parts of it, are as per engineering design and that documentation required to support further commissioning is available.

Figure 2-2 Qualification Practices and the Relationship with GEP



2.4.2 Enhanced Design Review

Enhanced Design Review is not essential for compliance of manufacturing facilities regulated by the FDA. EDR is not referenced in any regulatory publication as regulation, rules, or guidelinesl; however, design is well referenced in current Good Manufacturing Practice. A structured review of the design of facilities, utilities, and equipment is considered by the authors of this guide to be the smart way to prepare for IQ and OQ activities. It is in the interests of all to reveal design or specification problems through a rigorous, structured review process early in a project, rather than discover them later at the IQ or OQ stages, where a remedy might involve significant delay and expense. This, however, remains a business risk driven choice, not a regulatory expectation.

The process, findings, and recommendations resulting from the Enhanced Design Review should inform the formal Impact Assessment. The rigor of the method by which the design is examined should be commensurate with:

- The impact of the system
- System complexity
- Familiarity or degree of novelty with the system and/or the supplier
- The novelty in application of “standard” equipment

2.4.3 Installation Qualification

Installation Qualification is defined for "Direct Impact" systems as:

"The documented verification that all aspects of a facility, utility or equipment that can affect product quality adhere to approved specifications (e.g., construction, materials) and are correctly installed."

This process at task level (i.e., how) corresponds to the Inspection requirements demanded by GEP, which, when performed within the controls of **Qualification Practices** will comprise IQ.

2.4.4 Operational Qualification

Operational Qualification for "Direct Impact" systems is defined as:

"The documented verification that all aspects of a facility, utility, or equipment that can affect product quality operate as intended throughout all anticipated ranges."

This process at task level (i.e., how) corresponds to the **setting-to-work, regulation,** and **testing** requirements demanded by GEP, which when performed within the controls of Qualification Practices will comprise OQ.

2.4.5 Performance Qualification

Performance Qualification is defined as:

"The documented verification that all aspects of a facility, utility, or equipment that can affect product quality perform as intended meeting predetermined acceptance criteria."

PQ tests feature one or more of the following characteristics:

- Performance is a high-level measurement, usually in units of direct relevance to product quality (e.g., particulate count, clean room temperature and %RH, WFI quality, autoclave heat penetration test) that are usually cited within a User Requirements Brief
- Performance over a period of time under production conditions is demonstrated
- The correct operation of several systems (both "Direct Impact" and "Indirect Impact") working in an integrated fashion is challenged
- Substitute demonstration materials are used
- No further testing could usefully be performed without introducing product

It should be noted that it is usually neither practical nor necessary to test for all combinations of conditions that integrated systems are likely to encounter because:

- Testing at the OQ stage will have stress tested individual systems, utilities, etc.
- PQ parameters are high-level performance indicators, amenable to continuous monitoring and recording with associated alarms

Performance Qualification must not be confused with Process Validation or Qualification that is the verification that good product is made, with validated cleaning and analytical methods. This is beyond the scope of this Guide; however, it should be noted that PQ would form part of the effort required for Process Validation.

2.5 BASIC QUALIFICATION RELATIONSHIPS - THE V-MODELS

2.5.1 Overview

The V-Model (see Figure 2-3 V-Model for "Direct Impact" systems and Figure 2-4 V-Model for "Indirect Impact" systems) is a simple and easily understood means of describing the relationship between the User Requirements, and the designs and specifications prepared to meet them, and the levels of inspection and testing performed as part of Commissioning and Qualification. In addition, the contribution of Pre-delivery Inspections (PDI) and Factory Acceptance Tests (FAT) to the Commissioning and Qualification effort are shown.

Figure 2-4 is the V-Model for an "Indirect Impact" system; these systems require commissioning only (GEP) and the terminology is that in common use outside of the pharmaceutical industry.

Figure 2-3 is the V-Model for a "Direct Impact" system requiring Qualification; the Qualification tasks are equivalent to those described for commissioning but are supplemented by the more rigorous controls of Qualification Practices. The V-Model illustrates:

- To Commission or Qualify a system effectively, the performance, construction, and operational requirements of the system(s) should be known
- PQ is used to verify the User Requirements and (typically) will challenge a collection of systems (both "Direct Impact" and "Indirect Impact") working together.
- OQ verifies the functional requirements (of an individual system)
- IQ verifies the construction and installation
- Factory Acceptance Tests are operational checks and these can and should contribute to the OQ where practical
- Pre-delivery Inspection are construction checks, and these can and should contribute to IQ where practical

For some items of equipment, the construction and operation can be checked almost completely at the supplier's works, leaving only the inspections associated with site installation and the testing associated with integration with other systems. This is an opportunity to progress the IQ and OQ.

The allocation of responsibilities (at task level) will vary depending on the engineering system in question and the contract strategy adopted (e.g., in-house design, design and build, End-User employs design agent) however in general:

- The End-User remains responsible (in the wider sense) for effective Qualification
- The nearer the top of the 'V' in the process; the greater the participation and direct involvement of the End-User, especially where PQ makes a contribution to Process Validation
- Contractors or suppliers will usually be responsible for Implementation

2.5.2 Supplier and Contractor Engineering Process

The V-Model focuses on the basic lifecycle required by the End-User; however, this neglects the contribution that could be made by the procedures, systems, and documentation used and followed by the supplier or contractor. In many cases, the supplier or contractor will have their own quality system (e.g., ISO 9001 parts 1-3) that demands a structured approach with equivalent relationships between Qualification tasks as represented by the V-Model; in effect their own V-Model. Where this is the case, the usual practices of the contractor or supplier should be integrated within the Qualification effort owned by the End-User.

2.6 THE ROLE OF QUALITY ASSURANCE

The Quality Assurance department plays an essential role during the Commissioning and Qualification process. It is a role that takes on different responsibilities during the different stages of the project and in some situations is required by regulation.

Although in the past Quality Assurance (QA) has not been involved with Commissioning and Qualification until late in the process, where it is required by regulation, early involvement is being encouraged and promoted due to the advantages it brings to the project.

Commissioning has historically been viewed as an engineering activity that was early in the process where QA involvement was not necessary. This idea was supported by the fact that engineering standards and not direct FDA regulation guide these activities; however, the role of QA during the commissioning process has been evolving and brings the following advantages:

- An understanding of the facility, processes and equipment well before use in commercial manufacture
- An opportunity to use some commissioning activities to support or eliminate duplication of qualification activities
- Ensuring appropriate documentation is being generated and appropriately reviewed and approved
- Establishing a partnership to ensure efficient hand-over for qualification and commercial start-up

Qualification, which has historically been viewed as the point of QA entrance into a project, can be greatly enhanced and streamlined by involvement of QA during commissioning.

Throughout the Guide, involvement of QA will be highlighted and encouraged. The opportunities and advantages will be discussed in the respective sections.

Figure 2-3 V-Model for "Direct Impact" systems

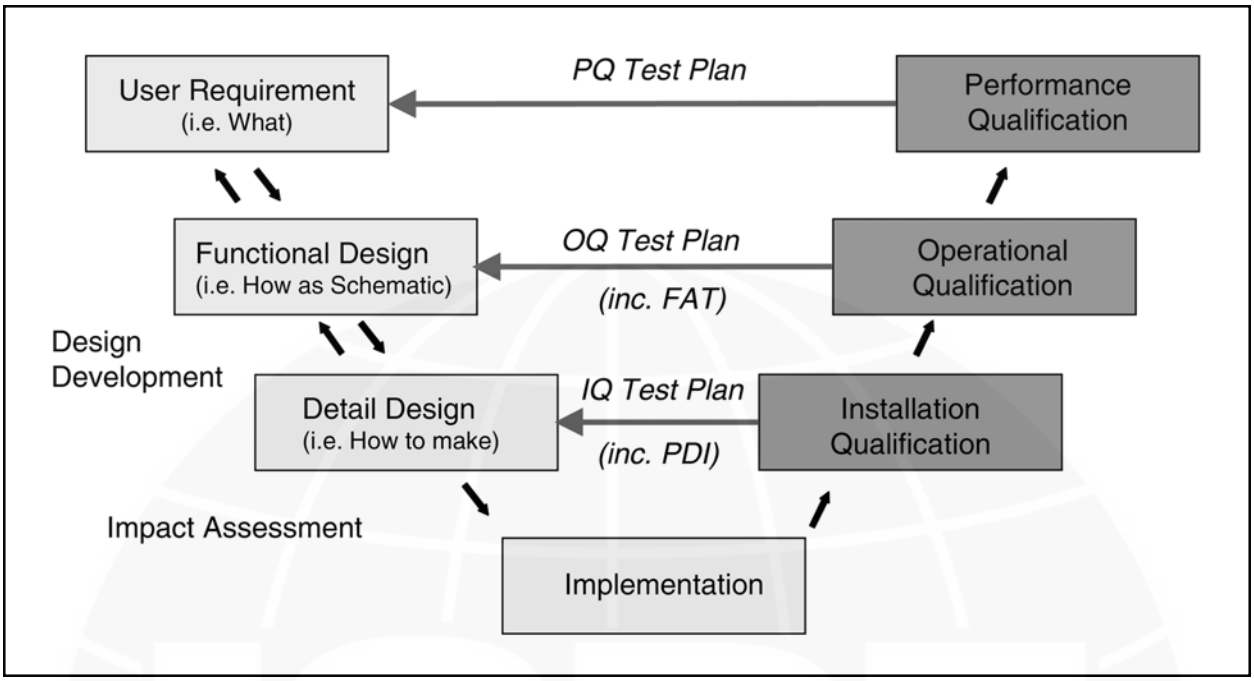
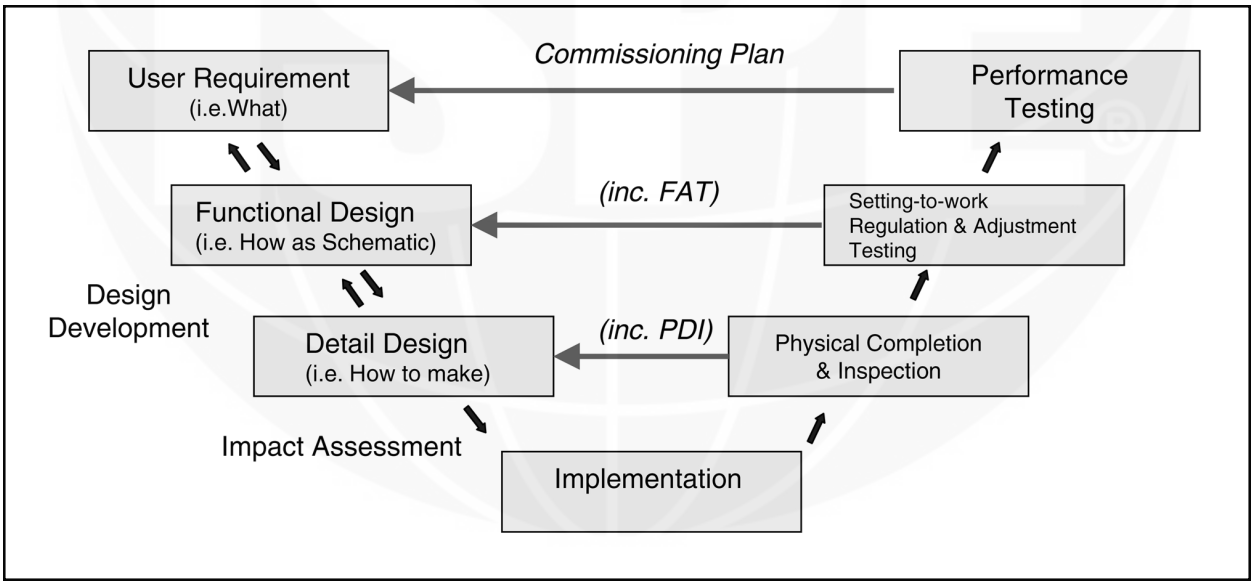
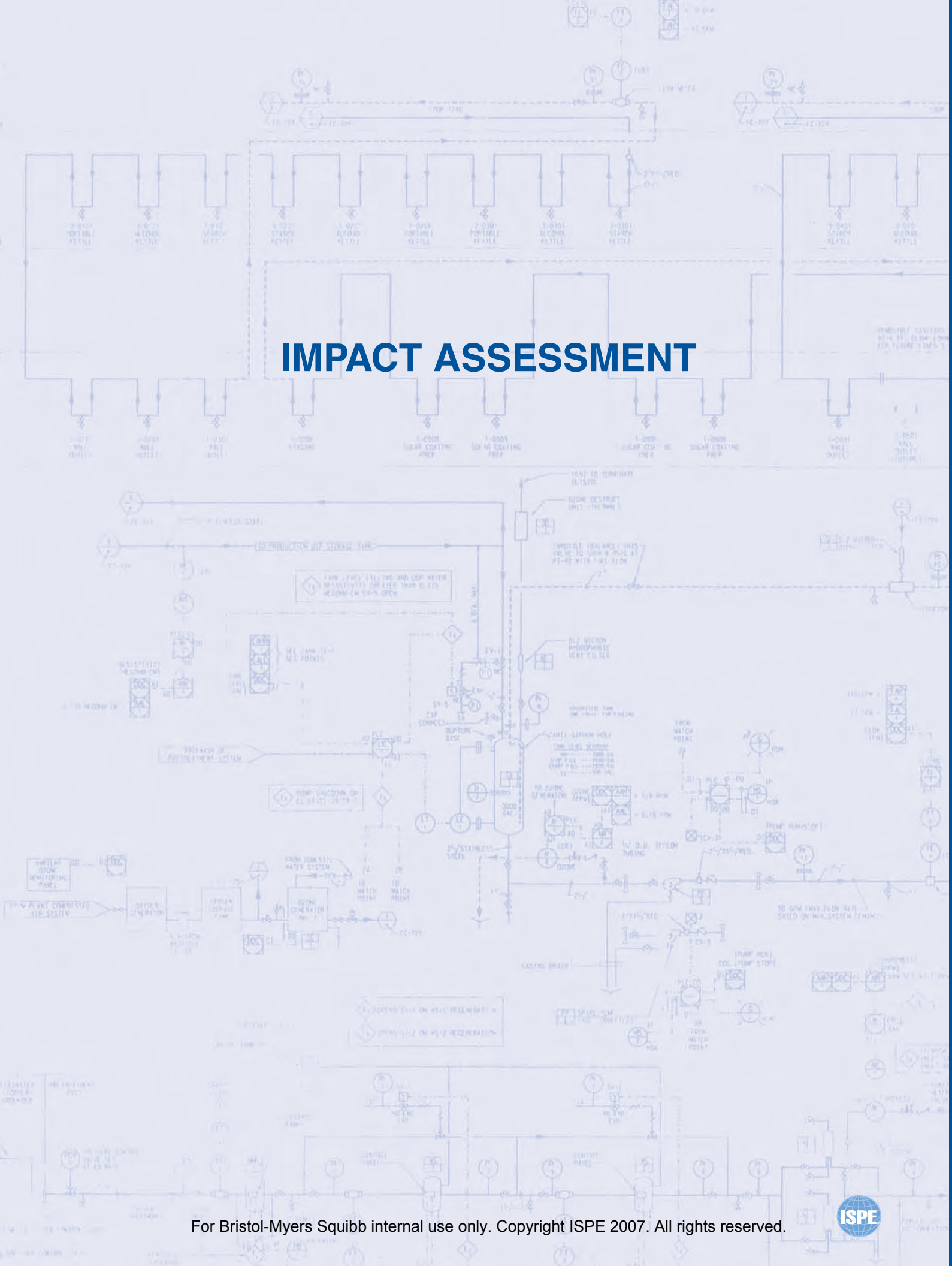


Figure 2-4 V-Model for "Indirect Impact" systems



IMPACT ASSESSMENT



3. IMPACT ASSESSMENT

3.1 INTRODUCTION

Impact Assessment is the process by which the impact of a system on product quality is evaluated, and the critical components within those systems are identified.

Those systems having a direct impact on product quality are subject *to* **Qualification Practices** in addition to **Good Engineering Practice** (GEP). "Indirect Impact" or "No Impact" systems and their components are designed, installed, and commissioned according to GEP only. This process allows appropriate effort and focus to be concentrated on the quality impacting systems and components.

This chapter will consider the Impact Assessment process. A method is suggested for defining the steps of a system assessment process, including a discussion of the benefits, and a list of the criteria for determining system impact and component criticality.

3.2 DEFINITIONS

3.2.1 System

An organization of engineering components that have a defined operational function (e.g., piping, instrumentation, equipment, facilities, computer hardware, computer software, etc.).

3.2.2 System Boundary

A limit drawn around a system to logically define what is, and is not, included in the system.

3.2.3 Impact Assessment

The process of evaluating the impact of the operating, controlling, alarming, and failure conditions of a system, on the quality of a product.

3.2.4 Critical Component

A component within a system where the operation, contact, data, control, alarm, or failure may have a direct impact on the quality of the product.

3.2.5 Non-Critical Component

A component within a system where the operation, contact, data control, alarm, or failure will have an indirect impact, or no impact, on the quality of the product.

3.2.6 Impact Altering Change

Certain changes may affect commissioning or qualification plans, tests, or documentation that are developed from the project design documents. Changes identified through the **Engineering Change Management** process (see Section 4.8.4) should be assessed for potential impact and communicated to the appropriate team members based on agreed criteria. For "Direct Impact" systems, changes that affect the User Requirements Brief, the design concept, or the System Impact Assessment should be communicated for review and approved by Quality Assurance.

3.3 SUGGESTED ASSESSMENT PROCESS

3.3.1 Introduction

Prior to assessing system impact, the number of systems and the scope of each should be clearly defined.

The Impact Assessment process has two levels of evaluation:

SYSTEM

Evaluation of the impact of a system on product quality.

This is a high level assessment of the system. Through Design for Impact (see Section 3.3.7), the design objectives and boundaries for systems are established at the outset of the project, with consideration given to incorporating "Direct Impact" functions into the most appropriate systems.

It should be noted that any assessment of system impact prior to development of a fully detailed system design would be preliminary, until a complete component level assessment of the system is performed.

COMPONENT

Evaluation of the criticality of components within each system with respect to their role in assuring product quality.

The "Direct Impact" systems, along with their critical components, are subject to Qualification Practices as described in Chapter 6.

System Impact and Component Criticality assessment can be a significant exercise and should be planned, managed, and documented accordingly.

3.3.2 Identifying Systems

At this level of assessment, systems only are considered, rather than the individual components within each system. Examples of systems include:

- Chilled water
- Clean steam
- WFI
- HVAC
- Tablet presses
- Fire protection

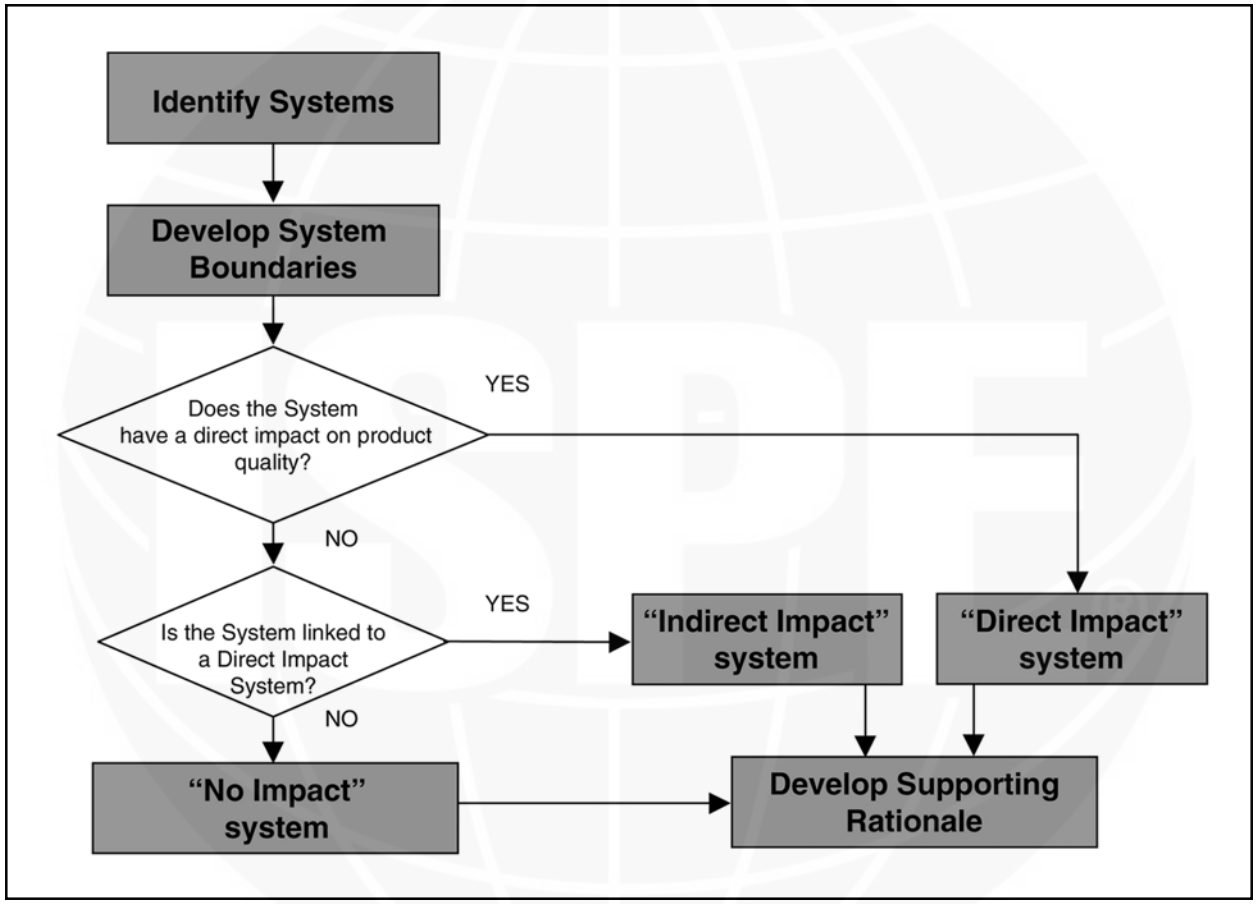
Once defined, these systems should form the basis of a project referencing system or be integrated within it.

3.3.3 System Boundaries

The system definitions and the boundaries that describe the scope of each system should be reflected within all relevant and appropriate engineering documentation, including drawings, specifications, P&IDs, and equipment schedules. This will support the **Engineering Change Management** process in identifying **Impact Altering Changes**.

Systems consisting of a single component should be assessed using the criteria employed for component assessment.

Figure 3-1 System Impact Assessment Process Overview



3.3.4 System Impact Assessment Process

Applicability of any of the following criteria will provide an indication that a system has a "Direct Impact":

1) The system has direct contact with the product (e.g., air quality)

2) The system provides an excipient, or produces an ingredient or solvent (e.g., water for injection)

3) The system is used in cleaning or sterilizing (e.g., Clean Steam)

4) The system preserves product status (e.g., Nitrogen)

5) The system produces data which is used to accept or reject product (e.g., Electronic Batch Record System, or critical process parameter chart recorder)

6) The system is a process control system (e.g., PLC, DCS) that may affect product quality and there is no system for independent verification of control system performance in place

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

3.3.5 Component Criticality Assessment Process

The components within "Direct Impact", "Indirect Impact" and in some cases "No Impact" systems should be assessed for criticality. This is suggested to ensure that systems previously judged to be "Indirect Impact" or "No Impact" in the early, high level assessment, have not subsequently acquired a critical function as the detailed design has progressed to conclusion.

Applicability of any of the following criteria to a given component will provide an indication that the component is critical:

1) The component is used to demonstrate compliance with the registered process

2) The normal operation or control of the component has a direct effect on product quality

3) Failure or alarm of the component will have a direct effect on product quality or efficacy

4) Information from this component is recorded as part of the batch record, lot release data, or other GMP-related documentation

5) The component has direct contact with product or product components

6) The component controls critical process elements that may affect product quality, without independent verification of the control system performance

7) The component is used to create or preserve a critical status of a system

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

It is worthy of note that the nature of component criticality can be multi-faceted. Consider for example an instrument, the function of which is purely for engineering diagnostics (i.e., non-product quality related) which is in contact with the product or an excipient. In such a case, installation and construction material will be a **Qualification** issue while function can be managed within a **Good Engineering Practice** approach.

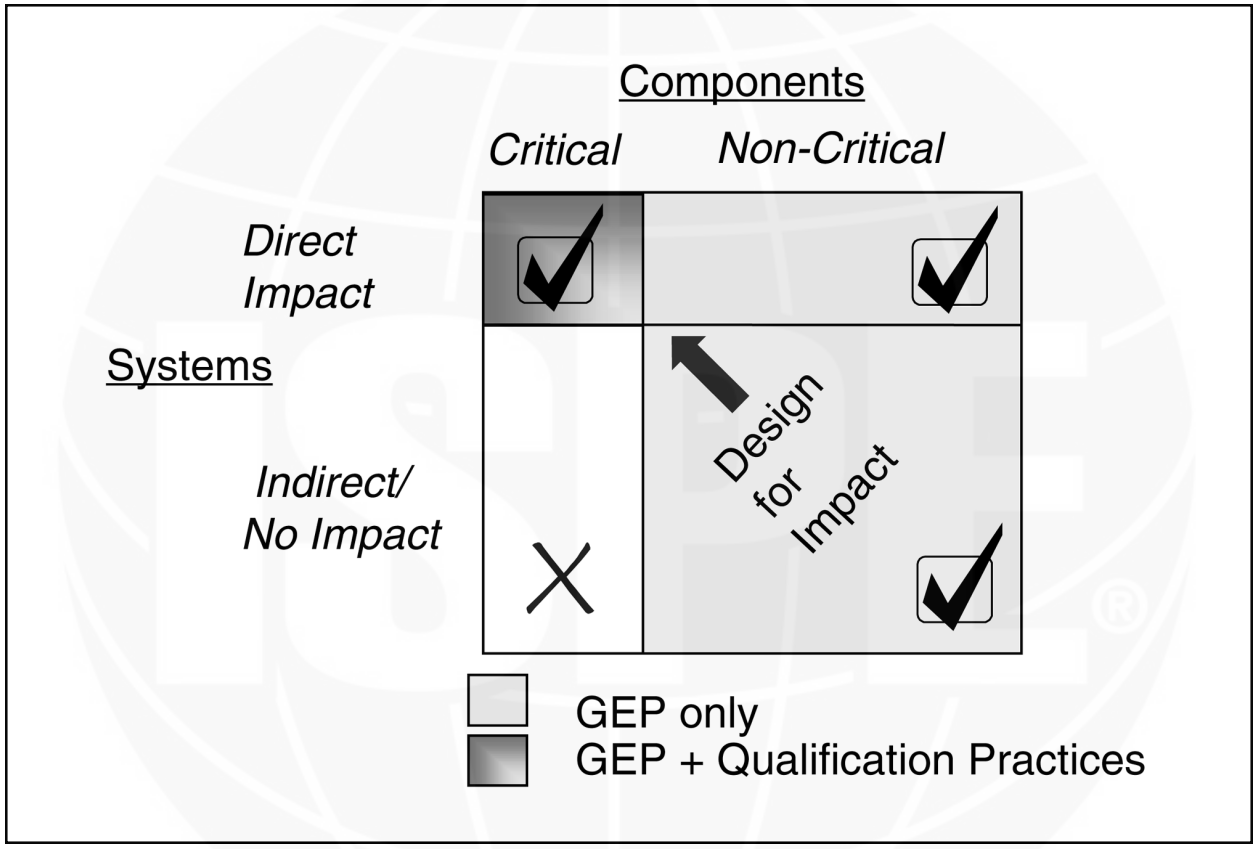
3.3.6 System Impact and Component Criticality

Figure 3-2 illustrates a summary of the impact assessment process described so far; additional points of note are:

- "Indirect Impact" or "No Impact" systems are comprised of non-critical components only.

- "Direct Impact" systems have both critical and non-critical components. Components deemed non-critical may be managed within GEP alone. (i.e., distinct sub-systems and components peripheral to the quality-related system functions may be managed within GEP.)
- **"Design for Impact"** reduces the scope of systems and components subject to **Qualification Practices,** allowing appropriate focus on the components presenting a risk to product quality
- Should an "Indirect Impact" or "No Impact" system incorporate one or more critical components, either the system has been mis-classified, or the component wrongly assessed.

Figure 3-2 Relationship between Systems and Components



Example: The control valve for chilled water distribution to a heat exchanger serving a Water For Injection distribution loop

The valve is in a control loop with a temperature transmitter on a sub-loop to a WFI system. Information recorded from the temperature transmitter is used to support WFI quality-related decisions. In this example, the component that has an effect on the product quality is the temperature transmitter. In contrast, the control valve on the chilled water distribution is **not** a critical component as the temperature component can detect a problem with the WFI system temperature, which for the purposes of this example is deemed critical to the product quality.

3.3.7 Design for Impact

"Design for Impact" is used to describe the practice of making conscious design decisions with respect to the impact of a system **at the beginning of design development.** There are many systems in a typical project, and the impact of each of these systems will be determined by their design and application. By careful design, the number of systems capable of having a direct impact can be reduced. The direct impact **functions** remain but are logically incorporated into the most appropriate systems by the designer to preclude excessive and unnecessary qualification and validation work later on.

Where possible, the impact of systems should be set as design objectives early on in the design process. This will provide a "roadmap" for the designers and also will preclude costly surprises and delays during the formal impact assessment process.

3.3.8 Documenting the Impact Assessment Process

System Impact Assessment is an informed judgment, made by a group of appropriately qualified stakeholders (see Section 3.3.10), and should be based on a comprehensive understanding of the product, process, and the nature of the systems and components. This decision should be justified and made explicit, in a concise manner, through the production of a QA-endorsed **Impact Assessment Rationale** for each system.

The **Impact Assessment Rationale** for each system also should document the component criticality assessment in a similar manner.

3.3.9 Timing

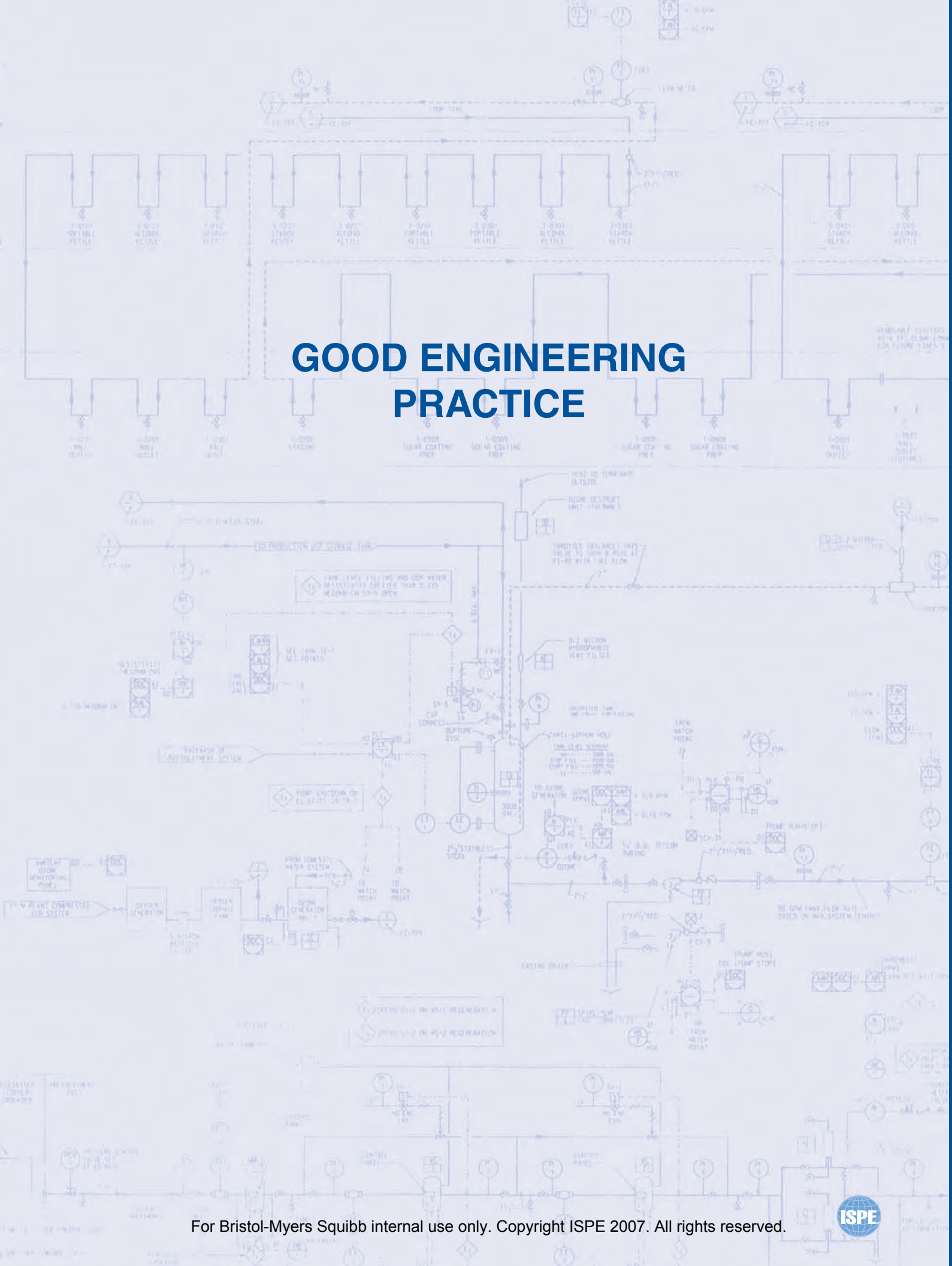
It is suggested that a preliminary System Impact Assessment be made early in the project, between system definition and equipment ordering. Component criticality assessment should be performed once the detailed design is sufficiently developed to do so. Following the assessment of component criticality, the impact status of each system can then be confirmed.

Impact Assessment should be integrated into the project schedule. The effort required will correspond with the complexity of the systems and the processes involved, and it is important that sufficient time is allowed within the schedule.

3.3.10 Responsibilities

The assessment should be carried out by those with the appropriate skills and experience necessary to make an informed decision. Typical stakeholders may include:

- User Representative
- Process Experts
- Relevant Engineering Disciplines
- Validation Manager
- Quality Assurance Representative



GOOD ENGINEERING PRACTICE

4. GOOD ENGINEERING PRACTICE

4.1 INTRODUCTION

The primary objectives of this chapter include:

- Provide an overview of the various project phases and sequence, from inception through commissioning, qualification, and operation
- Define "Good Engineering Practice" (GEP) and the associated concepts
- Describe the types of activities that occur and documentation that is created through GEP
- Provide an overview of effective project team concepts and organization
- Provide an overview of effective project controls
- Demonstrate how GEP, as applied throughout the project lifecycle, provides a basis for effective qualification

4.1.1 Project Phases and Sequence

Typical phases of a project normally follow a logical sequence; however, in practice, some phases may overlap and there may be some iteration between phases. Specific activities and deliverables are typically associated with each phase. A clear understanding of the typical activities, purpose and required content of the deliverables, and roles and responsibilities will foster effective communication and help ensure project success.

4.2 GOOD ENGINEERING PRACTICE CONCEPTS

Good Engineering Practice (GEP) is defined by this Guide as:

"Established engineering methods and standards that are applied throughout the project lifecycle to deliver appropriate cost-effective solutions."

As such, GEP is comprised of the following:

- Professional and competent project management (processes, procedures, and staff)
- Professional and competent engineering design, procurement, construction, and commissioning
- Full consideration of applicable safety, health, and environmental statutory requirements
- Full consideration of operation and maintenance requirements
- Full consideration of recognized industry standards and guidance
- Appropriate documentation for ongoing operation and maintenance, and to demonstrate compliance with applicable regulations and codes

Engineers typically have formal training in one or more disciplines (e.g., chemical, civil, electrical, mechanical, construction management, etc.). In addition, many engineers are licensed by specific professional bodies, and this provides added assurance of engineering competence.

Additionally, engineering organizations, institutes, and other learned bodies have published numerous design guides, engineering standards, codes of practice, etc., which are accepted as GEP. These documents are based on technical and/or business requirements, and may be applied to all facilities, utilities, and equipment, regardless of industry. While significant technical guidance is available, it is important to remember that all projects are unique. Engineering requires significant judgment to find the optimal solution for the specific circumstances, and finding the appropriate balance between time, cost, engineering quality, and business risk.

4.3 DOCUMENTATION

Good Engineering Practice recommends that:

- Each component should be built in accordance with plans and specifications, approved or authorized by the appropriate individuals
- Each component should be inspected, tested, and documented by qualified individuals
- A minimum level of documentation should be provided for all systems and equipment
- Documentation should cover design, fabrication, construction, inspection, and commissioning

Engineering firms, suppliers, contractors, and owners provide the documentation necessary for design, construction, commissioning, qualification, operation, and technical support of the facility, utilities, equipment, and other systems. A clear understanding of these documents maximizes their value and eliminates redundancy.

If these documents are appropriately planned, created, organized, and authorized, they may become an integral part of the qualification support documentation for "Direct Impact" systems.

"Direct Impact" systems require **"enhanced documentation"**, which may involve additional tests, documentation, QA change control, and QA review/approval. Enhanced documentation should complement (and not repeat) the documentation that is created through Good Engineering Practice. Enhanced documentation is achieved through the qualification process, which begins in design and culminates with qualification (IQ, OQ, and PQ) and change control. Further information on this topic is provided in Chapter 6.

This Guide recommends that a document matrix is established to encompass:

- All of the documents that are to be prepared or collected throughout the project
- The required timing
- Who is responsible for preparation (or collection), review and approval, and in what capacity the approval is made

4.4 PROJECT TEAMS

4.4.1 Project Team Concepts

Project Team activities are interdependent. To enable timely and cost-effective project completion, it is essential to have excellent communication, planning, and coordination between operations, engineering, construction, commissioning, and qualification personnel. An integrated approach toward project management is strongly encouraged.

ORGANIZATION AND COMMUNICATIONS

Project team representation should be based on the project scope, resource requirements, and the key stakeholders. (A stakeholder is defined as an individual, group, customer, or agency that is impacted by the project outcomes, either directly or indirectly. A stakeholder is typically responsible for the operation, support, or acceptance of the facility, utilities, and equipment.) Identifying the stakeholders at the outset of the project will help establish a line of communication and enable the project manager to understand potential requirements and concerns. A high level, focused effort by all stakeholders is essential during the scope development phase of the project. The involvement of selected stakeholders can be reduced appropriately during design development.

Individual team members need to understand the roles, responsibilities, and levels of authority, for both the team leader and other team members. They also must appreciate how the team will be managed (e.g., meeting frequency, reports, communications, problem resolution, etc.). Both a project member contact list and an organizational chart, which identifies each team member, should be generated.

Typical functions and roles that make up a project team include:

- **Project Sponsor**

  Provides high-level support, guidance, and visibility for the project and project team. The sponsor helps establish high-level objectives and enables sufficient financial and staffing resources.

- **Project Manager**

  Has ultimate responsibility for project planning and execution, and the management of associated costs, schedule, and quality. The Project Manager leads the cross-functional project team.

- **Engineer(s)**

  The engineering staff may be comprised of process and/or facility engineers. These representatives assist with identifying user requirements and are responsible for facility and system design and specification, in accordance with applicable codes and regulations. The engineers are responsible for providing input into test plans and documents.

- **Procurement**

  Assists with the purchase of the necessary owner-supplied services and materials.

- **Construction**

  Responsible for construction planning, estimating, bidding, contracting, and execution, and may be from the owner firm or contracted.

- **Commissioning Leader**

  Responsible for planning and executing the commissioning activities.

- **Operations/Production**

  This is the ultimate owner of the facility or process. This individual or group must identify the user requirements, participate in periodic design reviews, and provide input into specific test plans and documents. Before turnover, Operations must ensure that sufficient training has been undertaken and that there is a sufficient understanding of the facility operation and equipment operation.

- **Maintenance**

  Provides input from a maintenance and calibration perspective. Maintenance may participate in periodic design reviews and provide input regarding equipment selection. Maintenance must gain sufficient understanding of the facility and equipment to provide ongoing support. Maintenance should plan for appropriate resources to participate in commissioning activities, training activities, and developing required procedures.

- **Cost Controller**

  Performs the detailed tracking and reporting of project cost information.

- **Schedule Controller**

  Performs detailed planning, tracking, and reporting of the project schedule.

Other possible functions may include:

- **Document Coordinator**

  To manage the acquisition and organization of project documents.

- **Research and Development**

  To assist with process engineering, scale-up, and/or technology transfer to production.

- **Safety**

  To lead or contribute toward safety reviews and safety program administration.

- **Technical Writer**

  To assist with procedures and other documents, as required.

For a GMP regulated project, representatives from the following groups also should be included:

- **Validation**

  Ensures that the facility and system qualification requirements are communicated and met. Typical responsibilities include qualification planning, (e.g., Validation Master Plan development, qualification resource and cost estimates, and protocol development), coordination, and execution. Validation also may provide design input for “Direct Impact” systems or specific facility attributes.

- **Quality Control**

  Coordinates the activities associated with analytical test planning and execution. Typical responsibilities include design input for specific systems or facility attributes, test plan development, resource and cost estimates, internal or external laboratory coordination, and interpretation of results.

- **Quality Assurance**

  Ensures that the facility and systems meet GMP requirements. Quality Assurance helps identify “Direct Impact” and ”Indirect Impact” systems, and reviews/approves the associated qualification plans, protocols, and reports. Quality Assurance also provides input to resolve qualification problems and reviews specific types of changes to “Direct Impact” systems. The role of Quality Assurance is described further in Section 2.6.

4.5 REQUIREMENTS PHASE

A successful project is dependent on clear definition, communication and understanding of the project scope and objectives, as defined by the user and other stakeholder requirements.

4.5.1 User Requirements Brief

At the outset of a project, the user must provide sufficient information to the engineering service provider to enable the development and assessment of specific options. User requirements should focus on what is needed, without being overly prescriptive, as to how the requirements should be met. The amount of detail provided will vary by project, particularly according to size, complexity, and the mutual understanding between the user and engineering service provider.

Project Purpose and Justification

Existing background information and the rationale for the project request should be communicated. Items that may be included are:

- Statement of existing conditions
- Project justification (e.g., new product(s), increased demand, problem remediation, cost savings, process improvement)

Product and/or Process Requirements

A list of affected products and associated details provide the fundamental basis for the scope development. Much of this information may be obtained from development reports, technical reports, batch records, regulatory submissions, sales/marketing data, and staff input. Information to be considered includes:

- Product forecasts (and ranges)
- Potential or restrictive batch sizes or ranges
- Process descriptions, flow charts, and estimated processing times
- Known operating ranges and tolerances for critical process parameters
- Known operating restrictions or difficulties

- Safety information for the associated materials and processes
- Known compatibility or incompatibility for materials of construction (including seals)
- Cleaning methods, agents, and limits
- Past experience with current products or current processes
- Past experience with similar products or similar processes
- Preferred equipment suppliers (and basis for preferences)
- Site-specific requirements (e.g., local suppliers, spare parts)

Allowable operating ranges and limits (or tolerances) provide the basis for future design, commissioning, and qualification requirements. Operating limits are defined as the minimum and/or maximum values that will ensure that product and safety requirements are met. Appropriate values must be provided to ensure that meaningful set points, alert values, and alarm values can be established, thus eliminating potential nuisance alarms.

Operational Considerations

Operational considerations should be communicated to ensure that the user intent, and the flexibility and/or constraints, are understood. Items to consider include:

- Planned or expected plant operating schedule (e.g., one shift x five days, three shifts x five days, three shifts x seven days)
- Planned staffing for new or renovated facility/area (e.g., use existing staff, hire new staff)
- Potential or allowable disruption of existing operations (especially in cases of renovation or plant expansion)
- Potential or allowable impact on existing operations (especially in cases of renovation or plant expansion)

4.5.2 Maintenance and Technical Support Requirements

Staff responsible for facility (and utility system) operation, utility system and equipment maintenance, and technical support (e.g., plant and process engineering) offer a different perspective than the End-User. Key support staff should be consulted at this stage to incorporate their requirements, and possible constraints, into the scope document. Information to be considered includes:

- Past experience with products, processes, equipment, and systems
- Preferred equipment suppliers (and basis for preferences)
- Site-specific requirements (e.g., local suppliers, spare parts, internal standards)

4.5.3 Compliance Requirements

It is important that external compliance requirements (especially those for cGMP, safety, or environment) are clearly communicated. Particular emphasis is warranted where there are newly formed regulatory requirements, or local requirements, that differ from FDA requirements. The project team should consult with QA on project-specific compliance requirements.

4.5.4 Deliverables

This phase typically yields the following key deliverables:

- A final User Requirements Brief
- A Requirement Specification for each system
- A Project Execution Plan

User Requirements Brief

At the completion of this phase, it is recommended that a final User Requirements Brief is prepared and appropriately authorized by key stakeholders. This document will provide a basis for the development of future project documentation, including the Requirement Specifications for individual systems.

Requirement Specification(s)

These are a detailed documents used to specify the requirements of the user for individual aspects of the facility, item of equipment, utility, and systems in terms of function, throughput, operability, and applicable local standards. Each of these documents should be appropriately authorized by key stakeholders.

Both the User Requirements Brief and Requirement Specifications should be subject to change control during their development, with involvement from the appropriate stakeholders.

Project Execution Plan

A written plan is an effective means for the project manager to communicate to the user and other stakeholders, the approach to be taken for project execution. A plan should be developed with input from the project team as early as is practical.

The following topic areas may be considered for discussion within the plan:

- Project purpose, scope, and key business objectives
- Expected milestones and timing
- Funding strategy and budget status
- Resource strategy (for design, construction, and commissioning)
- Strategy for control of schedule, cost, quality, and scope
- Strategy for management and control of documentation
- Impact on existing operations, including required shutdowns or accommodation of existing operations
- Project leadership, stakeholders, and project team representation
- Supplier selection criteria and process
    - Past performance experience (e.g., delivery, support, flexibility, reliability)
    - Yields

- Critical design features
- Financial stability
- Documentation practices
- Audit feedback (e.g., software development practices)
- Corporate technology (e.g., standardization)
- Corporate purchasing strategy (e.g., negotiated buying)

- Other critical constraints or issues

4.6 DESIGN

4.6.1 Conceptual Design

The conceptual design stage is used, where necessary, to generate various alternatives for evaluation in response to the demands of the final User Requirements Brief and the Requirement Specifications for individual systems. The project team selects the concepts to be taken forward into the functional design stage.

4.6.2 Functional (or Schematic) Design

The functional design stage generates the key design documents, which are used as a framework for the detailed design process. These documents include:

- Site plans
- Floor plans
- Process and Material flow diagrams
- Air flow diagrams and HVAC schedules
- Electrical one-line diagrams

A sequence of operations is prepared for each system. It provides a detailed description of:

- System Start-Up
- Normal operation and cleaning (as applicable)
- Process monitoring
- Data acquisition and Archive
- Alarm conditions and response
- Shut-Down

A desired sequence of operations provides the basis for the system design; however, the sequence of operations will be updated to reflect the nature of the completed system(s). It is this final version of the sequence of operations that is used during procedure writing, commissioning, qualification, and system maintenance.

The design review at this stage should assess the facility and systems for expected performance or behavior, under both planned and emergency situations. System start-up, commissioning, and qualification activities should be considered to ensure that associated requirements, such as whether the design accommodates commissioning by e.g., providing test points, are evaluated and met.

Appropriate representatives from Engineering, Operations, Validation, Maintenance, Safety, and for "Direct Impact" systems, Quality Assurance, should review the relevant design documents based on the appropriate System Impact Assessment.

4.6.3 Detail Design

The detail design stage produces the documents required for construction bidding and contracting, system and equipment purchase, fabrication, installation, and testing.

Piping and Instrumentation Diagrams

P&IDs serve as the primary source of design information for utility systems and process equipment. They are used to depict the process flow, equipment configuration, process parameters, instrumentation, and materials of construction. They also are used to perform overall material and energy balances along with pressure balances. The following guidelines are recommended to obtain the maximum benefit from these drawings:

- Ensure that the CADD software is compatible with existing plant drawing management system
- Use CADD system capability to identify system components and generate component schedules. Component schedules facilitate the commissioning and qualification process and future assignment of tag numbers.
- Indicate entering/leaving support services and process streams; include reference to appropriate drawing and/or sheet number
- Identify system boundaries, with respect to support services and entering/leaving process streams
- Identify the battery limits of skid-mounted (or packaged) equipment
- Identify all components with appropriate tag numbers, using nomenclature consistent with existing plant practices. This eliminates the need for re-numbering or cross-reference listings.
- Indicate line number, service, line size, and direction of flow for all piping and tubing
- Indicate material type and insulation type/thickness (if applicable) for all pipe lines
- Indicate use (purpose), size, capacity, material type, and insulation type/thickness (if applicable) for all equipment (e.g., tanks, pumps, heat exchangers)
- Indicate size, type, and material type of all valves
- Provide material and energy balance information for each line number

Good Engineering Practice suggests that these documents be kept up to date throughout the project and the life of the facility or system.

Specifications

Detailed specifications should explicitly define the system requirements, codes, and standards to be followed during fabrication and construction, test requirements, acceptance criteria, and the associated deliverables. To prevent unnecessary costs and delays, the following items should be considered:

- Who is responsible for what
- Service or equipment to be provided
- Timing of service or equipment provision
- System performance requirements
- Factory test requirements (including written test plan review, revision, and approval)
- Installation requirements
- Construction inspections and test requirements (including test methods, acceptance criteria, planned witnessing, and means of documentation)
- Start-up, commissioning, and qualification requirements
- Training requirements (including scope, number of participants, duration, timing)
- Documentation requirements (including manuals, operation, maintenance, cleaning, and calibration procedures, cut sheets, drawings)
- Language of drawings, specifications, and other documentation

Appropriate representatives from Engineering, Operations, Validation, Maintenance, Safety, and for systems which QA has agreed are “Direct Impact” systems, Quality Assurance should review and approve the specifications.

Construction Drawings

Construction drawings are prepared for each discipline (e.g., Validation). They include two- or three-dimensional drawings of all systems, schedules, details, dimensions, notes, references, etc. The level of detail varies with the individual owner and engineering firm. Many of these drawings are “red lined” during the construction phase and updated at project completion. Many of these drawings are kept up to date for maintenance, safety, or GMP reasons.

Other Design Considerations

Many design firms and facility owners use design guides and checklists for different facility types, utility systems, equipment, and control systems. Design features that will enable smooth and effective commissioning and qualification (e.g., location and access of test ports) must be given adequate attention. Additional information is provided in Chapter 7.

4.7 CONSTRUCTION

4.7.1 Project Site Logistics

Well-planned project logistics are crucial to the success of every project. One of the first deliverables from the construction leader should be a project logistics plan. This should be developed with input from all members of the project team. The plan should identify locations for items such as, material/equipment storage, laydown, staging, temporary offices, dumpsters, break/lunch areas, and temporary utilities. Methods of maintaining and monitoring cGMP conditions of existing operations and support areas during demolition and construction should be established. All items such as, temporary walls, exhaust fans, impacts on the existing air balance, particulate monitoring, and cleaning requirements should be defined.

The logistics plan should delineate construction personnel, material, and equipment access to the project site during each phase of construction. The plan also should incorporate any revised operational personnel and material flows during each phase of the project. The facility owner should approve the plan and subsequent modifications. The approved plan should be included in each subcontractor bid package and posted near the operating area during construction.

4.7.2 Project Quality Control

The importance of Project Quality Control (QC) is second only to safety. Quality control starts with the prequalification of the appropriate suppliers, contractors and, where applicable, the construction management firms and their proposed project teams. Each company's QC program should be reviewed and evaluated, and previous project references contacted. The contractor's QC program should include documents and procedures applicable to the pharmaceutical industry, and could potentially be used to satisfy qualification requirements. If a construction manager is assigned, their QC program should be reviewed for evidence of periodic qualification of potential subcontractors.

- The construction leader should develop a project specific QC plan that incorporates the facility owner's requirements and procedures with those of construction leader. The owner's requirements also should reflect commissioning and qualification requirements. The QC plan should be developed prior to starting the procurement process and should be included in each applicable bid package. The following are some of the topics which should be addressed in a QC plan:
    - Identification of project team members with specific QC responsibilities
    - Schedule of QC audits
    - List of QC documents and procedures to be used
    - Methods of identifying, notifying, and tracking the resolution of quality deviations
    - Plan for material and equipment receipt, verification, and reporting
    - QC checkpoints to identify and correct defective work prior to starting subsequent work (e.g., wall and ceiling inspection/closure forms, concrete pour cards)
    - Shop drawing procedures and responsibilities
    - Submittal procedures and responsibilities
    - Factory Acceptance Testing (FAT) and inspections
    - System pre-installation meetings

- Controls and documents to be used for installation checks, testing, flushing, and cleaning
- Security, control, and management of critical documents
- Periodic verification of record ("as built") documentation
- Operational checks
- Punch-list management

Quality Control databases such as deviation logs, material receiving reports, and the punch-list must be capable of being sorted by system, area, and contractor. This allows their status, and effect on the start or completion of the commissioning of a system, to be identified throughout the course of the project.

A common pitfall is the generation and publication of multiple punch-lists. The construction firm or construction manager should maintain a single official punch-list. All members of the project team should be encouraged to identify potential punch-list items, but they must be directed to the team member responsible for the punch-list. The initiator or designee (i.e. the persons who have identified the punch-list item or the person charged with pursuing its resolution) should review the item when complete. Items beyond the original scope to the punch-list should be segregated and prioritized based on their effect on commissioning and qualification activities.

4.7.3 Estimating

If the majority of the project cost is for construction, then it is recommended to have the construction manager (if contracted) participate in the budget estimate. Otherwise, the design firm should perform the budget estimate. Historical unit rates based on pharmaceutical experience should be used for estimating. Common industry practice is to develop estimates for larger projects at 30%, 60% and 90% design. Smaller projects may warrant only one or two estimates. The 30% estimate is usually used for either interim or final funding. Each estimate should include a "Basis of Estimate" narrative, which explains all assumptions or clarifications made in developing the estimate. Each estimate should identify and explain the differences from the preceding estimate. It should be possible to sort the estimate by bid package to allow a direct comparison of quantities, person-hours, and material cost during procurement.

4.7.4 Procurement

A procurement plan and status report should be developed for the project. The report should identify all bid packages and proposed pre-qualified bidders. The report should list the scope of each bid package along with the contract terms (e.g., lump sum, or time and materials, which are not to be exceeded). The projected dates for issuing bid packages, pre-bid meetings, and the bid award should be listed.

Prior to sending out the first bid package, the project team should develop standards for bid packages for subcontracts, material, and equipment purchases. These standards may include commissioning, training and start-up, procedural, and documentation requirements. Some specific items to consider are:

- Instructions to Bidders
- Logistics plan
- Schedule
- Scope of Work (description, drawings, specifications, commissioning and start-up requirements, training, warranties)

- Tax requirements
- Shipping requirements
- Insurance requirements
- Sample subcontract or Purchase order
- Safety Manual (subcontracts)
- Quality Control plan
- Bid Breakdown Form (with a specific line item for the cost and person-hours allowed for commissioning and training)
- Commissioning and Start-Up plan
- Project Turnover requirements
- Operations and Maintenance (O&M) manual requirements
- Payment terms

4.7.5 Safety

The project team should develop a safety plan, which is specific to the project, during construction planning. This plan should incorporate the requirements of both the construction firm and owner. Construction safety hazard analysis reviews are needed to identify activities that have higher than normal risk to employees and property. Specific plans, procedures, and training should be implemented to address the hazards identified.

Certain activities may be defined as critical, if they present unusual safety requirements or if associated problems could severely impact the schedule. For example, equipment rigging may require special procedures if the equipment value, or fabrication time, is such that an accident could severely impact the project cost or schedule. Safety requirements and procedures should be included in each bid package.

The construction firm should provide safety and job-site orientation for all employees, as a pre-requisite to being able to work on-site. An orientation specific to the project should be developed. The orientation of the employees must be documented.

4.7.6 Meetings and Reporting

Before construction begins, the required periodic meetings and reports should be established. Typical meetings and frequencies (for major projects) include:

- Weekly subcontractor coordination
- Weekly status/coordination meetings
- Monthly status meeting

These meetings typically include the owner, design firm, and construction firm. Each meeting should have an agenda and meeting minutes. Discussion topics for the subcontractor coordination meetings include safety, clean up, schedule, quality control, and the project “Critical Items” list. A periodic commissioning planning and status meeting should be established, to ensure appropriate planning for this stage of the project.

Planned reports should have agreed frequency and distribution lists. Typical project reports and frequencies (for a major project) include:

- 3-week Look-Ahead schedule (weekly)
- Open Items report (weekly)
- Critical Items report (weekly)
- Quality Deviation report (weekly)
- Cost report (monthly)
- Schedule update (monthly)
- Project Status report (monthly)
- Procurement plan and Status report (monthly)
- Equipment Expediting report (monthly)
- Safety report (monthly)
- Quality Control report (monthly)

4.8 PROJECT CONTROLS

The Project Manager should establish project controls for all projects. The project controls should monitor, report, and control the cost, changes to schedule, documentation, and engineering. The optimal level of detail, and frequency of updating, will vary with the scope, complexity, and cost of the project.

4.8.1 Cost Controls

The Project Manager is responsible for the management of the owner's costs, and should ensure that a cost report is developed and maintained. As a minimum, the cost report for each project account, should include the:

- Original budget
- Revised budget
- Expenditures to date
- Committed cost to date
- Projected cost to completion
- Variance from the current budget

Actual costs should be recorded for each account budget and commitment. Commitments should be recorded from approved purchase orders. A narrative explaining significant changes during the period and significant variances from the budget should accompany the report. For major projects, a monthly report is common.

Budgets are established from the initial approved estimate and are maintained as the project is further developed. The following should be included when establishing a baseline budget for commissioning and qualification:

- Factory visits
- System assembly
- Contractor assistance
- Procedure development
- Training
- Test equipment rental
- Consumables
- Fluids
- Analytical testing

Prior to the start of commissioning and qualification activities, the estimates may be converted to more detailed person-hour and material estimates, which helps to provide a better means of control.

4.8.2 Schedule Development and Control

A single, integrated, master schedule should be developed with input from the entire project team. This schedule should be updated and issued regularly. An integrated schedule, using a critical path method, will increase the awareness of dependent activities and provide a clear understanding of the critical path. Including all project team members in the schedule development will engage the team members and foster better planning. All team members should comprehend the schedule format.

The schedule should be coded so that it can sort by responsibility, area, discipline, or system. Sorting by system will enable an orderly start-up, commissioning, and qualification process.

The schedule should include activities for design, procurement, construction, commissioning, and qualification. In the early stages of schedule development, these sections of the schedule should include at least one activity, or task, per system. This will ensure that the activities and prescribed duration will be accounted for in the overall project schedule. Additional detail and major milestones for these phases of the project should be added, as the information becomes available.

Items that are often overlooked in schedule development include mobilization, subcontractor procurement activities, shop drawings/submittal activities, pre-delivery inspection (PDI), factory acceptance testing (FAT), flushing and cleaning, detailed commissioning activities, and required sequencing, training, procedure writing, adequate punch-list duration, and schedule contingency. Therefore, it is imperative to develop the schedule with input from all groups involved in these activities. In the bidding process, a project schedule should be included in each bid package to effectively communicate the schedule requirements to those involved.

The schedule baseline should be established relative to defined milestones, to track target versus actual dates, and to facilitate action plans for schedule recovery when necessary. The schedule should be coupled to a progress performance measurement system, to track actual progress against projected progress. Some projects may warrant person-loading the schedule, to identify resource-leveling requirements and to track resource utilization.

The schedule should be updated and issued on a regular basis. For major projects, a three-week "look ahead" schedule should be developed by each subcontractor, and incorporated into the project master schedule, which is issued and reviewed at the subcontractor coordination meeting. A critical path analysis may be issued on a monthly basis and included in the monthly project status report.

Each month the schedule controller should verify the percentage completion of each activity, based on installed quantities. Verified progress versus planned progress curves should be generated for the schedule on a monthly basis. For larger projects, earned progress by discipline, area, and system may need to be generated.

4.8.3 Document Planning and Control

The Project Manager should ensure that a document plan and appropriate document control procedures are established to satisfy engineering, commissioning, qualification, operations, and maintenance requirements.

The plan should define responsibilities for document preparation, collection, review and approval, and how the documents will be organized. This Guide recommends that a document matrix be considered as a means of planning and communicating these responsibilities. Certain documents are typically logged and tracked for current status. These commonly include drawings, specifications, correspondence, transmittals, requests for information, submittals (shop drawings, manufacturers data sheets), change order requests, change orders, schedules, open items list, critical items lists, quality control deviations, the punch-list, and project reports.

Procedures should provide rigorous version control and notations, such as dating or reason for issue (e.g., for review, for construction). With the increased use of electronic mail for document distribution, procedures also should stipulate that the document "controller" receives copies of project e-mails for filing.

4.8.4 Engineering Change Management

Engineering change management is defined as a process by which a qualified representative(s) reviews proposed or actual changes for their impact, approves or denies the requests, and manages and tracks their implementation. Engineering change management is a good engineering practice, to effectively manage the project execution and the associated costs and schedule.

An engineering change management process may contain the following attributes:

- Record the name of the originator and date
- Describe the change, the affected system or area, and intended purpose
- Assess the potential impact of the change on:
    - Project schedule
    - Project budget (relative to the latest approved budget)
    - System scope, design or performance requirements (including safety, operability, reliability) construction, commissioning, operations, and maintenance
    - Other systems
    - Engineering documentation
    - Qualification documents (including the System Impact Assessment)

- Notify others who need to know of the proposed change
- Record the approval or denial of proposed changes
- Track through completion

A single, engineering change management process for the entire project should be employed during design, construction, and commissioning. The process should be based on the degree of control required and the levels of authority delegated to the project team members. Any change should be identified, evaluated with the stakeholders for impact, and approved by the facility owner, before proceeding. The changes should be sequentially numbered and logged to track the changes through to resolution. The reason for each change may be categorized to provide information for subsequent review. It is highly recommended that larger projects use a database to facilitate tracking of system changes and affected documents, and to enable subsequent review and analysis of the data.

Certain changes may affect commissioning or qualification plans, tests, or documentation, which are developed from the project design documents. Changes should be assessed for potential impact and communicated to the appropriate team members, based on agreed criteria. For "Direct Impact" systems, changes that affect the User Requirements Brief, Requirement Specification(s), the design concept or the System Impact Assessment should be communicated for review by quality assurance (QA).

4.9 COMMISSIONING AND QUALIFICATION

The project manager should ensure the development and execution of the Commissioning Plan and Qualification Plan (e.g., Validation Master Plan) as an integral part of the project plan and schedule. The project manager also should establish the framework necessary to ensure clear and consistent communication between construction, commissioning, and qualification personnel.

A Commissioning Leader may be designated to lead the commissioning activities and provide a single point of contact. Frequent (often daily) commissioning meetings may be employed to ensure coordination and prioritization of tasks. For "Direct Impact" systems, representatives from Validation, Quality Control and Quality Assurance should be included as necessary to ensure satisfactory resolution of problems and to optimize the use of commissioning deliverables to satisfy qualification requirements. Additional information is provided in Chapters 5 and 6.

4.10 PROJECT CLOSEOUT AND TURNOVER

Project closeout procedures, deliverables, and responsibilities must be clearly defined well before construction commences. The method of project turnover, whether phased or a single project completion turnover package, should be defined.

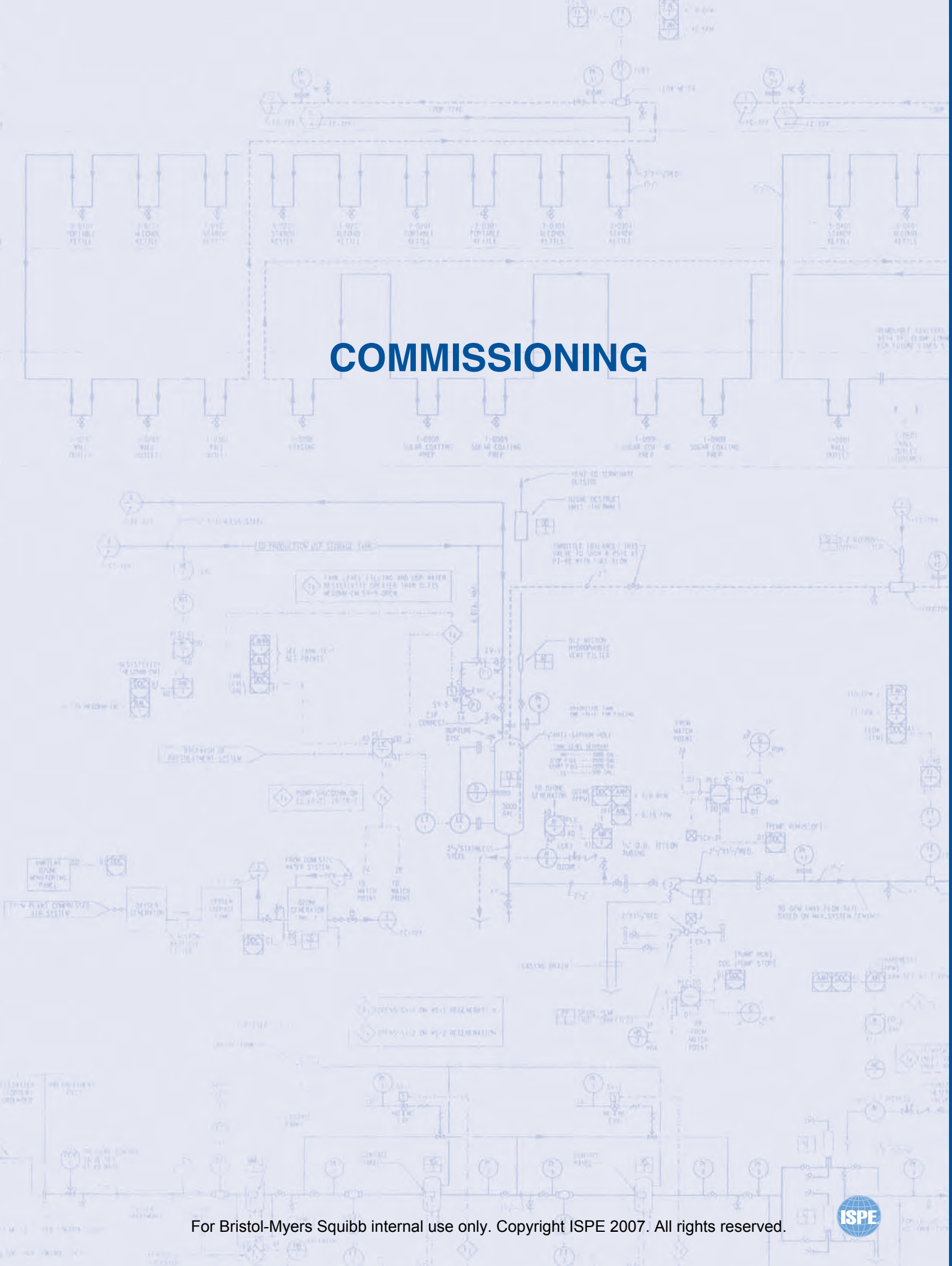
Phased turnover by system or area can allow the facility owner to qualify and use prioritized parts of the project earlier. Phased turnover also can allow the facility owner to level personnel resources, avoiding peaks that may affect either existing operations or project completion. Phased turnover requires significantly more coordination and interface between construction and operations.

A common pitfall is not having the procedures, personnel and facilities in place to receive and update the turnover documentation. Another pitfall is not identifying early in the project what documentation is considered living and what will be historic.

The phased turnover approach complements normal commissioning logic, which is either sequential or phased. For instance, a deionized water system may supply a clean steam system that, in turn, supplies clean steam for an autoclave. In each case, the predecessor must be commissioned and/or qualified prior to the successor.

The following is a list of deliverables, which should be included at project closeout and turnover.

- Final release of liens (i.e., documentation that demonstrates that there are no outstanding facility owner obligations or liabilities related to the project)
- Final project report
- Certificate of occupancy
- Finalized punch-list
- Signed project acceptance
- Subcontractor evaluation report
- 'Lessons learned' meetings with subcontractors, design firm, construction, and owner
- The owner should receive a complete set of all original project files. The construction firm or manager should be required to maintain a copy of all project files for an established period, and to notify the owner prior to properly disposing of files. Contracts that have confidentiality agreements should require certification of the destruction of the documents.
- The owner and validation manager should receive the agreed system documentation (e.g., system manuals). Typical documents include specifications, purchase orders, supplier contact list, certified supplier drawings, approved submittals, approved punch-list, O&M manuals, PLC and programming information, spare parts list, warranties, and commissioning documents.
- "As Built" drawings and specifications"



COMMISSIONING

5. COMMISSIONING

5.1 INTRODUCTION

The purpose of this chapter is to:

- Define the term “commissioning”
- Describe the organization and content of the Commissioning Plan document
- Provide guidance in the management and execution of the commissioning activities
- Position commissioning within the context of the qualification effort

The bio/pharmaceutical industry has no generally accepted definition of the term “commissioning”. This Baseline® Guide defines “commissioning” as:

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

Table 5-1 summarizes the differing stakeholders according to system impact.

Table 5-1 Commissioning Stakeholders

System Impact	Stakeholder Group
Direct	Engineering, Manufacturing, Quality Assurance, Validation, Contracting, Supply
Indirect	Engineering, Manufacturing, Supply, Contracting
None	Engineering, Manufacturing, Supply, Contracting

Commissioning requires timely planning, documentation, and managed resources. Commissioning encompasses much of the start-up activities of a project’s lifecycle. Commissioning execution typically occurs between **Physical Completion**[5] and turnover to either the operational/maintenance End-User or the validation team.

A successful commissioning effort requires the close cooperation of a multi-disciplined team and relies on the concepts and activities discussed elsewhere in this Baseline® Guide (e.g., Impact Assessment and Good Engineering Practices). Guidance on specific activities is available from other documents issued by recognized industry organizations, such as ASHRAE, CIBSE, IEEE, etc.

Some of the project lifecycle phases may overlap or be iterative in nature. Commissioning planning begins in the design phase and the last commissioning activities (e.g., final approval of the Commissioning Plan Summary Report) may occur during the validation or operation/maintenance lifecycle phases.

[5] **Physical Completion** is a project milestone where the installation of a system is complete as per engineering design, and the documentation required to support commissioning is available.

5.2 SCOPE AND STRATEGY

The Commissioning Plan should define the facilities, systems, and equipment that will be commissioned, based on the system boundaries described in Section 5.4.

There are many equally valid strategies to commissioning; each is dependent on specific circumstances. Depending on the intent of the system, commissioning may be a precursor to Process Validation or it may be the final activity prior to routine operations. If commissioning documentation will be used to support Process Validation, it is critical to involve the validation leader in the planning and coordination of commissioning activities and deliverables (e.g., the Validation Master Plan and Commissioning Plan may cross-reference each other).

The Commissioning Plan should define the coordination required between predecessor and successor lifecycle activities (e.g., Construction, Process Validation, or Operations/Maintenance).

Where possible, advantage should be taken of the opportunity to inspect (Pre-delivery Inspection (PDI)) and test (Factory Acceptance Test (FAT)) systems or major system components before delivery to site. This allows quicker and more efficient remedy of any failings, and avoids the delays to schedule that would result from discovering problems later, on-site. Where such systems have a direct impact on product quality, every effort should be made to incorporate the PDI and FAT into the qualification effort, through the application of Qualification Practices.

5.3 PLAN APPROVAL AND CHANGES

The Commissioning Plan should be prepared and approved in advance of Physical Completion. Approvers include the Design, Construction, Quality, and Validation (as necessary), and End-User management representatives. Changes to the Plan should be reviewed and approved by the original approvers (or their designate) and a revision history should be maintained of significant changes to the Plan. Formal signatures and signature explanations should be included on the Commissioning Plan approval page.

5.4 SYSTEM(S) OVERVIEW

The Commissioning Plan should include a description of equipment and systems to be commissioned (e.g., process and utilities), including their means of automation. The system overview should be a high-level process narrative including system boundaries, based on operational/functional requirements. The Commissioning Leader should provide input in defining system boundaries in the early project phases, to develop an executable Commissioning Plan. It is often possible to gather much of the system overview information from other project documentation.

5.5 DELIVERABLES

The commissioning deliverables should be separated into “Living” and “Historical” documents. “Living” documents are maintained throughout the commissioning period as the system or project requirements are modified or updated. “Historical” documents represent a point-in-time (“snapshot”) and are not updated continuously. Table 5-2 lists typical commissioning deliverables.

Table 5-2 Typical Commissioning Deliverables

Deliverable	Maintenance Status	
	"Living"	"Historical"
Commissioning Plan	•	
Commissioning Schedule	•	
Commissioning Budget	•	
Pre-delivery Inspection (PDI) Plan	•	
Pre-delivery Inspection (PDI) Report		•
Factory Acceptance Test (FAT) Plan	•	
Factory Acceptance Test (FAT) Report		•
Inspection Plan	•	
Inspection Report		•
Functional Test Plan This addresses: • Setting-to-work (including calibration[6]) • Regulation & Adjustment Testing & Performance Testing	•	
Functional Test Report(s)		•
System Test Summary Report(s)		•
Commissioning Plan Summary Report		•

The details of each deliverable may be incorporated in the Commissioning Plan or may exist in other documents. At a minimum, the Commissioning Plan should identify commissioning deliverables, due dates, and responsibilities. (See Section 5.6.) Due dates may be determined based on the system design, procurement, construction, receiving, start-up, testing, and system turnover schedules.

Other deliverables such as manufacturing Standard Operating Procedures (SOPs), preventive maintenance (PM) procedures, and End-User training documentation may be produced during the commissioning phase of the project. These types of documents are not typically considered the responsibility of the Commissioning Team to produce.

[6] The process by which measurements made by instruments is assured as sufficiently reliable for their application and the performance of the system with which they are associated.

5.6 ROLES AND RESPONSIBILITIES

It is critical to define the roles and responsibilities of each team, and each team member, to reduce overlapping of responsibilities and optimize resources.

For the purpose of this Guide, it is assumed that the project has been initiated, and the Project Manager has selected a Commissioning Leader. Depending on the project size and complexity, as well as the overall capability of the company performing the work, the project manager also may be the Commissioning Leader.

5.6.1 Commissioning Leader

The responsibilities of the Commissioning Leader may consist of, but are not limited to, the following:

- Generating the Commissioning Plan and managing revisions to the plan
- Forming the Commissioning Team with the appropriate skills for the scope of the commissioning work. For larger and more complex projects, the formation a Commissioning Steering Team (CST) may be appropriate.
- Clear definition of the roles, responsibilities, and deliverables expected of the Commissioning Team members
- Determining the level of commissioning activities (including documentation) required, with input from Engineering. The System Owner also may provide input for a given equipment or system
- Determining the appropriate level of commissioning training required for the Commissioning Team, and the End-User training required prior to the system turnover to the Facility Owner
- Coordinating and managing the overall start-up and commissioning activities
- Reviewing and following-up outstanding items during commissioning
- Coordinating and/or collecting deliverables, and if necessary, routing deliverables for approval to the appropriate departments (e.g., Engineering, Quality Assurance, Validation, Maintenance)
- Defining requirements (e.g., testing and documentation) for equipment/systems turnover, and turnover target dates
- Ensuring that the expectations of people such as contractors or suppliers, with respect to their contribution to commissioning, are reflected in the basis of their appointment

Depending on the size and the complexity of the project, the Commissioning Leader may be the Project Engineer, System Owner, General Contractor, or a combination of these.

5.6.2 Commissioning Steering Team (CST)

Where the scale and complexity of a project suggests the formation of a CST, this will usually comprise representatives from the major stakeholder and/or major decision-maker groups. Initiating and forming a CST early in the project will significantly help project progress, managing changes to the plan, and directing the detailed commissioning activities. The typical role of the CST is described below:

- Reviewing and approving the scope and the strategy of the commissioning activities, as defined in the Commissioning Plan

- Ensuring all roles and responsibilities have been appropriately defined for each member department involved in the commissioning activities, and that these roles and responsibilities are being maintained continuously

- Reviewing and approving requirements for standards and deliverables, as defined in the Commissioning Plan

- Reviewing and approving the standards and deliverables throughout the commissioning activities, to ensure that requirements are realistic and applicable to the project

- Reviewing and approving the final commissioning packages (this may be performed by the individual system owner or an appropriate delegate)

To ensure that all the necessary and required activities are included during commissioning, the CST should consist of representatives from Engineering, System Owner, those Contractors with commissioning and commissioning management responsibilities, Quality Assurance, Validation, and other departments as applicable. Table 5-3 shows a template of a typical deliverables responsibilities matrix. Allocation of these responsibilities varies depending on company policy and procedures.

Table 5-3 Typical Commissioning Deliverables Responsibilities Matrix

Legend: W = Write and maintain R = Review A = Approve E = Execute	Commissioning Leader	QA/Validation*	System Owner (Operational End User)	Project Engineer	Contractor(s)/Suppliers
Commissioning Plan	W&E	R	R	A	-
Commissioning Schedule	W	R	R	A	-
Commissioning Budget	W	R	R	A	-
Overall Test Plan	W&E	R	R	A	-
Pre-delivery Inspection (PDI) Plan	R	A	A	W	W&E
Pre-delivery Inspection (PDI) Report	R	A	A	W	W
Factory Acceptance Test (FAT) Plan	R	A	A	W	W&E
Factory Acceptance Test (FAT) Report	R	A	A	W	W
Inspection Plan	R	A	A	W	W&E
Inspection Report	R	A	A	W	W
Functional Test Plan	R	A	A	W	W&E
Functional Test Report	R	A	A	W	W
System Test Summary Report(s)	A	A	A	W	-
Final Commissioning Summary Report	W	A	A	A	-
*"Direct Impact" systems only					

In addition to the typical commissioning deliverables responsibilities shown above, the Commissioning Leader must make provisions for collecting Design and Construction phase deliverables that will be included in the commissioning turnover package. The "approve" and "review" capacities should be clearly defined.

5.7 RESPONSIBILITIES

5.7.1 Packaged Equipment Systems

The equipment supplier typically performs the commissioning of packaged equipment, as they are the most familiar with their own equipment. However, ownership and management remains the responsibility of the End-User. Prior to the equipment supplier arriving on-site, they will request pre-requisite activities be completed and documented. This will ensure the most efficient use of the supplier's time and experience.

It is highly recommended that the equipment supplier be notified early of the owner's documentation expectations. Ideally, these expectations will be defined within the terms of the supplier's appointment. The Commissioning Leader should provide advance determination of the level of documentation detail required of the equipment supplier. This will be based on the complexity, size, and (possibly) the Process Validation requirements of the associated equipment.

5.7.2 Engineering Systems Integrated On-site

These systems encompass multiple items of equipment and commissioning. Integration of such systems is typically led by the Commissioning Leader, and is a more complex series of activities involving the integration of packaged equipment systems with systems fabricated on-site. The commissioning of packaged equipment systems may form a subset of the commissioning of engineering systems that are integrated on-site. This process should follow a step-by-step description of activities, identified either on the schedule or in a separate listing of activities.

5.8 INSPECTION

Inspection is the process by which the construction and installation is verified as being in accordance with the detailed design, specified construction standards and materials, and any relevant legal or regulatory demands relating to these areas. Inspection may commence before or after a system is declared **Physically Complete,** depending on the nature of the system. Elements of a system may be complete and not liable to disturbance from the work remaining. In such a case, these elements can be inspected.

While Inspection is primarily a visual comparison task, there are situations where the correct construction, materials, installation etc. may be verified only through tests. For example, it would be very difficult to ensure that ductwork had been constructed to a low leakage specification by visual inspection alone, hence the need for pressure testing. These types of test are distinct from those described later (see Section 5.11) in that their objective is to confirm construction or materials rather than function or performance. Some examples of these two types of inspection task are listed below.

Visual Inspection:

- Drawing verifications
- Structural integrity tests
- Material certification reviews
- Code certification reviews

- Loop checks

Inspection Tests:

- Smoke/DOP tests
- Electrical voltage, resistance, and continuity tests
- Hydrostatic tests
- Pneumatic tests
- Flow and drain tests
- Pump and agitator rotation tests

Inspection may occur either off-site or on-site. For example, a Pre-delivery Inspection (PDI) may be performed at a supplier's location prior to shipping the equipment to the End-User's location. This can significantly reduce overall project timelines if performed properly (e.g., some or all of the PDI documentation may be used in lieu of on-site inspection if the appropriate approvals were obtained prior to PDI execution).

Where the opportunity exists to either fully or partially inspect at the supplier's facility, it should, in general, be taken and anticipated within the contractual demands placed on the supplier. However, there may be situations where the cost of attending the PDI may outweigh the benefits and risks in terms of schedule, and the inspection can be postponed until delivery on-site. This is a business cost-benefit decision.

Inspection performed during commissioning may be used to support Process Validation if the system is classified as "Direct Impact". Where this is the case, the inspection process should be managed and performed within the context of Qualification Practices.

5.9 SETTING-TO-WORK

This is defined as the process of setting a static system into motion.

Setting-to-work precedes 'Adjustment and Regulation' and includes the necessary calibration and preliminary adjustment of instruments, sensors, and mechanisms before initial energizing of systems. The prerequisites for setting-to-work include:

- A satisfactory inspection
- Safety/start-up procedures are in-place
- Training has been given
- Documented start-up sequences have been provided

The first stages of setting-to-work can be considered a "shake-down" of the system.

5.10 REGULATION AND ADJUSTMENT

Regulation and Adjustment describes the process of adjusting a system, or elements of it, to operate within the required tolerances. This includes activities such as balancing of chilled water and air conditioning systems, and the adjustment of a reject mechanism on a packaging line.

The task of 'Regulation and Adjustment' frequently reveals much of the data demanded by testing. Where this is the case, performing these activities concurrently, and involving the relevant team members in the process, will help reduce duplication of effort.

5.11 TESTING AND PERFORMANCE TESTING

Testing is the process by which:

- Adjustments to, and regulation of, individual systems are demonstrated as within the required tolerances
- System components are demonstrated as delivering the required capacity or duty
- The functions of the system are demonstrated to be as specified and appropriate[7]

Performance Testing is the process by which:

- The performance of interdependent systems is demonstrated as within the required tolerances
- The output of interdependent systems is demonstrated as delivering the required duty or capacity
- The interdependent functions of systems are demonstrated to be as specified and appropriate

Depending on the systems involved, Performance Testing may be the only testing required. However, where several systems are working together (e.g., air conditioning, chilled water, hot water, and Building Management Systems (BMS)) to deliver a performance requirement (e.g., a cleanroom environment), the individual systems will be subject to testing, while the combined output will be subject to Performance Testing.

Testing performed during commissioning may be used to support Process Validation, if the system is classified as "Direct Impact". Where this is the case, the testing process should be managed and performed within the context of Qualification Practices.

Testing may occur either off-site or on-site. For example, a Factory Acceptance Test (FAT) may be performed at a supplier's location prior to shipping the equipment to the End-User's location. This type of testing can significantly reduce overall project timelines if performed properly (e.g., some or all of the FAT documentation may be used in lieu of on-site testing, if the appropriate approvals were obtained prior to Factory Acceptance Testing).

Where possible testing, either fully or partially, should be performed at the supplier's facility, and this should be included in the contractual demands placed on the supplier. However, there may be situations where the cost of attending the FAT may outweigh the benefits and risks in terms of schedule, and testing can be postponed until delivery on-site. This is a business cost-benefit decision.

5.11.1 Testing Objectives

Several objectives of testing performed during commissioning should be carefully considered while preparing and executing individual test plans. These include:

[7] The need for some functions may only become apparent once the system has been constructed and set-to-work.

- The test must prove that the elements of the system perform safely within the required operating range and meet the performance criteria
- The test should prove that the elements of the system meet the design criteria

The design criteria are often more demanding than the required operating range and/or performance criteria. Therefore, further analysis could be required during the commissioning phase. The following should be considered before rejecting a system or component because it fails to meet design criteria:

- The design safety factor used
- Whether the design criteria is achievable
- Any economic value in meeting the design criteria
- Future uses of the system, which may require meeting the design criteria
- Whether testing proves that the system meets all required codes and regulations
- The level of involvement of the validation team in approving and executing the test plan, if the test will be used to support subsequent Process Validation documents

5.11.2 Test Guidelines

The Commissioning Leader must determine the level of detail and content of the Test Plan, based on the scope of the project (and with input from the CST). Although the details of testing cannot always be defined early on in the project, a guideline for testing should be in place as part of the overall Commissioning Plan. The guideline may include the following elements:

- A system matrix that defines the project systems, the type of testing, the level of testing, the test approval authorities, and the testing status. This system matrix will evolve through the life of the project design, but should be finalized prior to fabrication or construction.
- A method for organizing and packaging documentation. This should include a standardized table of contents for the organization of information, and the packaging system desired (e.g., 3-ring binders with a maximum 4inch (10cm) spine).
- Defined documentation practices

The defined documentation practices should outline requirements and standards, and may include:

- Blue or black ballpoint ink (no felt tip markers, red ink, pencil or white out, etc.)
- Initial and date test results at the time of the test (no pre-dating or post-dating)
- Single line strike-outs (do not obscure the original entry)
- Initial and date all corrections
- A list of company standard abbreviations
- Company standards for format, layout, and numbering

- A guideline for how test incidents will be managed. This should include documentation, reporting, and re-testing requirements or guidelines.
- Defined status for each stage of a specific test. For example:
    - Draft
    - Approved for execution
    - Executed and issued for approval
    - Executed and approved
- A detailed test schedule. This may be incorporated into the system matrix, depending on the scope of the project.

Test guidelines can be extremely valuable for several reasons, including:

- A broad variety of tests can be required during the Commissioning phase of a project. The individual test plans will be developed, approved, executed, and witnessed by various project team members (suppliers, contractors, engineers, owner's representatives, certified consultants, local or federal agencies). Early definition and coordination of these efforts will help standardize the documentation, avoid unnecessary delays, and avoid unanticipated costs during the latter stages of the project.
- The commissioning effort may be used to support the subsequent validation effort. If this approach is taken, the validation leader must provide input on the testing and documentation procedures.
- Resource availability is often the cause of project delays during the commissioning phase. This includes the resources to review documentation, as well as the resources to execute the testing. A test plan ensures that resource allocation for these efforts can be built in to the overall project plan.

5.11.3 Test Procedures

The testing performed during the Commissioning phase should be designed to ensure that the systems have been constructed to, and will perform to, their design criteria (e.g., functional tests and performance tests). Examples of Testing and Performance Testing include:

Testing:

- Fluid flows (e.g., CHW or LTHW)
- Pump or Fan duties
- Alarm tests
- Valve tests (stroke, let-by, and authority)
- Emergency power tests
- Software unit/module tests

Performance Tests:

- Cleanroom particle counts
- Differential pressures between cleanrooms
- Heat load tests within cleanroom
- Cleanroom temperature and %RH stability tests
- Sequence of operation tests
- Failure modes
- Safety and other interlocks
- Power down/power up
- Site acceptance tests

These individual tests can be prepared, approved, executed, and witnessed by a variety of project participants. A well-developed Test Plan will ensure that the Commissioning Leader can efficiently consolidate the results for inclusion in the final project documentation.

5.12 TRAINING

Commissioning training is conducted to ensure that all employees, contractors, consultants, and other persons involved in the commissioning activities can perform their duties safely and within project procedures and guidelines. Experienced and qualified personnel should deliver training instruction.

These training activities should be scheduled to take place either before, or at the time of, systems or equipment operational testing. The Project Team should determine training material content, as well as the quality and the level of training required. Training materials and written records of attendance should be retained. Consultation with the End-User's training coordinator should be used to determine if training materials (curricula, attendance records, etc.) should become part of the commissioning deliverables.

Depending on the nature of the facility, system, or equipment being commissioned, along with the commissioning strategy, training deliverables may be required to conform to GMP requirements. A training coordinator and a formal system of notification of training requirements are recommended to help reduce schedule conflicts, especially for personnel who may be working on other systems or equipment.

Relevant regulatory requirements, specifically GMP, EPA, and OSHA requirements should be communicated as part of the training program.

Training efforts should be targeted towards the commissioning resources and the End-User's maintenance and operational groups and may include the following training courses:

Table 5-4 Training Courses

COURSE TOPIC	Commissioning Team	End-User Groups
GMP overview[8]	•	•
Test incident/deviation management	•	
Engineering change management	•	
Good documentation practices	•	
Documentation handling practices	•	
Personnel safety	•	•
Security	•	
Equipment, instrument, and computer use and maintenance	•	•

End-User training instruction and record keeping responsibilities are typically shared between the supplier and the End-User's training coordinator. Training instruction normally follows the End-User's training program requirements for items such as format, content, and attendance records.

5.13 TURNOVER

A turnover strategy, also known as "hand-over" or "transfer of responsibility", should be determined early in the planning stages of the project Commissioning Plan and should be included in the commissioning schedule.

Several key items drive the type of turnover strategy, including the size and complexity of the project and schedule constraints. Projects that are a "one-time" turnover of all systems and documents at the end of the project may be appropriate for small, less complex projects.

Larger, more complex projects, with tight schedule requirements, usually have an incremental turnover by system, over a period of time. This incremental type of turnover allows the construction and commissioning phases to be achieved without requiring an unmanageable amount of resources. The sequence of turnover is determined by the Commissioning Team to allow critical systems to be completed early.

The turnover of documentation also may be sequenced on large fast-track projects, by expediting the systems' physical completion for early turnover, so that qualification and validation can proceed while the documents are being prepared for turnover.

Strategies for turnover which also need to be established early in the Commissioning plan, include:

- The type of security measures to be implemented during commissioning

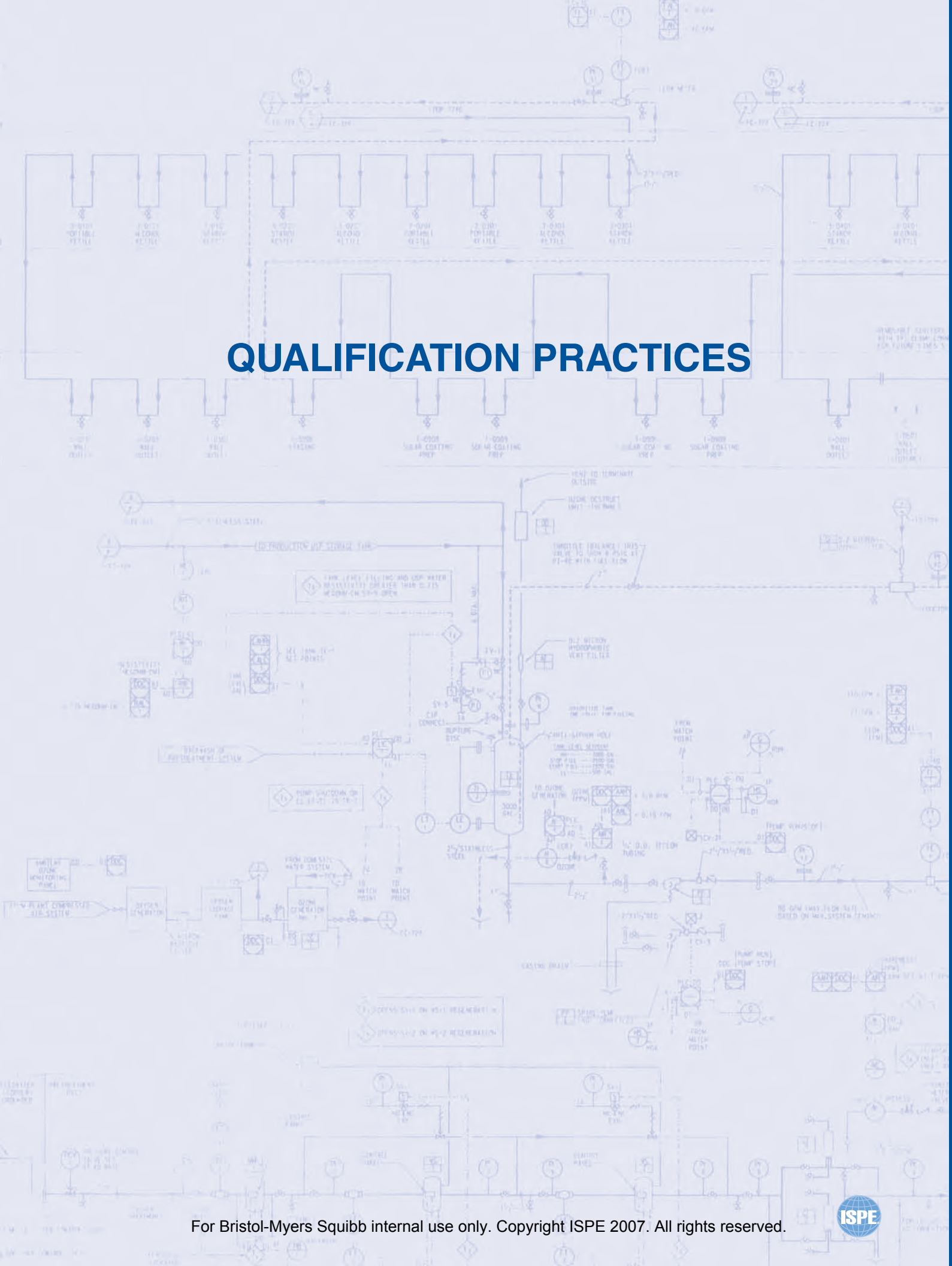
[8] GMP Overview training requirements depend on whether the facility, system, or equipment will be validated. In this case, consult with the validation leader to determine course content and instructor qualifications.

- The amount of control the team will have over the actual testing, witnessing, and documentation
- The monetary value assigned to the completed turnover packages in the contractor schedule of values

These strategies affect how easy or cumbersome the Commissioning Plan becomes and what impact it will have to the overall project schedule.

5.14 COMMISSIONING PLAN CLOSE-OUT

The Commissioning Plan should be summarized in a final written 'Turnover Report'. This report should include all aspects of the plan, from approval through execution, documentation, and turnover. The report should highlight any areas of concern or deviation from the original plan, explanations of the signature authority of those included, along with any changes in key personnel. This report is the formal 'close-out' of the Commissioning Plan and requires approval signatures and signature explanations.



QUALIFICATION PRACTICES

6. QUALIFICATION PRACTICES

6.1 PURPOSE

"Direct Impact" systems are subject to qualification practices that incorporate the enhanced review, control and testing against specifications and requirements necessary for compliance with current Good Manufacturing Practice. The purpose of this chapter is to introduce a high level overview of qualification practices that are required for "Direct Impact" systems. Specific details of qualification activities will be covered in subsequent chapters.

6.2 INTRODUCTION

The purpose of qualification for "Direct Impact" systems is to provide assurance that they have been properly designed, installed, and tested according to pre-determined acceptance criteria, based on assessment of those installation and operational characteristics, and parameters with potential product quality impact. While successful qualification serves as the foundation for successful process validation, the elements of Good Engineering Practice and commissioning in any project should provide substantial support for successful qualification of "Direct Impact" systems. In order to complete any successful and streamlined qualification effort, a comprehensive plan should be developed which bridges the GEP/commissioning phases of a project with the qualification phase of the project. A well-structured approach should be utilized. Testing should be based on scientific rationale and designed in a manner that is easily traceable.

6.3 VALIDATION MASTER PLAN

The Validation Master Plan (VMP) is a critical document for larger scale projects that encompass multiple systems and components. A VMP also may prove useful for some smaller scale projects. The VMP is a high level document, which establishes an over-arching validation plan for the entire project, to be used as guidance to the project team for resource and technical planning. Appropriate references should be made to other umbrella documents addressing pertinent areas not covered under the VMP.

As a guidance document, the VMP should outline the overall validation philosophy and approach to be used through the life of the project. This outline should:

- Include the strategy to be used for qualification and commissioning of the facility
- Position the impact assessment process, Good Engineering Practice, and Qualification
- Outline the relationship and interdependency of the qualification activity with the commissioning activity

The VMP is the key document that governs the testing and documentation required to satisfy the regulatory authorities. This document also brings structure to the verification of installation and operational testing. Ideally, this document is generated and approved during the planning stages, prior to commissioning and qualification, of the project.

Qualification planning and execution are subparts of the VMP. With respect to qualification practices, the following outlines examples of some of the issues that the VMP may address. It should be noted that this list is not necessarily all-inclusive, and aspects of the examples outlined below may require more detailed attention at later phases of the project. However, the need for recognition of such elements of the project should be identified within the VMP:

- **Qualification Rationale**

  An outline of the approach to be taken in assessing the qualification efforts, determining the extent and boundary limits of the qualification effort, and executing and assigning responsibility for the projects qualification activities

- **Listing of equipment, controls and systems**

  The listing of the equipment, controls, and systems is the building block of this document, clarifying the magnitude of the project. This list serves as the basis from which links can be established in order to develop a project plan, and resource requirements can be assessed.

- **System Impact Assessment**

  Based on the listing of equipment, controls, and systems, a System Impact Assessment should be performed. The classification of systems (e.g., as “Direct Impact” or “Indirect Impact” systems) should be clearly outlined, supported by explicit rationale and be reviewed and approved by Quality Assurance. This effort will provide the project team with a basis from which to determine whether a system or a set of systems will be subject to Good Engineering Practices alone, or whether the system(s) will require supplemental qualification.

- **Sequence of Testing**

  Once the equipment list and the System Impact Assessment are completed, a detailed schedule can be established. An analysis to determine the optimum sequence of testing from a system-to-system perspective should be completed, and interdependencies between systems and their support utilities determined. The sequence of testing in a new or modified facility should integrate the qualification activity with the overall construction, commissioning and start-up schedule, so that maximum leverage is made of the contract engineering firm’s efforts and associated documentation practices. The optimum sequence of testing should integrate automated systems where applicable, and wherever possible. Each equipment, control, or system should be evaluated to determine its predecessor and successor. The objective should be to minimize any duplication of effort and to ensure that procedures are implemented to incorporate already established good engineering and associated documentation practices to support the qualification efforts.

- **Documentation requirements**

  The Validation Master Plan should outline the documentation requirements for the project. Management of the qualification activities should include a comprehensive document management system. As the Validation Master Plan is an executive document, specific details should be placed within the subordinate individual documents. Examples of documentation requirements to be recognized as part of the Validation Master Plan may include the following:

  - Relevant standard operating procedures
  - Relevant maintenance procedures
  - Calibration records and procedures
  - Qualification and Validation protocols (IQ/OQ/PQ, automation, cleaning, analytical methods, process, etc.)
  - Vendor/Contract Engineering support documents

- Training and certification records
- Change Control

- **Key Roles and Responsibilities**

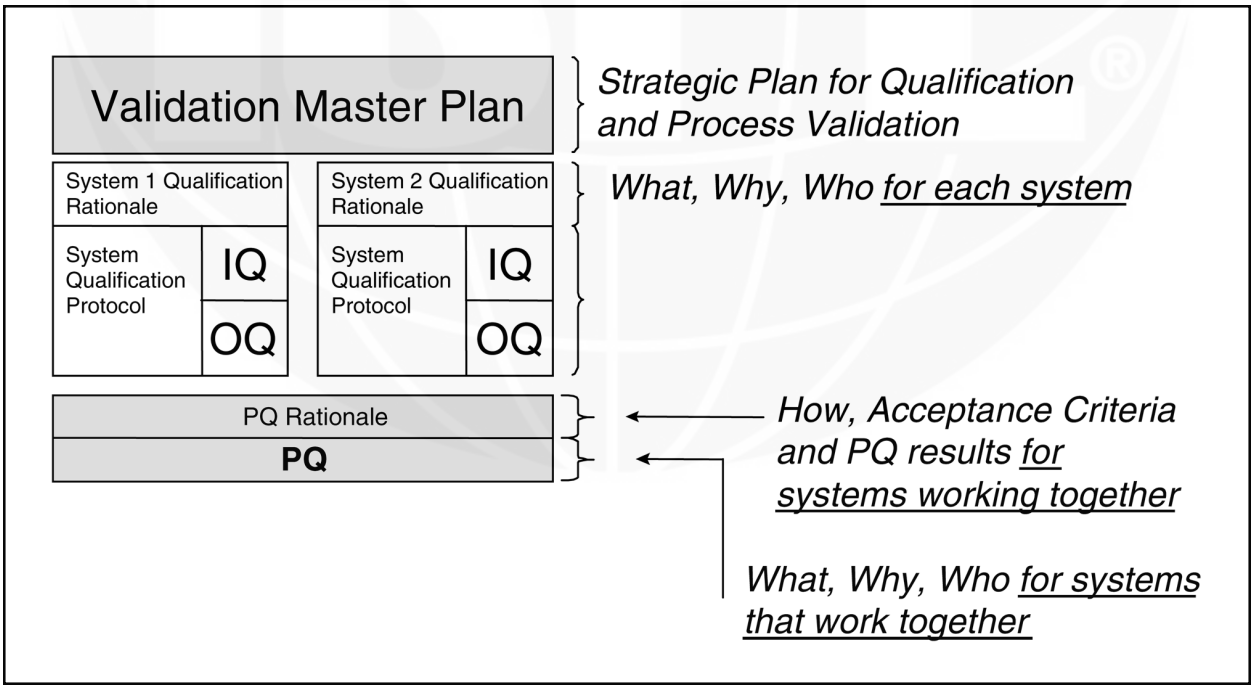
  The Validation Master Plan should identify key roles and responsibilities through the life of the project.

6.4 QUALIFICATION RATIONALES

A Qualification Rationale is a system-specific document that describes the inspection and testing requirements in summary, allocates responsibilities and justifies the approach being taken i.e. what, why and who for the system in question... The specifics of test methodology (i.e., how) and specifications (i.e., acceptance criteria) are detailed and recorded in the respective qualification protocol(s). It is important that a well thought out testing plan is developed, based on the use of the system and risk of failure.

The basis of the qualification rationale can be derived from the system impact and component assessment. Information from the enhanced design review also can be utilized to support the qualification rationale. The two principal documents that conventionally contain the qualification rationales are the Validation Master Plan (for small projects) and the Qualification Protocol (if the project is divided into systems). If desired, a separate qualification rationale can be generated. The decision can be based on several factors (e.g., project size, document management, nature of system interdependency, company's policies and procedures). This will be covered in more detail in Section 6.6. Figure 6-1 below demonstrates the relationships of these documents for an example of a project with two systems.

Figure 6-1 Relationship between Validation Master Plan, Qualification Protocol and Qualification Rationales



Some general contents of the Qualification Protocol(s) related to the Qualification Rationale are detailed in the sections below.

6.4.1 Qualification Protocol

The Qualification Protocol is an individual detailed document that describes the system under consideration, the testing plans, the acceptance criteria and the test results that ensure that a system is installed and operates in accordance with predetermined specifications - much of this material will usually be required for Commissioning. The Qualification Protocol should include those activities that are critical in nature and can affect the operation, safety of the equipment and its operator(s), processing parameters, and quality attributes of the product. A “Direct Impact” system requires a Qualification Protocol. Detailed discussion of qualification protocol requirements and contents are covered in subsequent chapters. Although, not always possible, it is recommended that the protocols be generated as early in the project as possible. Some of the items that a protocol may include are:

- **System Description**

  This is a general description of the system, describing its components, its designed unit operation functional capabilities, critical functions, and the boundaries of the system(s) covered under the protocol.

- **Documentation Deliverables**

  This is a list of the supporting documentation that should be received as part of the completed qualification package. It may include drawings (e.g., P&ID, As-Builds, wiring diagrams, etc.), manuals, preventative maintenance procedures, reports, calibration records, turnover documents, supplier test packages, etc.

- **Testing Requirements**

  This is a description of the testing requirements and challenges, testing sequence, and testing methodology. This may include items such as records and verification of the installation process, verification of installation and operational function procedures and records, instrument testing and calibration records, pre-requisite commissioning requirements, etc.

- **Forms for Documenting Results**

  The protocol should contain the format in which to collect and record pertinent data. Raw data may be captured within the protocol itself, or verification can be made within the protocol that relevant testing has been completed, results documented, analysed and accepted outside of the immediate protocol as meeting specified requirements. The format for collection or verification of testing data should allow for space to provide identification and execution date of the responsible party at inspection verification points throughout the protocol.

- **Acceptance Criteria**

  The expected result for each of the specified tests should be described. This should include enough detail information so an evaluation of pass or fail can be conducted.

- **Deviations**

  Pertinent deviations that occurred during the qualification phase of a project should be addressed in the protocols, with corrective actions and results described. A deviation/exceptions handling procedure should be established.

6.5 ACTIVE PARTICIPATION OF THE QUALITY ASSURANCE UNIT

6.5.1 The Role of Quality

The role of Quality throughout the commissioning and qualification process is discussed in Chapter 2. Early involvement by the Quality Assurance department will ensure clear understanding of the scope of the project, the facility, processes, and equipment. Early involvement should provide for clear communication of regulatory requirements, ensuring that procedures and practices are established up front for incorporation into the project. The goal is for the Quality Assurance department to work in partnership with engineering and other support functional groups involved with the project for a smooth, efficient hand-over, in compliance with regulatory expectations.

6.5.2 Reviews, Feedback and Approval

The basic premise of early involvement of the Quality Assurance department is to ensure that knowledge, expertise, and input in the areas of current Good Manufacturing Practice, regulatory expectations, and industry trends are incorporated into the project from design concepts forward. This involvement ensures that appropriate quality practices and procedures are adapted early in the project, to ensure that regulatory requirements and expectations are addressed, and to ensure that such requirements are met. The Quality Assurance department provides feedback and approves plans used to direct qualification activities, results and conclusions. Practical application of regulatory requirements is key in streamlining and efficiently managing the qualification activities.

Quality involvement should occur with participation in the decision as to whether or not qualification practices are needed, made by applying the System Impact Assessment, discussed in Chapter 3. This Impact Assessment provides for, and documents, a clear decision path to determine a system as a “Direct Impact” system or an “Indirect Impact” system. Thus, those systems that have been assessed as “Direct Impact “systems need to have qualification practices applied.

6.5.3 Change Control

Appropriate documented change control should exist throughout the life of the project, and should exist in the long-term maintenance of qualification post-project. In the early stages of a project, through design, construction, and commissioning, changes are handled by engineering following guidance set forth in Good Engineering Practices (GEP). Quality may not be routinely involved in the engineering change management process, as these changes are typically linked to technical management of the project. However, the engineering change management system should allow for Quality review and approval, and input into the change when one or more of the following conditions occurs:

- The change alters the Impact Assessment (i.e., it causes a formerly ”Indirect Impact” system to become a ”Direct Impact” system, or vice-versa).
- There is a fundamental change in the design concept
- The change results in a deviation from the demands of the original User Brief or User Requirement Specification for the system in question.

In general, active QA participation with change control is initiated by the System Impact Assessment exercise. A quality change control procedure applies to, and formalizes qualification activities (including commissioning activities, which supports the qualification activities) and on-going maintenance of a qualified state throughout the life of the facility, equipment, and ancillary systems involved.

Quality change control is defined as a process by which qualified representatives review proposed or actual changes for their impact, approves or denies the requests, and manages and tracks their implementation. Quality change control for "Direct Impact" systems is an essential part of GMP.

A quality change control process for "Direct Impact" system may contain the following attributes:

- Record the name of the originator and date
- Describe the change, the affected system or area, and intended purpose
- Assess the potential impact of the change on:
    - System scope, design, or performance requirements (including safety, operability, reliability), construction, commissioning, operations and maintenance
    - Other systems
    - Engineering documentation
    - Qualification documents (including the System Impact Assessment)
- Determine if additional testing is required. Describe the type of testing that is necessary. If additional testing is not required, provide rationale.
- Notify others who need to know of the proposed change
- Record the approval or denial of proposed changes
- Track through to completion

A single, quality change control process for the project should be employed. The process should be based on the degree of control required and the levels of authority delegated to key members of the project team (i.e., owner, engineering, validation, and Quality Assurance). Any change should be identified and evaluated with the stakeholders for impact, and approved by the owner before proceeding. The changes should be sequentially numbered and logged to track the changes through to resolution. The reason for each change may be categorized to provide information for subsequent review. It is highly recommended that larger projects utilize a database to facilitate tracking system changes and affected documents, and to enable subsequent review and analysis of the data.

6.6 ENHANCED DOCUMENTATION

6.6.1 Assessments, Rationales, Protocols and Plans

Impact Assessments, Qualification Rationales, Qualification Protocols and Validation Master Plans are examples of enhanced (commissioning) documents and require enhanced document management. The relationship between these documents can be found in Figure 6-2 and Figure 6-3.

Figure 6-2 **A Small Single System Project**

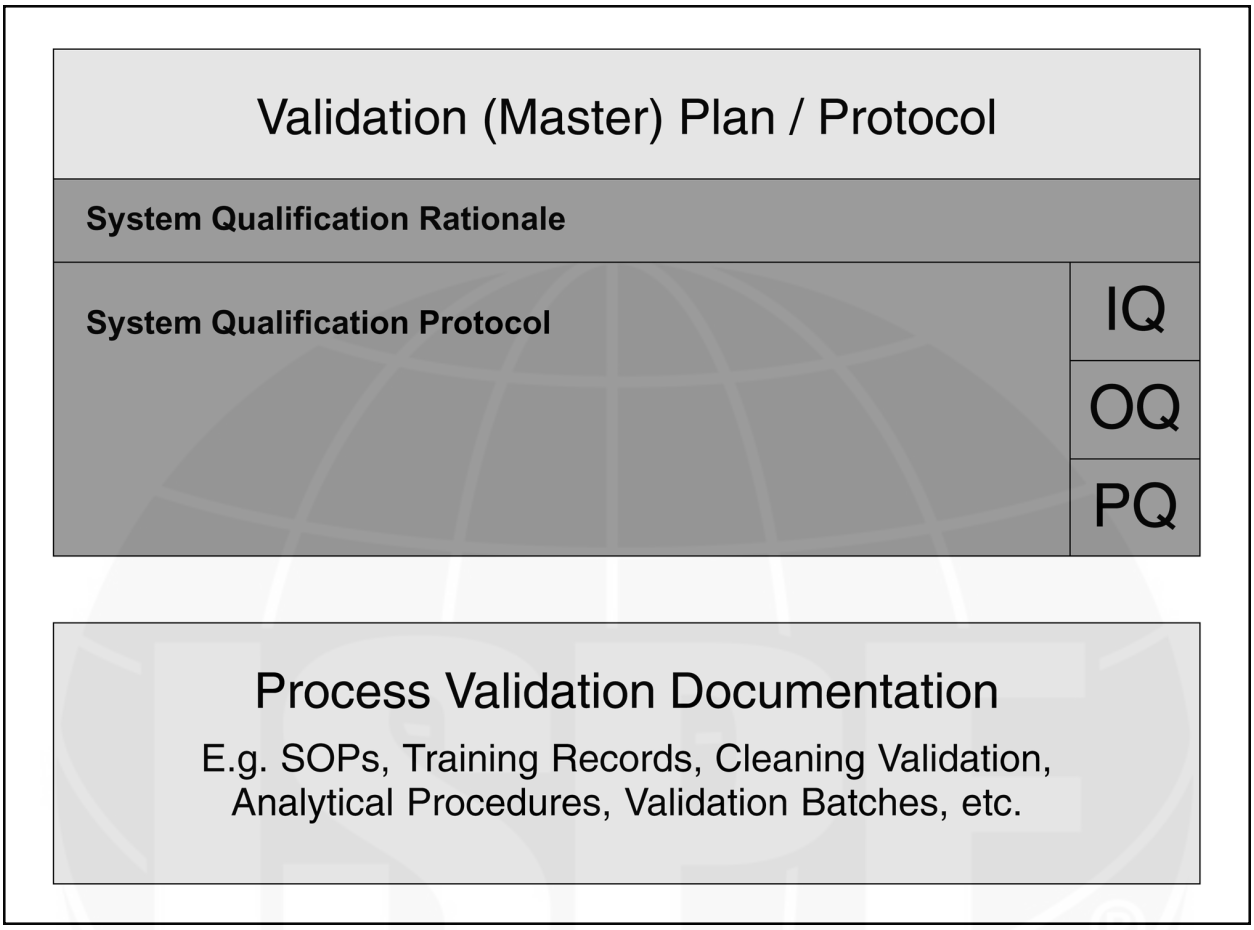


Figure 6-3 A Complex Project, Consisting of Many Systems and Components

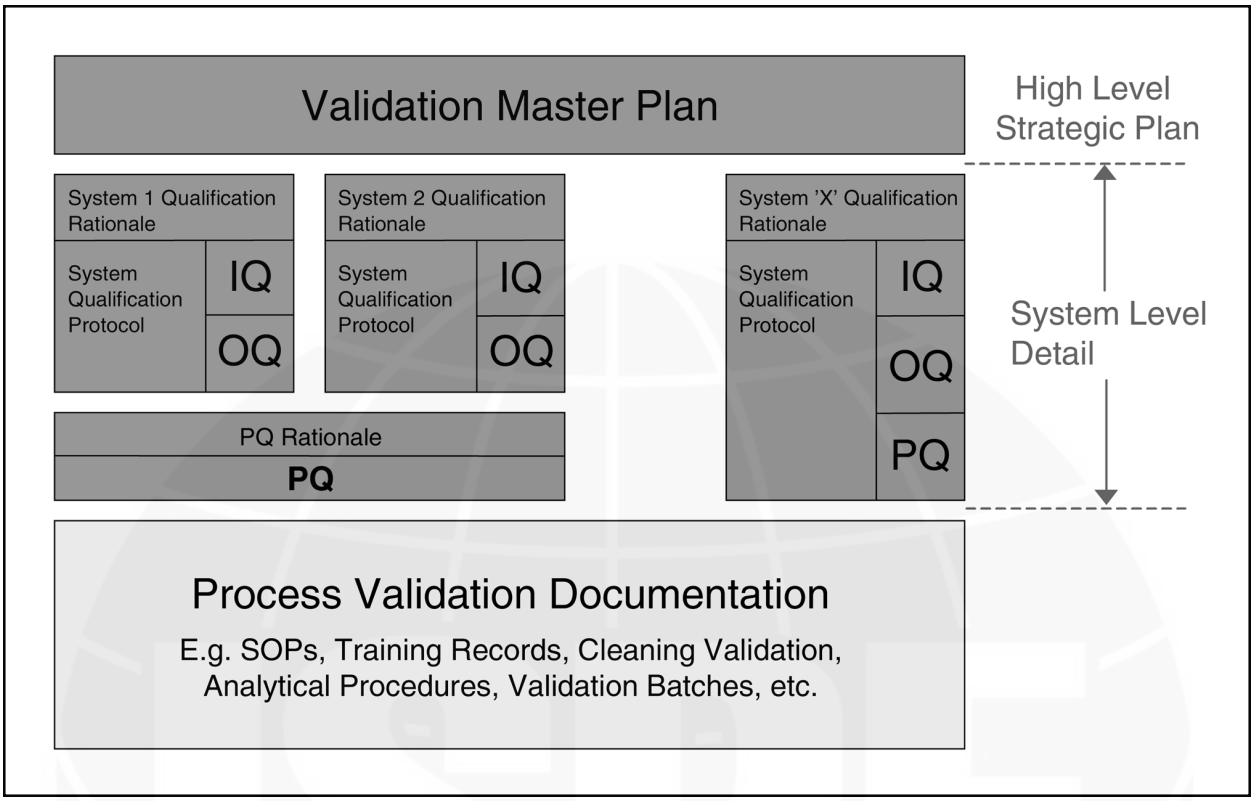


Figure 6-3 may represent a small single system project. All the requirements may be compiled into a single document (e.g. Qualification Protocol). Figure 6-4 represents a more complex project consisting of many systems and components. In this case, it would be advisable to break up the requirements, from the VMP, into various plans for better documentation management. The decision on the path should be at the discretion of the Facility Operator. Change control and documentation management should be the driver for the decision. For example, having larger documents that cover various systems may result in fewer approvals and less change management, but would lead to less flexibility and more difficult change management and vice versa. Enhanced documentation and document management typically incorporate the following requirements:

- Documents are required to be generated, reviewed, approved and archived because they are associated with a “Direct Impact” system
- Documents must provide an audit trail as to who approved something to be done, who did the work, when it was done, and who approved it upon completion
- Must have predetermined specification and acceptance criteria
- Must follow appropriate change control procedures
- Documents must be archived and stored in a well controlled area
- Documents must incorporate version control
- Original documents must be archived for a predetermined period of time

- Regulatory requirements for documentation must be met

6.6.2 Opportunities

The area of documentation provides significant opportunities for eliminating duplication of effort. Activities performed and documented as part of commissioning, if performed within the framework of enhanced documentation and documentation management, can be used to support the Qualification exercise.

Comprehensive planning during the early stages of a project is essential to the successful integration of commissioning activities in support of the qualification exercise.

6.7 GREATER END-USER PARTICIPATION

"Direct Impact" systems demand closer and more comprehensive "hands on" involvement from the End-User team; there should be credible ownership of the work associated with commissioning these systems.

6.7.1 Vendor Participation

Over the years, the supplier's role has changed substantially. A supplier's potential contribution towards qualifying a "Direct Impact" system has increased. Many suppliers have developed internal quality practices and procedures that facilitate their contribution to the overall qualification effort. Clearly outlined client expectations of the supplier, in terms of testing specifications, records, and deliverables, prior to procurement may provide opportunities to significantly streamline the qualification process. Some of the activities that may be of value are:

- **Supplier Audit**

  Supplier audits are often conducted at the beginning of the project to evaluate the supplier's ability to deliver a quality product/service. Results of such an audit may provide the basis for supplier/contractor selection, and provide the opportunity to clearly identify client expectations that also will serve to support the qualification efforts, minimizing any duplication of efforts in the process.

- **Supplier Documents**

  These are documents, which are provided to the End-User as records of system definition, system configuration, and applicable system testing, as verification against the purchase specifications. Early client definition of the elements of this turnover documentation from the supplier will facilitate its use to support the qualification efforts.

- **Factory Acceptance Tests (FAT)**

  Whenever appropriate, static and/or dynamic testing to support the qualification efforts should be conducted and documented at the supplier site. Supplier site testing will allow for troubleshooting and problem resolution of the system prior to shipment, providing for a higher level of assurance that the system will meet specifications and function properly upon delivery. Supplier site testing should be performed with the End-Users so the system can be challenged to best simulate actual production conditions.

6.7.2 Training

Training is a critical part of the Qualification Process. Training should address overall qualification requirements and practices, and the regulatory significance of training. Training should be provided to those functional areas that will participate in the qualification activities, and those that will complete documentation directly supporting qualification activities. These groups include members of the project team, appropriate members of the contract engineering firm(s), and subcontracted personnel. Documentation should exist that describes the training contents, and records should be maintained of personnel to whom training was administered.

6.8 ADDITIONAL TESTING

Many, if not most, of the inspection and testing requirements associated with the engineering systems found within pharmaceutical facilities are catered for within Good Engineering Practice, however there will be circumstances where testing or inspection requirements are unique to pharmaceutical applications and guidance, methods etc cannot be drawn from the field of general engineering practice. In such cases, additional testing will be required within the Qualification effort.

There may be tests where one successful trial is acceptable, yet for other tests reproducibility in multiple trials may be required. There also may be the need to challenge the range of intended use of the system. The number of tests performed, as well as any justifications, should be detailed in the qualification rationale. Quality Assurance approval of the protocol will indicate concurrence with the testing plan.

ENHANCED DESIGN REVIEW

7. ENHANCED DESIGN REVIEW

7.1 INTRODUCTION

Enhanced Design Review (EDR) is the term adopted by this Guide to describe the process by which engineering designs for pharmaceutical facilities, systems, and equipment are evaluated. This process compliments **Good Engineering Practice.**

EDR is defined as:

"A documented review of the design, at an appropriate stage in the project, for conformance to operational and regulatory expectations."

A structured review of the design of facilities, utilities and equipment is not an FDA demand, however the authors of this Guide consider it the "smart" way to prepare for IQ and OQ activities. It is in the interests of all to reveal design or specification problems through a rigorous, structured, and *appropriate* review process early in a project, rather than discover them later at the IQ or OQ stages, where a remedy might involve significant delay and expense. This, however, remains a business risk driven choice not an FDA expectation, and hence the reason for avoiding the term "DQ" in this context.

EDR may be used as a tool to provide a structured assessment of the design of facilities, utilities, and equipment. This should assure the regulatory authorities that the design process has been carried out in a controlled manner and that an audit trail exists from conception of the project up to the completion of the detailed design.

Historically, design documents tended to be held in a number of different locations. EDR aims to capture all assessed elements of the design into a formal index, which forms a cross-referenced 'route map' to the archived design documents.

EDR should define the break point between development of design and design changes that may demand full (Quality Approved) change control procedures.

EDR should be described in the Validation Master Plan (VMP) indicating intention, process to be followed, responsibilities of persons involved, and position of EDR with reference to GEP and Qualification Practices.

7.2 REGULATORY PERSPECTIVE

Enhanced Design Review (EDR) is not essential for compliance of manufacturing facilities regulated by the FDA. EDR is not referenced in any regulatory publications as regulations, rules, or guidelines.

However, design is well referenced in current Good Manufacturing Practices e.g.:

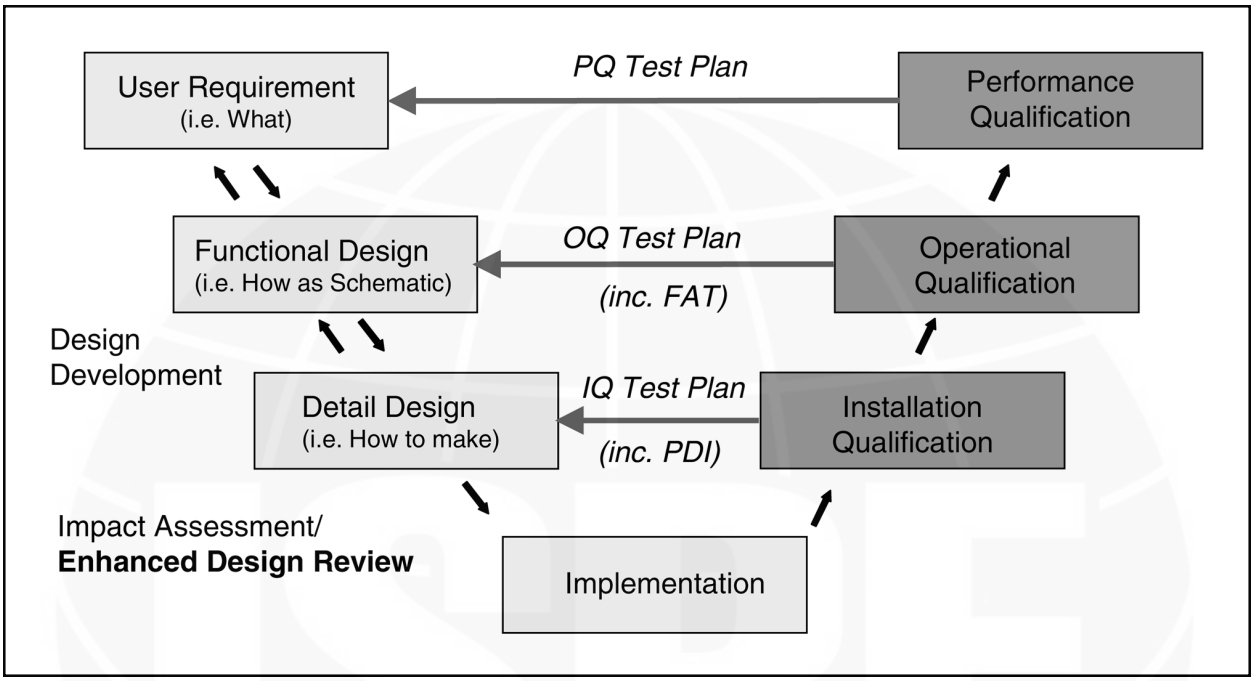
The code of federal regulations (CFR) title 21 Part 211 Subpart C - Buildings and Facilities and Subpart D - Equipment. These chapters make specific reference to "appropriate" design and to "suitable" or "adequate" size, construction and location for cleaning, maintenance and proper operation of facilities, utilities and equipment.

It is, however, worthy of note that there are some references to Design Qualification (DQ) issued, or in preparation by regulatory authorities other than the FDA.

7.3 EDR AND THE V-MODEL

The following diagram represents the position that EDR occupies in the overall structure of the V-Model (see Figure 2-3 and Figure 2-4).

Figure 7-1 Enhanced Design Review - position in V-Model for "Direct Impact" systems



Sufficient information must be available before a design may be fully assessed. The impact and complexity of the design will influence the depth of the review process. For example, it would be possible to evaluate a design at a conceptual level following completion of the Functional Design. (See Section 7.3.2.) However, a full assessment could only be made following completion of Detail Design. (See Section 7.3.3.)

7.3.1 EDR and User Requirements

The User Requirements Brief (see Section 7.3.1) provides the objectives for the design of the facility and the basis for the Validation Master Plan (VMP). It describes the requirements of the facility in terms of product to be manufactured, required throughput, and conditions in which the product should be made.

A **Requirement Specification** is a more detailed document, which is used to specify the requirements of the client for individual aspects of the facility, item of equipment, utility, and systems in terms of function, throughput, operability, and applicable local standards. All Requirement Specification documents should be approved by appropriate stakeholders (see Section 4.5.4), and used as primary reference documents.

The Requirement Specifications may be considered as being the point of reference for EDR and Qualification. As such, they should be subject to change only through a formal Quality Assurance change control process, which is endorsed by the End-User.

7.3.2 EDR and Functional Design

The functional design stage generates the key design documents, in the form of the Functional Design Specification (FDS), to be used as a framework for the detailed design process. (See Section 4.6.2.) Functional Design Specifications (FDSs) are frequently written by the supplier and are of prime importance to the Enhanced Design Review process. The FDS should describe acceptance criteria in terms of criteria such as, ranges and logic of operation, which should be defined and correlated with the URS.

It is important that GEP, GMP, and Risk Assessment reviews are carried out during this stage to ensure that the URS is not compromised in terms of Quality and GMP requirements, or Environmental and Safety issues. The EDR both checks and documents that this is the case.

7.3.3 EDR and Detailed Design

The detail design stage produces the documents required for construction bidding and contracting, as well as system and equipment purchase, fabrication, installation, and testing. (See Section 4.6.3.)

Planned design reviews should be held to ensure that a co-ordinated design is realised. The EDR both checks and documents that all concerned with the development of the detailed design have respected the User Requirements. A final check should be made to ensure that the 'best option' for a robust and economic design has been attained.

7.3.4 EDR and Impact Assessment

The initial determination of which systems should be commissioned in accordance with GEP, and which systems should be subject to Qualification Practices in addition to GEP, is usually carried out early in the project lifecycle. This process is described as Design for Impact. (See Section 2.2.6.) These design objectives may be included in the Validation Master Plan. (See Chapter 3.)

The Design Development and EDR processes should provide the engineering team with sufficient knowledge to make informed judgements regarding the impact of systems and the criticality of components within them. Component criticality assessment (see Section 3.3.5) may be planned during the EDR process.

7.3.5 EDR and Design Development

Design Development is the engineering process by which the generation of the design is managed. EDR is the process by which the design is confirmed as meeting the demands of the User.

While creation and modification of Requirement Specifications should be within a QA Change Control process, Design Development need only be subject to Engineering Change Management. (See Section 4.8.4.)

7.4 ENHANCED DESIGN REVIEW (EDR) PROCESS

7.4.1 EDR Rationale

The EDR Rationale should describe:

- What will be reviewed in terms of scope of each system
- What method or process will be followed
- Who will be involved

- The supporting case for the approach described

The rigor of the method by which a design is examined should correspond to:

- The impact of the system
- System complexity
- Familiarity or degree of novelty with the system and-or the supplier
- The novelty in application of "standard" equipment

This is described in more detail later in this chapter. (See Section 7.6.)

7.4.2 EDR Plan

An EDR plan may be written for each system, and should describe how the review will be performed. A Summary Report also may be written to state the outcome of the review process, confirm that the design is satisfactory, and should reference, review and index all aspects of the design including:

- Minutes of all GEP/GMP review meetings (see Section 6.6.2) held during the Design Development
- Relevant documents: Typical documents may include URS(s), VMP, functional or technical specifications, suppliers tenders, method statements purchase orders, and Acknowledgements
- Drawings: Comparison with approved versions (Client Definition Drawings) to ensure compliance with User Requirements and GMP. Typical drawings may include: layouts, P&IDs, piping isometrics, materials flows, personnel flow, HVAC zoning (including differential pressure regimes, temperatures, humidity, and particulate level requirements), and fabrication drawings (including materials of construction, finish standards)
- Room Data Sheets: These ensure that materials of construction, finishes, utilities supply, etc. comply with the User Requirements and GMP (where necessary).

The EDR report, following the procedures set out in the plan, should be used to confirm and record:

- Constraints or assumptions made in evaluating the design
- Reference to supplier/contractor pre-qualification: (This should define whether the supplier or contractor is capable of carrying out the works to the required quality, have sufficient experience in GMP projects or have been recently audited)
- Future testing requirements (e.g., Factory Acceptance (FAT) and Site Acceptance Testing (SAT))
- Any deviations together with a remedial action plan (including follow-up and closeout procedures)
- The location of all design documents: These should be referenced within the EDR report to assist potential inspection by regulatory authorities or internal auditors.
- The result of the component criticality assessment and adjustment to system boundaries, as appropriate

The Role of the Users and Quality Assurance is very important to the success of the Enhanced Design Review. As EDR is the main formal review of the completed design, 'buy-in' (preferably by sign off of the EDR Summary Report by the appropriate stakeholders) is of paramount importance as this establishes that the design will meet the User Requirements Brief and Requirement Specifications.

7.4.3 EDR Team and Responsibilities

The EDR participants should be fully aware of the objectives of the EDR, their responsibilities (see Section 4.4.1) and required contribution. A typical list of participants is as follows:

- Project Manager
- Discipline Engineers
- Design Representatives from Contractors and Suppliers
- Representatives from Operations/Production, Maintenance, Quality, Validation, Safety, and Environmental control, as appropriate

7.5 SUGGESTED EDR METHODS

7.5.1 Summary

Two complimentary methods of evaluating designs are suggested here, namely:

- Structured Design Review
- FMEA and FMECA

Both of these may be either the basis for self-evaluation by the project team, or, alternatively, the basis of a peer-review process. The peer group will usually be able view the design with greater objectivity. It is stressed that there are other structured methods by which designs can be assessed (e.g., HAZOP, HAZAN and Fault Tree Analysis, as appropriate).

7.5.2 Structured Design Review

By identification of the characteristics of a good design, the design review may be structured, ensuring all relevant and appropriate aspects of it are examined. This approach also has the advantage that the process produces positive statements of compliance, rather than just a list of deficiencies that is typical of a design review process.

Listed below are suggested criteria for use in assessing design.

QUALIFICATION REQUIREMENT

- Design satisfies GMPs and other regulatory requirements
- Design meets Performance Criteria (User Requirements documents and FDS)
- Design considers Facility Airflow and Pressure Regimes
- Design considers Process Flow - potential for product contamination
- Design considers Personnel Flow
- Design considers Materials of Construction
- Design considers Cleaning

- Design considers Reliability and Efficiency
- Design considers the requirements for Commissioning
- Design considers 'Constructability' and Installation of Equipment
- Design considers Maintenance and Access to 'quality critical' equipment and instrumentation
- Design considers Start-Up and Shut-Down Process
- Design considers Safety and Environmental Impact
- Design considers Degree of Innovation
- Design considers Use of "Standard" Solutions
- Design considers the Required Documentation is specified

The checks made using these criteria should be documented, together with any remedial action or further issues to be resolved.

The use of these criteria may be supported with the use of system-specific design checklists. A secondary benefit of EDR is to facilitate the development of such checklists.

7.5.3 Failure Mode Analysis

There are two types of failure mode analysis: **Failure Modes Effect Analysis (FMEA)** and **Failure Modes Effect and Criticality Analysis (FMECA).**

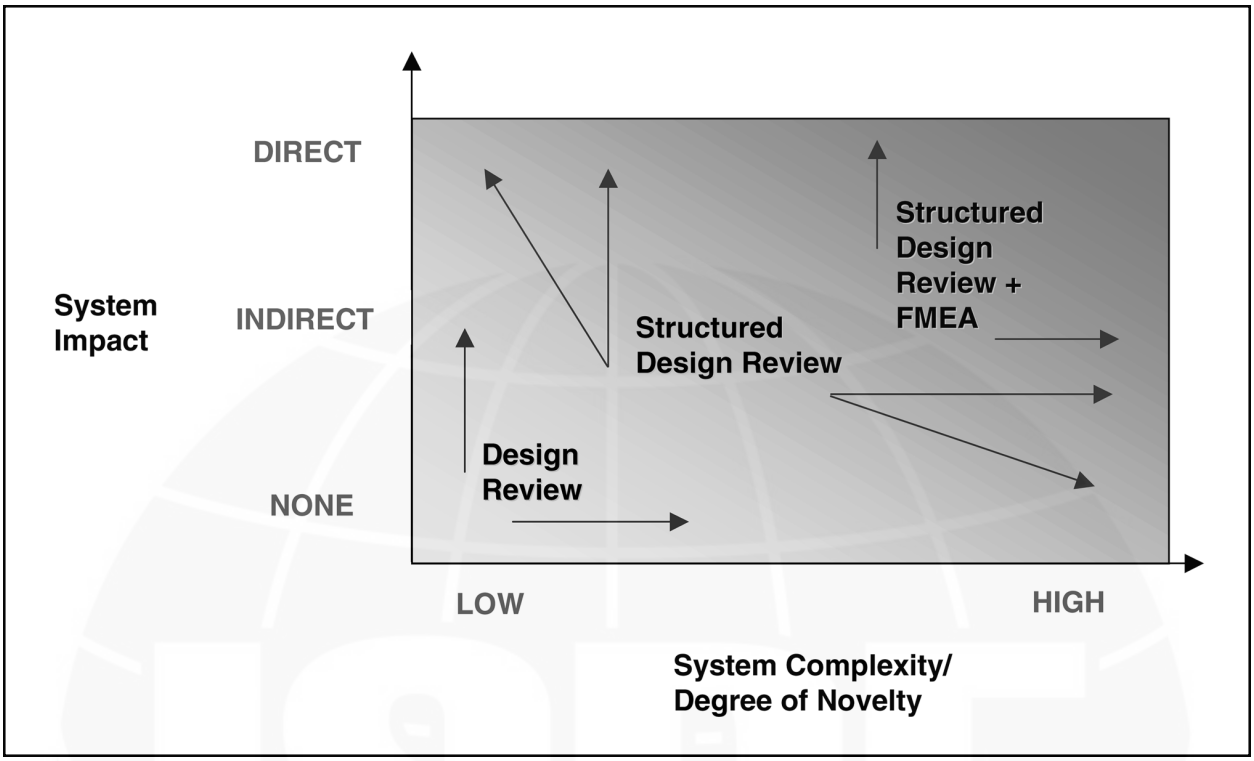
The FMECA process produces a quantified measure of reliability; this requires reliability data e.g., Mean Time Between Failures (MTBF). In practice, this might be difficult to obtain and this will either restrict the assessment to an FMEA or a more qualitative form of FMECA.

For a comprehensive discussion of these techniques, see Appendix 2.

7.6 SELECTING METHODS FOR ENHANCED DESIGN REVIEW

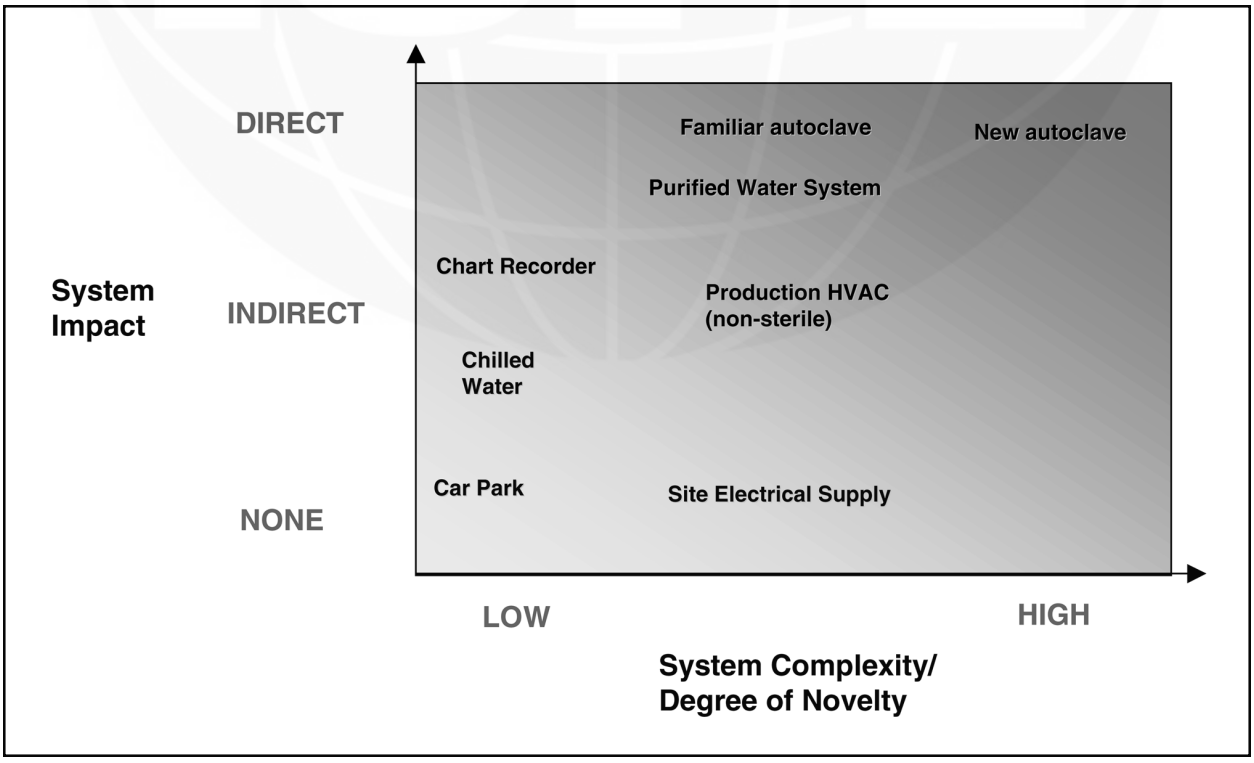
In deciding the methods by which a design will be assessed, due consideration should be given to the complexity and novelty (to the user) of each system, and the impact of each system on product quality. (See Figure 7-2 and Figure 7-3.)

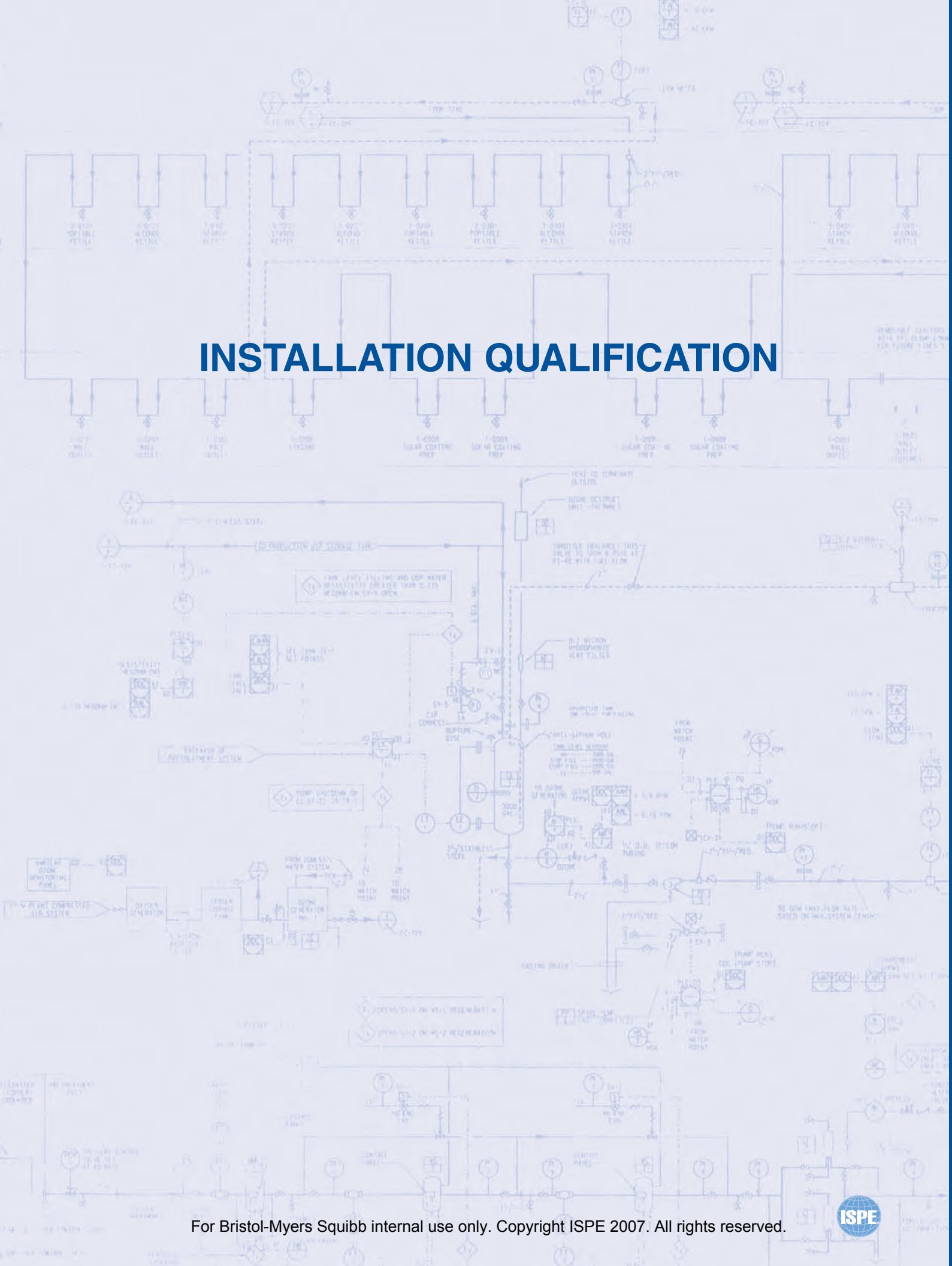
Figure 7-2 System Impact vs. System Complexity/Novelty - Tool Map



Highly complex, "Direct Impact" systems, with which the End-User is inexperienced will in general, warrant a greater degree of scrutiny than simple, familiar systems of no impact.

Figure 7-3 System Impact vs. System Complexity/Novelty - Example Systems





INSTALLATION QUALIFICATION

8. INSTALLATION QUALIFICATION

8.1 INTRODUCTION

Installation Qualification (IQ) is an activity that is regulated by the FDA, and is a part of final qualification activities before Process Validation begins.

This Guide has defined Installation Qualification for "Direct Impact" systems as:

"The documented verification that all aspects of a facility, utility or equipment that can affect product quality adhere to approved specifications (e.g., construction, materials) and are correctly installed."

It is the process of checking and verifying the installation to ensure that the critical components meet the approved specifications and that they are installed correctly.

Only "Direct Impact" systems will be subject to IQ. Installation Qualification is subject to QA approval and any change subsequent to this stage requires QA review and approval.

According to the V-Model, (see Figure 2-3) the Installation Qualification relates to detailed design for "Direct Impact" systems, verifying the construction and installation of the facility, utility, or equipment.

The primary objectives of this chapter are to:

- Provide an overview of the IQ process
- Describe the types of activities that occur, and documentation that is needed, for the IQ process
- Describe how IQ fits in with the overall qualification process
- Describe how commissioning integrates within the IQ process

8.2 PURPOSE OF IQ

The purpose of Installation Qualification is to establish that the critical components are installed correctly and in accordance with design documentation requirements (i.e., specifications, purchase orders, contracts, bid packages, etc.). Supporting documentation should be in place and of suitable quality, and instruments should be calibrated.

Calibration is a related program for qualification, and also could be verified at the start of OQ, prior to the commencement of testing. Critical instruments should be calibrated before undergoing any qualification testing.

The purpose of an approved protocol (IQ protocol) is to record the checks and verifications described above for critical components in "Direct Impact" systems.

8.3 BEFORE IQ PROTOCOL WRITING BEGINS

The following items should be completed before the IQ protocol writing process starts:

- **Impact Assessment**

  The System Impact Assessment should have been performed, and documented.

- **Component Criticality Assessment**

  This should have been performed for the specific system. For some systems (e.g., a single piece of process equipment), this could be performed prior to IQ, or as part of the IQ process.

- **Design**

  Sufficient design details should be available, with all systems defined (including detailed P&IDs, where applicable).

- **Scope**

  The extent and scope of commissioning and qualification necessary (inspection, testing, etc.) for each system should be finalized.

- **Schedule**

  The milestone activities of both writing and executing the protocols should be available.

- **Team identification**

  The scope, roles, and responsibilities of the project team, including contractors and suppliers, should be determined. Responsibilities also should include who will write, review, approve, and execute the protocols, who will coordinate the IQ within the company, and who will verify that the test requirements are completed.

- **Training**

  The training of the validation team in the procedures used in IQ should be complete.

- **Validation Master Plan**

  Ensure that the IQ follows the overall Validation Master Plan.

- **Installation Qualification process documents**

  Decisions regarding the documentation deliverables required for IQ should be made during the design phase and establishment of the design specifications for a system, and during the preparation of bid packages and contracts. These deliverables should be verified during the IQ phase to ensure that the systems are in parity with the documentation.

- **Changes**

  The QA change control procedure and the engineering change management procedure should be in place.

8.4 COMMISSIONING INTEGRATION WITH IQ

Commissioning, in accordance with GEP, can support qualification if performed within a qualification regime. A qualification regime is characterized by the application of qualification practices. When integrating commissioning activities in a project, it is critical to define the over-all scope of the tests and verifications to be performed for a system, before starting any commissioning or qualification work. The list of these tests and verifications should be compared against the requirements in the various purchase orders and contracts to be placed for the given system.

PDI, FAT, and commissioning activities performed in support of qualification should incorporate qualification practices in addition to GEP. Once the scope of both the commissioning and qualification of a system has been defined, the scheduling and execution of the activities can commence according to the practices described in this Guide.

Examples of commissioning integration with IQ include:

1) The P&ID of a system can be verified during the "Physical Completion" and Inspection phase of commissioning. If this activity has been performed following qualification practices, the exercise will not have to be repeated in the IQ phase.

2) Instruments and equipment can be verified (manufacture, model number, materials of construction, etc.) at the supplier's site during a Pre-Delivery Inspection (PDI) or Factory Acceptance Testing (FAT). If these items are not altered or dismantled in any way for transport, these checks, if properly documented, could be used in support of qualification activities, and would not have to be repeated.

8.5 DOCUMENTATION REQUIRED TO WRITE THE IQ PROTOCOL

Sufficient engineering information and documentation should be available to write the IQ protocol. If engineering documents are appropriately planned, created, organized, and authorized, they can be an integral part of the qualification support documentation for "Direct Impact" systems. The following is a list of documentation, per system, that is typically required to write an IQ protocol:

a) Validation Master Plan (VMP)

b) User Requirements Brief and Requirement Specification

c) Supplier Drawings and Specifications, including:

- Purchase Orders and Contracts
- Manufacturer's Data Sheets
- Process Description
- P&IDs
- Equipment List
- System Hardware/Software Specifications
- Instrument List

8.6 ORGANIZING AND WRITING THE IQ PROTOCOL

There is no standard IQ protocol style or format. Contents will vary from company to company, from contractor to contractor, and are dependent on the scope of the protocol. IQ protocols should be written in accordance with, and supported by, a Standard Operating Procedure (SOP). The following are examples of what is typically included in an IQ protocol:

a) Approval Page: Initial and final document review and approval should be done in accordance with company policies and procedures, and should include a review and approval by QA.

b) Pre-requisites: Those actions that must be performed prior to beginning the execution of the protocol.

c) Objectives: Describes the purpose of the IQ

d) System Description: Description of the equipment and/or process, and of the system critical components. This may include the component name, location, tag numbers, etc., and an overall description of the system's functionality. This description also can include a boundary description and/or point to a document defining the boundary.

e) Responsibilities: Specific responsibilities for IQ preparation, review, approval, and execution.

f) Qualification Requirements (including acceptance criteria): Acceptance criteria should be selected carefully, based on what is important to the process, product, or material. It is not unusual for the design conditions for a particular system to be different (more stringent) than the acceptance criteria stated in the Qualification Protocol.

g) Engineering Documentation Requirements: List of pertinent documentation required to support the system which includes:

- Record of Signatures
- Qualification Test Instruments List
- Product Contact Materials Review
- Utilities Verification
- Control System Verification
- Instrument/Control Devices Verification
- Equipment Verification
- Piping Installation Verification
- "As Built" P&IDs
- Specifications
- Qualification Acceptance

h) Discrepancy/Justification and Corrective Action: All amendments and deviations must be adequately addressed and approved by all appropriate individuals prior to proceeding to OQ.

i) Installation Qualification Summary

j) References: List of the references, guidelines, and specifications used in developing the IQ

k) Attachments/Appendices

8.7 IQ PROTOCOL APPROVAL BEFORE EXECUTION

Once the protocol has been written, it should be approved. This may be a time consuming process and several ways to streamline this process, include:

- Minimizing the number of approvals required
- Clarifying the review process with all parties early in the project
- Using existing or standardized templates wherever possible
- Collecting all comments from all parties on one master document
- Instituting a formalized protocol tracking process
- Minimizing the number of review cycles allowed by the team
- Implementing a simple review and approval project procedure
- Instituting protocol comment review meetings for all parties involved
- Assuring the protocol review and approval process is included in the overall project schedule

Once the IQ protocol has been approved, it is ready for execution.

8.8 DOCUMENTS REQUIRED TO EXECUTE THE IQ PROTOCOL

The following is a list of documents that are typically required to execute an IQ protocol:

- P&IDs and drawings
- Instrument List
- Equipment List
- Material Certifications
- Spare Parts List
- Change Parts List
- Installation Check Sheets
- Lubricants Schedule
- Calibration Check if done during the IQ phase

8.9 TRAINING BEFORE IQ EXECUTION

The overall IQ process can be streamlined if a proper training program has been put in place before IQ execution. Key factors that should be addressed in training End-Users on a new system include:

- The purpose of the equipment/system
- Use of test equipment
- Applicable SOPs
- cGMP documentation training

All training should be documented. Training requirements should be periodically reviewed.

8.10 IQ PROTOCOL EXECUTION

The execution of the IQ protocol will involve comparison of the installed system with the approved installation documents.

During construction, as sections of systems or whole systems are completed, they should be inspected, and the results recorded in the IQ protocol. The installation should be checked against the construction drawings, to make sure that all the relevant components are properly installed. Any deviations from the specifications, including poor workmanship, should be recorded and evaluated.

Wherever possible, documented inspection PDI and FAT of systems, or major system components, should be performed before delivery to site. This allows a faster and more efficient remedy of any failings, and avoids schedule delays that could result from on-site problem discovery. Where such systems have a direct impact on product quality, every effort should be made to incorporate the PDI and FAT into the qualification (IQ and OQ, respectively) effort, through the application of qualification practices. The PDI and/or FAT decision should be based on a cost/benefit analysis.

8.11 IQ APPROVAL AFTER EXECUTION

After protocol execution is complete and deviations evaluated, post execution approval/acceptance is required. Generally this requires signoff by the original signatories. Signoff of the executed protocol is acceptance that the system IQ is complete and that OQ can proceed.

IQ execution should be complete and approved prior to the start of OQ. Exceptions to this should be evaluated. For example, completion of the IQ may include gathering and updating outstanding documentation which takes time, and which could have no direct impact on the start of OQ. An assessment of the impact on OQ should be completed prior to starting OQ.

8.12 IQ SUMMARY REPORT

When the installation phase of a particular system is complete, the Installation Qualification results should be reviewed. If it is considered necessary, based on company policies and procedures, a formal report may be prepared at this stage. If this is not done, there are several options to summarize the results and provide data analysis, including:

- Summarizing the data in the IQ protocol

- Generating a report, combining the details of IQ/OQ
- Generating a report at the completion of the IQ/OQ/PQ process

8.13 IQ SCHEDULE

Integrated schedules should be developed with input from the construction and validation project teams, and should be maintained and re-issued regularly.

The schedule should include durations for writing, reviewing, approving, and executing each IQ, by system. In the early stages of schedule development, these sections of the schedule may be just one line item per system.

Timing of IQ execution varies from company to company. IQ may be part of the Physical Completion, thus tying IQ closely to the construction contractor's scope of work. To avoid the effort and inconvenience of discovering and rectifying basic problems within the context of a closely controlled qualification regime, it is recommended that all systems go through an informal shake-down phase before IQ commences. This will help ensure a smooth transition between IQ and OQ, and minimize the number of changes, during IQ and OQ, which may, or may not, need to be documented.

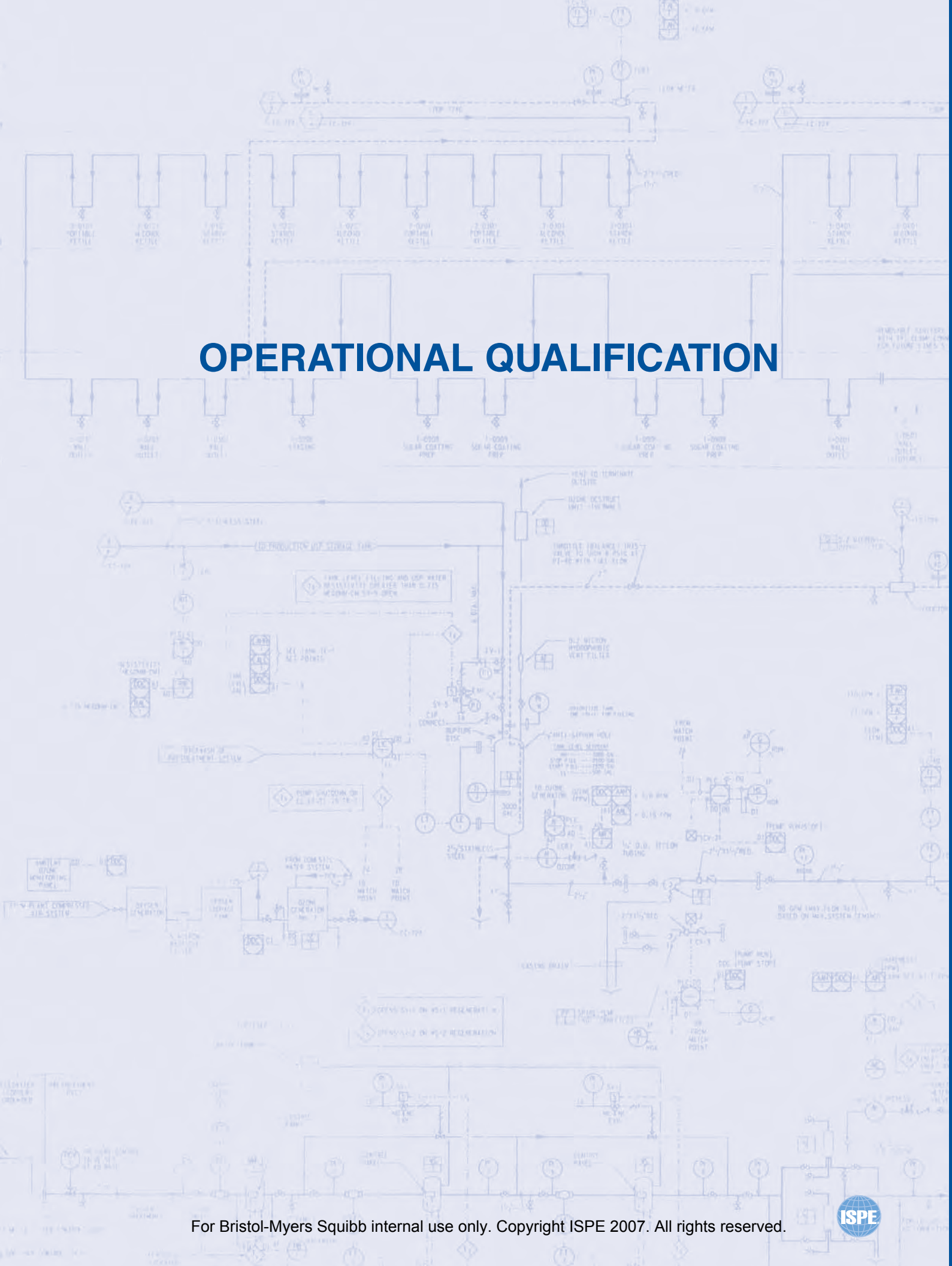
8.14 CHANGE CONTROL DURING IQ

For "Direct Impact" systems, certain changes may affect qualification plans, tests, or documentation. Changes to "Direct Impact" systems should be assessed for potential impact and communicated to the appropriate team members. Agreement should be obtained from the approval signatories before implementation of the change.

Prior to beginning IQ, and throughout the lifecycle of the project, the engineering change management system should allow for QA review and input into changes when one or more of the following conditions occur:

- The change alters the Impact Assessment (I.e., it causes a formerly "Indirect Impact" system to now be a "Direct Impact" system, or vice-versa.)
- There is a fundamental change in the design concept
- There is a change in the User Requirements Brief or Requirement Specifications

OPERATIONAL QUALIFICATION



9. OPERATIONAL QUALIFICATION

9.1 INTRODUCTION

Operational Qualification (OQ) is an activity that is regulated by the FDA, and is a part of final qualification activities before Performance Qualification, or Process Validation begins.

The Guide has defined Operational Qualification for "Direct Impact" systems as:

"The documented verification that all aspects of a facility, utility, or equipment that can affect product quality operate as intended throughout all anticipated ranges."

It is the process of testing to ensure that individual components and systems operate as specified, and how that information is recorded.

Only "Direct Impact" systems will be subject to OQ. Operational Qualification is subject to QA approval and any change subsequent to this stage requires QA review and approval.

According to the V-Model, (see Figure 2-3) the OQ relates to the Functional Design for "Direct Impact" systems. The OQ process at task level (i.e., how), corresponds to the Setting-to-work, Regulation, and Testing requirements demanded by GEP, which when performed within the controls of Qualification Practices, will comprise OQ.

The primary objectives of this chapter are to:

- Provide an overview of the OQ process
- Describe the types of activities that occur and documentation that is needed for the OQ process
- Describe how OQ fits in with the overall qualification process
- Describe how the commissioning process integrates within OQ

9.2 PURPOSE OF OQ

The purpose of OQ is to establish, through documented testing, that all critical components and "Direct Impact" systems are capable of operating within established limits and tolerances.

The OQ is performed on systems, which may consist of facilities, utilities, and/or equipment; to verify operation within specified parameters, such as temperature, pressure, flow, etc. Execution of the OQ involves testing parameters that regulate the process or product quality. Verification of proper operation of controllers, indicators, recorders, alarms, and interlocks, is performed and documented during the OQ testing.

The Functional Design Specification (see Section 4.6.2) should address the permanent recording, visual indication, design/specification range, normal operating range, alert and alarm limits, and the functional interrelationships of each component within the system. All of these requirements should be verified during the OQ phase to ensure that they operate as planned, and that the requirements have been anticipated correctly.

The purpose of an approved protocol (OQ protocol) is to establish confidence that the facility/utility/equipment is capable of operating within these established limits and tolerances.

9.3 BEFORE OQ PROTOCOL WRITING BEGINS

The following items should be completed before the OQ protocol writing process starts, and are identical to those required before IQ:

- **Impact Assessment**

  The System Impact Assessment should have been performed and documented.

- **Component Criticality Assessment**

  This should have been performed for the specific system. For some systems (e.g. single piece of process equipment), this could be performed prior to OQ, or as part of the OQ process.

- **Design**

  Sufficient design details should be available, with all systems defined (including detailed P&IDs, if applicable).

- **Scope**

  The extent and scope of commissioning and qualification necessary (inspection, testing, etc) for each system should be finalized.

- **Schedule**

  The milestone activities of both writing and executing the protocols should be available.

- **Team identification**

  The scope, roles and responsibilities of the project team, including contractors and suppliers should be determined. Responsibilities also should include who will write, review, approve, and execute the protocols, who will coordinate the OQ within the company, and who will verify that the test requirements are completed.

- **Training**

  The training of the validation team in the procedures used in OQ should be complete.

- **Validation Master Plan**

  Ensure that the OQ follows the overall Validation Master Plan.

- **Changes**

  The QA change control procedure should be approved in order to control any changes made during the OQ process. Also, any design changes should follow the overall engineering change management procedure.

9.4 COMMISSIONING INTEGRATION WITH OQ

The IQ chapter describes how to approach the integration of commissioning with qualification, by defining a list of tests and verifications to be performed on a system. Again, with OQ, the same types of relationships can be made. The "Setting to Work", "Regulation", and "Testing" of instruments, equipment, alarms, interlocks, sequences, etc., can be performed at various stages of a project and performed in support of OQ.

If Factory Acceptance Testing (FAT) is executed for the equipment, some or all of these tests can be performed at the supplier's site. If the system is a distribution system, or another type of system, which can only be assembled on site, these tests can be performed as part of the commissioning activities. The tests that could not be performed prior to this point in time, for critical components of "Direct Impact" systems, are then performed as part of the Operation Qualification.

Examples include:

1) Capacity testing (worst case) of the WFI system distribution may be tested during the "Regulation" activities in commissioning. These results can be referenced in support of OQ if qualification practices were followed during the preparation, testing, and data recording.

2) Alarms, interlocks, and sequencing may be tested during the "Setting to Work" phase of the project, as well as during FAT, if performed. Again, by following the qualification practices these results can be used in support of OQ.

9.5 DOCUMENTATION REQUIRED TO WRITE THE OQ PROTOCOL

Sufficient engineering information and documentation should be available to write the OQ protocol. If engineering documents are appropriately planned, created, organized, and authorized, they can be an integral part of the qualification support documentation for "Direct Impact" systems. The following is a list of documentation that is typically required to write an OQ protocol:

a) P&IDs

b) Functional Requirement Specification

c) Equipment operations manuals

d) Standard operating procedures

e) Supplier Drawings and Specifications, including:

- Process Description
- Equipment List
- Instrument List
- Alarm/Interlock schedule
- Control system operation manuals
- References for local, national, and international codes and standards

9.6 ORGANIZING AND WRITING THE OQ PROTOCOL

There is no standard OQ protocol style or format. Contents will vary from company to company, from contractor to contractor, and are dependent on the scope of the protocol. OQ protocols should be written in accordance with, and supported by, a Standard Operating Procedure (SOP). The following are examples of what is typically included in an OQ protocol:

a) Approval Page: Initial and final document review and approval should be done in accordance with your company policies and procedures, and should include a review and approval by quality

b) Pre-requisites: Those actions, which must be, performed prior to beginning the execution of the protocol

c) Objectives: Describes the purpose of the OQ

d) System Description: Description of the equipment and/or process, and of the system critical components. Include a statement of how the identified unit should normally operate. Also include a statement describing any limiting parameters of the equipment (e.g. bottle size such as smallest, largest and most commonly used size, if appropriate)

e) Responsibilities: Specific responsibilities for OQ preparation, review, approval, and execution

f) Qualification Requirements (including acceptance criteria): Acceptance criteria should be selected carefully, based on what is important to the process, product or material. It is not unusual for the design conditions for a particular system to be different (more stringent) than the acceptance criteria stated in the qualification protocol. Equipment must meet all of the operational challenge tests performed on the system over the full operating range as defined by the specification. The OQ should clearly list all critical operating parameters and their corresponding test functions

g) Record of Signatures

h) Qualification Test equipment/instruments list: Include all critical measuring and monitoring devices such as timers, pressure indicators, temperature sensors and any chart records that document performance

i) Overall OQ Test Plan:

- Instrument/Control Devices OQ
- Verification of the proper operation of switches, indicators, recorders, valves, etc.
- Alarms and Interlocks tests including safety devices and alarms

j) Operation testing: Test runs analyzing unit operational functions (e.g. temperature, pressure, speed, rotation, flow, volume, handling, weight, timing, etc.)

- Capacity Testing
- Radio Interference Testing
- Power Failure Testing
- Sequence testing

k) Test data sheets: Sheets to document all testing

l) Standard Operating Procedures: SOPs that were used to perform the OQ

m) Qualification Acceptance: Summary of acceptance criteria

n) Modification/Field Change Control

o) Discrepancy/Justification and Corrective Action: All amendments and deviations must be adequately addressed and approved by all appropriate individuals prior to proceeding to PQ

p) OQ Summary

q) References: List of the references, guidelines, and specifications used in developing the OQ

r) Attachments/Appendices:

- Verification of test instrument calibration
- Chart recordings
- P&IDs
- Printouts

9.7 OQ PROTOCOL APPROVAL BEFORE EXECUTION

Once the protocol has been written, it should be approved. This may be a time consuming process and several ways to streamline this process, include:

- Minimizing the number of approvals required
- Clarifying the review process with all parties early in the project
- Using existing or standardized templates wherever possible
- Collecting all comments from all parties on one master document
- Instituting a formalized protocol tracking process
- Minimizing the number of review cycles allowed by the team
- Implementing a simple review and approval project procedure
- Instituting protocol comment review meetings for all parties involved
- Assuring the protocol review and approval process is included in the overall project schedule

Once the OQ protocol has been approved, it is ready for execution.

9.8 DOCUMENTS REQUIRED TO EXECUTE THE OQ PROTOCOL

The following is a list of documents that are typically required to execute an OQ protocol:

- P&IDs
- Instrument List
- Equipment List
- Calibration Check, if done during the OQ phase
- SOPs (Operational)
- Approved IQ Protocol

A completed and approved IQ protocol is required before OQ can start on any given "Direct Impact" system. This approval can be given with restrictions on the OQ, and when this is done, a rational argument for the approval should be documented. For example, completion of an IQ may have some outstanding documentation, which will take time to be updated, and it may have no direct impact on the release of the OQ.

9.9 TRAINING BEFORE OQ EXECUTION

The overall OQ process can be streamlined, if a proper training program has been put in place before OQ execution. Key factors that should be addressed in training employees on a new system include:

- The purpose of the equipment/system
- How to correctly operate the equipment/system
- How to ensure that the equipment/system is working properly
- What action to take when it is not working properly
- What is required to keep it working properly (e.g., calibration, preventive maintenance procedures, etc.)
- Change control procedures throughout installation, qualification, and operation
- Applicable SOPs

All training should be documented. Training requirements should be periodically reviewed.

9.10 OQ PROTOCOL EXECUTION

OQ specifically tests each function of the system (e.g., unit operational functions, specific equipment functional testing, etc.) to ensure that the intended tasks will be performed when the system is properly adjusted and operated throughout the recommended operating ranges. The OQ execution process provides an assessment of the system operation. Its goal is to confirm that the system can sequence through its operating steps, and that key process parameters or functions are checked, to ensure that they are in compliance with the operating specifications. OQ also should ensure that the system does not operate in ways that are undesirable (these functions can co-exist with 'normal' modes of operation) and also that the system responds appropriately under fault or failure conditions.

Once the results of the IQ execution have been reviewed and approved, the OQ execution can begin. A review should be done, to ensure that the installed system is ready for OQ. The review should include items such as, confirming that support systems operate correctly before turning equipment on. (E.g., the electrical supply and emergency stop for a motor should be tested before it is operated.)

Wherever possible, documented PDI and FAT of systems, or major system components, should be performed before delivery to site. This allows a faster and more efficient remedy of any failings and avoids schedule delays that could result from on-site problem discovery. Where such systems have a direct impact on product quality, every effort should be made to incorporate the PDI and FAT into the qualification (IQ and OQ, respectively) effort, through the application of qualification practices. The PDI and/or FAT decision should be based on a cost/benefit analysis.
All critical instruments must be calibrated at this time.

9.11 OQ APPROVAL AFTER EXECUTION

After protocol execution is complete and deviations evaluated, post execution approval/acceptance is required. Generally, this requires signoff by the original signatories. Signoff of the executed protocol is acceptance that the system OQ is complete and that PQ can proceed.

OQ execution should be complete and approved prior to the start of PQ. Exceptions to this should be evaluated. An assessment of the impact on PQ/PV (Process Validation) should be completed prior to starting PQ.

9.12 OQ SUMMARY REPORT

When the operational phase of a particular system is complete, the OQ results should be reviewed. If it is considered necessary, based on the manufacturing company's policies and procedures, a formal report may be prepared at this stage. If this is not done, there are several options to summarize the results and provide data analysis, including:

- Summarizing the data in the OQ protocol
- Generating a report, combining the details of IQ/OQ
- Generating a report at the completion of the IQ/OQ/PQ process

9.13 OQ SCHEDULE

An integrated schedule should be developed with input from the construction and validation project teams, and should be maintained and re-issued regularly.

The schedule should include durations for writing, reviewing, approving and executing each OQ, by system. In the early stages of schedule development, these sections of the schedule may be just one line item per system.

Timing of OQ execution varies from company to company. Regardless of the timing, when scheduling OQ writing and execution, a systematic approach for operational testing can optimize the project schedule. By identifying the critical operational criteria that require testing prior to the facility, utility, or equipment being used in production, and planning the schedule accordingly, the duration of testing can be shortened.

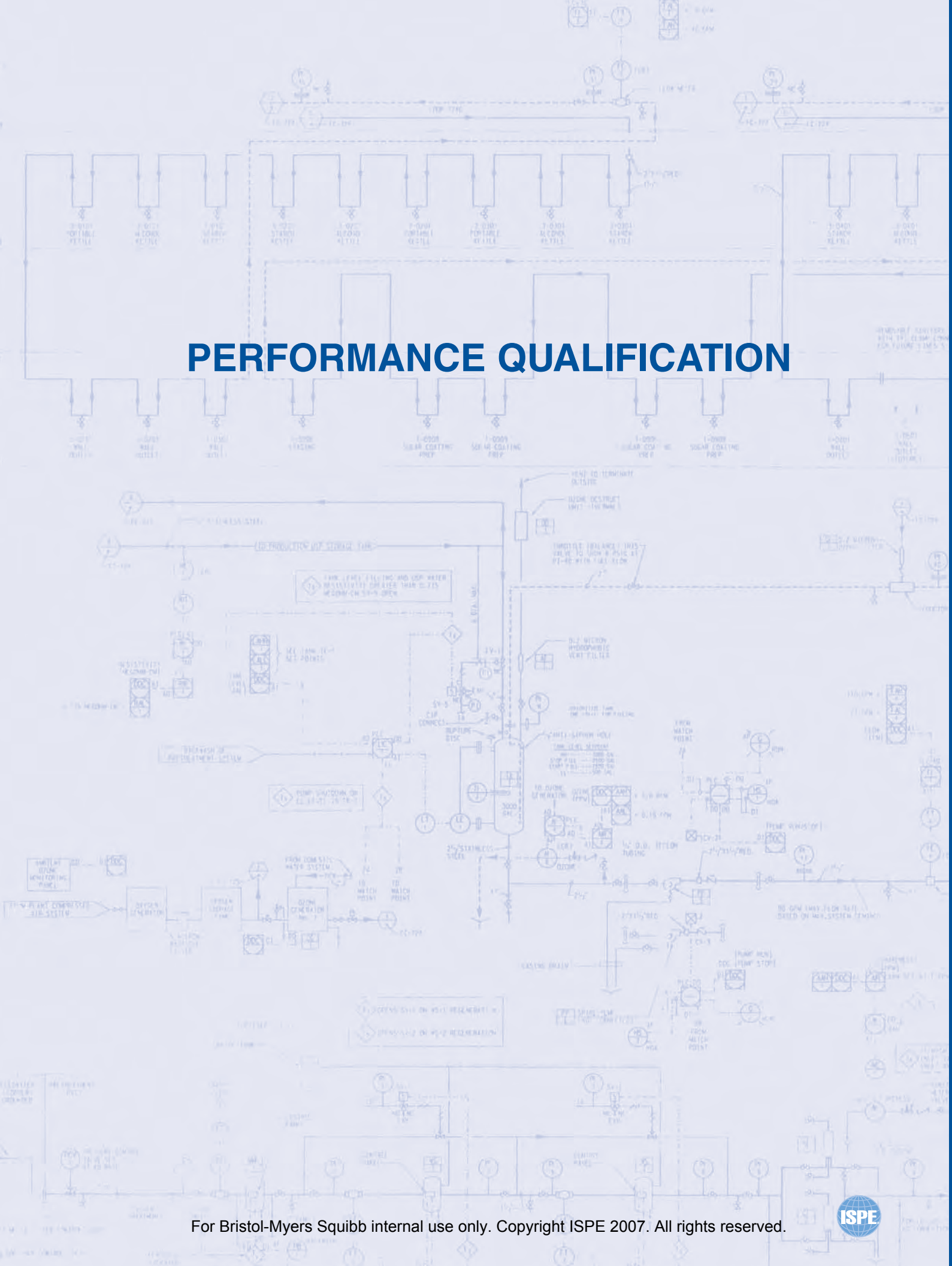
To avoid the effort and inconvenience of discovering and rectifying basic problems within the context of a closely controlled qualification regime, it is recommended that all systems go through an informal shake-down phase before OQ commences. This will help ensure a smooth transition between IQ and OQ, and minimize the number of changes during IQ and OQ, which may, or may not, be documented.

9.14 CHANGE CONTROL DURING OQ

For "Direct Impact" systems, certain changes may affect qualification plans, tests, or documentation. Changes to "Direct Impact" systems should be assessed for potential impact and communicated to the appropriate team members. "Indirect Impact" systems can become "Direct Impact" systems as a result of a change. Proper QA involvement within engineering change management is discussed in earlier chapters. Agreement should be obtained from the approval signatories before implementation of the change.

The engineering change management system also should allow for QA review and approval and input into changes when one or more of the following conditions occur:

- The change alters the Impact Assessment (i.e., it causes a formerly "Indirect Impact" system to now be a "Direct Impact" system, or vice-versa.)
- There is a fundamental change in the design concept
- There is a change in the User Requirements Brief or the Requirement Specifications



PERFORMANCE QUALIFICATION

10. PERFORMANCE QUALIFICATION

10.1 INTRODUCTION

Performance Qualification (PQ) is an activity that is regulated by the FDA, and is the final qualification activity before the remainder of Process Validation begins. For pharmaceutical grade utilities and certain support systems, PQ is the final qualification step.

This Guide has defined Performance Qualification for "Direct Impact" systems as:

"The documented verification that all aspects of a facility, utility, or equipment that can affect product quality perform as intended meeting predetermined acceptance criteria."

Only "Direct Impact" systems or a combination thereof, will be subject to Performance Qualification. Performance Qualification is subject to QA approval. As with the IQ and OQ phases, changes subsequent to the PQ stage require QA review and approval.

According to the V-Model (see Figure 2-3), the Performance Qualification relates to the User Requirements Brief for "Direct Impact" systems. Once the system (or systems) have gone through IQ and OQ execution and have been approved/accepted the PQ can be performed.

The primary objectives of this chapter are to:

- Provide an overview of the Performance Qualification process
- Describe the types of activities that occur, and documentation that is needed, for the Performance Qualification process
- Describe how Performance Qualification fits in with the overall qualification process
- Describe how the commissioning process integrates within Performance Qualification

10.2 PURPOSE

The PQ integrates procedures, personnel, systems, and materials to verify that the pharmaceutical grade utility, environment, equipment, or support system produces the required output. This output may be a product contact utility (clean compressed air, WFI, etc.), sterilization condition (autoclave, depyrogenation oven), or environment (HVAC system, isolator).

Performance Qualification must not be confused with Process Validation (PV) (or qualification that is the verification that good product is made), or with validated cleaning and analytical methods; these are beyond the scope of this Guide.

10.3 BEFORE PQ PROTOCOL WRITING BEGINS

Since PQ is the final step in the qualification process (prior to PV), it is assumed that the pre-requisites regarding System Impact Assessment and component criticality (indicated in Chapters 8 and 9) have already been addressed, and therefore, will not be repeated here. The following items and activities should be defined before the PQ protocol writing process starts.

a) Scope: The extent of PQ should be finalized. The Validation Master Plan should be referred to for definition of the scope of PQ.

b) Schedule: The milestone activities of both writing and executing the protocols should be available. Of the qualification phases, PQ execution often involves the greatest amount of time. Although the schedule is not needed to write the PQ, the schedule should be viewed against the PQ document to ensure that sufficient time has been allotted for extended sampling, sample analysis, repetitive testing, etc.

c) Responsibilities: Identification of who will carry out the work should be determined, including the scope, role, and responsibilities of all contractors, suppliers, and owners. Responsibilities also include who will write, review, approve, and execute the protocols, who will coordinate the PQ within the company, who will be responsible for sampling and analytical testing, who will provide test instruments, and who will verify that the test requirements are completed.

   This is particularly critical during PQ. For example, the PQ may define a sampling plan which an owner's analytical laboratory cannot support. Therefore, plans must be made to subcontract analytical testing to an outside laboratory. Such a decision must be made well in advance of PQ execution activities.

d) Validation Master Plan: Ensure that the PQ follows the overall Validation Master Plan.

e) Changes: The QA change control procedure should be approved in order to control any changes made during the PQ process. In addition, any design changes should follow the overall engineering change management procedure.

10.4 COMMISSIONING INTEGRATION WITH PQ

At this point of the qualification exercise, the commissioning activities are normally complete. Performance testing carried out as part of commissioning can contribute to PQ, if performed within a regime of qualification practices.

10.5 DOCUMENTATION REQUIRED TO WRITE THE PQ PROTOCOL

The following is a list of documentation that is typically required to write a PQ protocol:

a) Piping and Instrumentation Diagrams: The PQ should reference specific sampling points, instrumentation, and equipment as indicated on the P&ID.

b) User Requirement documents: The system owner specification should be used in developing acceptance criteria for the PQ document. Note that this may be different from the design specification and the equipment supplier specification. The owner requirements may be less stringent than the design specification. The goal of the PQ is to ensure that user requirements are met, and not to qualify the design.

c) Pertinent regulations, guidelines, and owner specifications.

d) System Acceptance Criteria: System acceptance criteria must be clearly indicated in the PQ document. If available, the user requirement specification for the system should provide this information. Depending on the system, acceptance criteria may be contained in the following documentation (This list is not all-inclusive, but given to provide an indication of typical references for acceptance criteria):

- **HVAC Systems**

  Zoning Diagrams, (showing area classifications, room pressurizations), Industry Standards (such as Federal Standard 209E). Additionally, many firms have internal specifications based on process needs.

- **Pharmaceutical Grade Water Systems**

  Acceptance criteria for standard grades of water such as WFI and Purified Water are given in the U.S. Pharmacopoeia (USP) and other industry references. Additionally, many firms have grades of water, which are unique to their process needs. Acceptance criteria for these would be given in company specifications.

- **Clean Compressed Gases (product contact)**

  Broad acceptance criteria are included in the USP. Most firms have internal specifications for acceptance criteria for product contact gases.

e) SOPs: The PQ document will reference specific SOPs to ensure that the system is operating consistently, samples are taken correctly, and analytical procedures are followed. SOPs should not be repeated in the protocol document; however, SOPs must be available to reference.

10.6 ORGANIZING AND WRITING THE PQ PROTOCOL

There is no standard PQ protocol style or format. Format and content will vary depending on the user, system(s), scope, and project. PQ protocols should be written in accordance with, and supported by a Standard Operating Procedure (SOP). The following is an example of the typical contents of a PQ protocol:

a) Approval Page: Initial and final document review and approval should be done in accordance with company policies and procedures, and should include a review and approval by QA.

b) Pre-requisites: This includes of listing of actions, which must be performed prior to beginning the execution of the protocol. Examples of pre-requisites may include the following:

- IQ and OQ are complete
- All critical punch-list items from IQ and OQ have been resolved
- Pertinent SOPs have been approved
- Training in pertinent SOPs is complete and documented

c) Objectives: Describes the purpose of the PQ.

d) System Description: Description of the equipment and/or process, and of the system critical components. Includes a statement of how the identified unit should normally operate. Also, includes a statement describing any limiting parameters of the equipment (e.g., bottle size such as smallest, largest, and most commonly used size, if appropriate).

e) Responsibilities: Specific responsibilities for PQ preparation, review, approval, and execution.

f) References: Listing of the regulations, guidelines, and specifications used in developing the PQ.

g) PQ Test Plan: The test plan should describe the specific testing to be conducted during the PQ, the rationale for testing, and specific acceptance criteria. Examples are given below:

- **Pharmaceutical Grade Utility**

  The test plan would generally consist of a detailed sampling plan for the duration of PQ testing, along with the rationale for the plan. Specific chemical/physical/microbiological acceptance criteria should be indicated.

- **Autoclave/Depyrogenation Oven**

  The test plan would generally consist of a description of the load configurations, the number of repetitive tests that will be conducted, a description of how heat delivery and lethality will be monitored, and acceptance criteria.

- **HVAC System**

  The test plan generally consists of a detailed environmental monitoring plan under active and inactive conditions for a specified time period and acceptance criteria. Filling Line:

  The test plan may consist of a description of a simulated aseptic filling operation utilizing a growth promoting media, and acceptance criteria.

h) Challenge Test Plan: PQ testing often includes an appropriate "challenge" test to ensure that the system continues to meet process needs after it has been challenged. (For example, does the WFI system continue to produce WFI meeting USP criteria after it has been shut down for a defined time period.)

i) Record of Signatures

j) Test Equipment/Instrument List: A listing of all test instruments used in execution of the PQ, along with a verification of calibration.

k) Test Data Sheets: Data sheets to document all testing and test results.

l) Standard Operating Procedures: Listing of SOPs that were used to perform the PQ.

m) Qualification Acceptance

n) Summary of Acceptance Criteria

o) Discrepancy/Justification and Corrective Action: A description of any discrepancies/test failure encountered during PQ testing, along with a description of the corrective actions taken (or the rationale for not taking corrective actions).

p) Attachments/Appendices: Examples may include the following:

- Verification of test instrument calibration
- Chart recordings
- P&IDs
- Printouts

q) Analytical Test Results

10.7 PQ PROTOCOL APPROVAL BEFORE EXECUTION

Once the protocol has been written, it will need to be approved by the appropriate departments, including Quality Assurance. The PQ document often receives the greatest amount of scrutiny from the approval team. This often results in a lengthier approval process and an adequate amount of time should be allowed in the project schedule for this. The methods described in the IQ and OQ chapters for streamlining this process are recommended. Once the PQ protocol has been approved, it is ready for execution.

10.8 DOCUMENTS REQUIRED TO EXECUTE THE PQ PROTOCOL

The following is a list of documents typically required to execute a PQ protocol. (Several of these documents have already been cited in Chapters 8 and 9 as requirements for writing IQ and OQ):

- P&IDs
- Approved SOPs for system operation
- Approved SOPs for operation of test equipment
- Approved Sampling SOPs
- Approved Analytical SOPs
- Load Configuration Diagrams (for autoclaves, washers, etc.)
- Method in place for analysis of all samples
- Calibration Certificates (for process instrumentation and test instrumentation used in executing the PQ)

10.9 TRAINING BEFORE PQ EXECUTION

The overall PQ process can be streamlined if a proper training program has been put in place before PQ execution. Key factors that should be addressed in training employees on a new system include:

- Analytical SOPs
- Sampling
- Swabbing
- Analytical Equipment (HPLC, TOC, etc.)
- Gowning
- Use of Test Equipment
- Environmental Monitoring (viables, non-viables, temperature, pressure, etc.)
- Handling of out of specification test results

- Change Control
- Applicable Equipment/System SOPs
- cGMP Documentation Training

All training should be documented. Training requirements should be periodically reviewed.

10.10 PQ PROTOCOL EXECUTION

PQ execution will involve testing to ensure that the system performance consistently achieves acceptance criteria as defined in the PQ document. This may involve testing over an extended time period, or it may involve repetitive testing.

It is imperative that the system is operated as per approved SOPs during PQ testing. This will ensure that the same performance is achieved after qualification during routine operation. For the same reason, it is imperative that the team responsible for system operation during PQ are properly trained, with the training documented.

Depending on the system, PQ testing may involve the following: (**Note:** The following examples are for illustrative purposes only. Actual PQ testing will depend on individual process requirements. Depending on company practices, elements of the testing described below also may be included in OQ.)

a) HVAC System: For "Direct Impact" areas, testing may involve environmental monitoring under inactive (static) and active (dynamic) conditions for a period of time.

b) Pharmaceutical Grade Utilities: Testing will involve sampling over an extended period of time for quality attributes as defined in the PQ document.

c) Sterilizers: Testing will involve heat penetration studies to verify that the accumulated F_0 (kill) value is achieved during the exposure period to the load. Kill cycles are generally verified using thermocouples and biological indicators (autoclaves) or endotoxin challenge vials (depyrogenation ovens).

d) Filling Lines: PQ testing may involve the verification of the capability of the line to aseptically fill sterile vials using a growth promoting media (media fills). Testing also may involve the verification that the system can accurately fill sterile media at the design fill rate within a certain accuracy of the design volume.

Acceptance criteria should be clearly indicated within the PQ document. Deviations from acceptance criteria should be recorded and evaluated. Failure to achieve acceptance criteria should be clearly documented and evaluated. SOPs must be available for the evaluation and handling of specification test results.

10.11 PQ APPROVAL AFTER EXECUTION

After protocol execution is complete and deviations evaluated, post execution approval is required. Generally, this requires signoff by the original signatories. Signoff of the executed protocol is acceptance that the system Performance Qualification is complete, and that PV (where required) can proceed.

10.12 PQ SUMMARY REPORT

When the performance phase of a particular system is complete, the Performance Qualification test results should be reviewed with documented analysis of the test data. If it is considered necessary, based on company policies and procedures, a formal report may be prepared at this stage, with a conclusion about the ability of the system to consistently achieve acceptance criteria. There are several options to summarize the results and provide data analysis, including:

- Summarizing the data in the PQ protocol
- Generating a report, summarizing the results of the PQ testing only
- Generating a report at the completion of the IQ/OQ/PQ process

10.13 PQ SCHEDULE

An integrated project schedule should be developed and maintained by the project team.

Scheduling of PQ is particularly critical. PQ testing is often the most time consuming part of the qualification and also should take into account prerequisites, which should be achieved prior to PQ execution, (such as the commissioning of all support systems, availability of SOPs, system interdependencies).

10.14 CHANGE CONTROL DURING PQ

If there is a need to change:

- Specifications/Acceptance Criteria
- Operating Procedures
- Critical Equipment
- Components of a system that has already undergone PQ

Changes must be implemented in accordance with QA change control SOPs.

Each change should be evaluated to determine if revalidation is necessary, and to determine if notification of regulatory authorities is required.

In addition, the engineering change management system should allow for QA review and approval, and input into changes when one or more of the following conditions occur:

- The change alters the Impact Assessment (i.e., it causes a formerly “Indirect Impact” system to now be a “Direct Impact” system, or vice-versa)
- There is a fundamental change in the design concept
- There is a change in the User Requirements Brief or the Requirement Specifications

RELATED PROGRAMS

11. RELATED PROGRAMS

Related Programs are those programs that are undertaken to provide assistance and information in support of the qualification activities. Some of these programs can be applied to “Direct Impact”, “Indirect Impact” and “No Impact” systems and their components. The activities within these programs can be addressed and managed through the Validation Master Plan (VMP), or through independent plans and programs referenced within the VMP, or through the company’s validation policy document or quality plan. Where these programs are undertaken in support of qualification activities, the appropriate qualification practices must be followed to ensure that the compliance of the over-all qualification effort is not compromised.

11.1 SAFETY

Safe operation is a necessary requirement for all systems (“Direct Impact”, “Indirect Impact” and “No Impact”). The regulation and enforcement of safety related issues, reviews, and accidents are performed by local and national institutions, which can differ from country to country. These institutions are **not** the same as the ones concerned with the quality of drug products. The reviews of potential safety hazards are normally carried out in a HAZOP review for the project. These reviews are very structured and follow established principles and practices. This is similar to an Impact Assessment of the project design, in accordance with regulatory expectations, guidance documents, and legislation; except that it is the safety of the operations and maintenance staff that is considered, not the safety of the product.

Safety can be managed in a similar way to the qualification program. The project team can develop a safety plan specific to the project during construction planning, to manage safety. This plan can incorporate:

- Safety Hazard Reviews (HAZOPS)
- Safety Procedures and Training
- Required Safety Gear
- Detailed plans for addressing Safety Issues
- Responsibilities for safety by suppliers, contractors, and in-house staff

11.2 STANDARD OPERATING PROCEDURES

Standard Operating Procedures (SOPs) are established to ensure that activities are performed the same way at all times. A comprehensive SOP program must be in place in any regulated organization and includes:

- Periodic Review and Updating
- Defined Approval Process, which includes Signatory Responsibility
- Training on the SOP content
- A system of Archiving and Version Control

It is recommended that the SOP program is established early on in the project lifecycle. SOPs detailing the operation, maintenance, and calibration of equipment, as well as SOPs for facility and equipment cleaning, should be written and finalized prior to, or during, the OQ, so they can be used and referenced during PQ.

11.3 TRAINING

Training is listed as a requirement for compliance with cGMPs, as listed in 21 CFR 211.25, Personnel Qualifications, and in 211.34 Consultants. In this Guide, training is listed as a "Qualification Practice". These practices are those that are performed in support of GEP (Good Engineering Practices) for "Direct Impact" systems and components. Training is listed here as a support program for validation, as it is a necessary piece of the documentation audit trail for the project. Project documentation normally outlines any/all 'specific project training requirements'. Other training necessities, those which support all project-work but are initiated and funded outside the project, may include familiarity and application of company procedures administered by the company's QA department. The project training, as well as the on-going training during the lifecycle of the facility, can be administered within a training program. This program provides an organized approach to training and a method for documenting what has occurred.

The following considerations should be given to training program development:

- Training for project work, including commissioning/qualification activities
- Training and understanding of the facility and equipment operation for production staff
- Training requirements for equipment and systems (including scope, number of participants, duration, and timing)
- Maintenance training during commissioning/qualification phase of the project
- Including time for training in the over-all schedule and the time to develop the necessary materials
- Experienced people delivering the training
- Documenting and recording training activities for all participants
- A training matrix to support training activities
- Relevant regulatory requirements, specifically GMP, EPA, and OSHA requirements should be communicated as part of the training program
- Training requirements for operations and maintenance should be periodically reviewed

11.4 PREVENTIVE MAINTENANCE AND CALIBRATION

Preventative Maintenance and Calibration are programs typically applied to components of all systems within a project, regardless of the impact on the product quality. Components which have been determined to be critical to product quality, will most likely have more frequent calibration and maintenance schedules. In this manner, these programs are key for maintaining a "Direct Impact" system in a validated and controlled state. These activities must be managed and documented effectively by appropriately qualified and trained personnel with good technical knowledge and practical understanding.

The process of setting up clear procedures and carrying out a formal criticality assessment (see Chapter 3) will allow preventative maintenance and calibration activities to be managed to concentrate the resource where it is most needed. In this manner, the calibration of the critical instruments will be verified in IQ (or as a pre-requisite of OQ) before undergoing any qualification testing, to ensure that the test results are valid. This verification, along with the calibration certificates and procedures, provides the documented evidence required to demonstrate that a system operates in a controlled state.

The following can be considered when developing a calibration and preventative maintenance schedule:

- Supplier/contractor recommendations
- Company history and experience with the component in critical applications
- Costs for performing the maintenance or calibration
- Practicality of Planned Maintenance and calibration (e.g., accessibility to component)
- Staffing required to maintain the critical components within compliance
- System and method of maintaining the components in a validated and controlled state
- The documentation required for these activities

11.5 COMPUTER SYSTEMS VALIDATION

The commissioning and qualification of facilities, equipment, and utilities cannot be performed without considering the level of computerization of the systems that they contain. In the development of this Guide, a conscious effort was made to identify the need for computer systems validation, but not to include details.

There are two basic approaches to computer validation. They are:

a) Stand-alone systems: These are computer systems such as, a Distributed Control System (DCS), Building Management System (BMS), and System Control and Data Acquisition (SCADA), which link or control multiple systems and equipment. These systems are typically qualified as independent systems with their respective Qualification Plans and Protocols.

b) Integrated Control systems: These are computer systems such as, Programmable Logic Controllers (PLCs), Single Board Computers, Personal Computers (PCs), and Proprietary Control Systems, which control a single system or piece of equipment. These systems are typically qualified within the Qualification Protocols of the system or equipment.

There is already expert guidance on this topic, which can easily be integrated with the concepts in this Guide, most notably the GAMP Guide for Validation of Automated Systems in Pharmaceutical Manufacture (see References). Internal company policies, procedures, and guidelines also should be consulted.

11.6 CLEANING VALIDATION

The consistent preparation of high quality medicinal products and investigation medicinal products depends on the use of clean premises, equipment, and materials. This message is supported by the mention of cleaning in 21 CFR 211.182, Equipment Cleaning and Use Log. All cleaning systems, activities, and procedures that have a direct impact on product quality must be validated prior to release of product for intended use. In addition, cleaning materials and methods used on product contact parts must be approved for use and be of the required standard(s). These requirements are mainly in-place to prevent cross contamination by other products, or the carry-over from previous batches of the same product.

Types of cleaning include:

a) Cleaning In Place (CIP): These activities are normally included in the qualification program as described in this Guide.

b) Cleaning Out of Place (COP): These activities are normally included in the qualification program as described in this Guide.

c) Manual Cleaning: This involves human intervention and the following of procedures in a consistent, repeatable manner. These activities are typically covered within Process Validation.

An effective strategy for the development and confirmation of effective cleaning procedures consists of following three phases.

1) Assessment of risk and the development of strategies for minimization for cross contamination

2) Validation of cleaning procedures

3) Development of monitoring techniques

For successful cleaning validation, the following items should be considered:

- Plan in advance
- Identify multiple product and difficult to clean equipment in design
- Review piping and equipment designs for cleaning
- Review surface contact materials before ordering
- Review access and instruments for sampling
- Plan time in the schedule for cleaning cycle development
- Plan for delivery, handling, and storage of bulk cleaning agents
- Identify the analytical laboratory to be utilized, and give advance notice of number of samples and the schedule for the analyses

11.7 ANALYTICAL METHOD VALIDATION

Analytical method validation must be completed before process validation and cleaning validation can begin, since the predetermined specifications and quality attributes in both of these validation activities are analytically based. This ensures that the analytical results generated are accurate and reproducible. In the development of this Guide, a conscious effort was made to identify the need for analytical method validation, but not to include details.

There is already expert guidance on the topic, which can easily be integrated into the concepts in this Guide, most notably the following:

ICH Harmonised Tripartite Guideline:

- Q2; Validation of Analytical Procedures
- Q2A; Text on Validation of Analytical Procedures
- Q2B; Methodology

FDA: Federal Register, Vol. 60, March 1, 1995, pages 11260

EU: Adopted by CPMP, November 1994, issued as CPMP/ICH/381/95

MHW: Adopted July 1995, PAB/PCD Notification No. 755.

11.8 PROCESS VALIDATION

Process Validation is defined by the Food and Drug Administration as the process of establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes.

Before process validation can begin, the facilities, equipment, and utilities that will be employed for the process validation activities must themselves be qualified. Although process validation is not discussed in this Guide, this is the philosophy that has been used in positioning commissioning and qualification as the "foundation" for Process Validation.

For additional information, please refer to Food and Drug Administration Guidance Document, "Guideline of General Principles of Process Validation", May 1987.

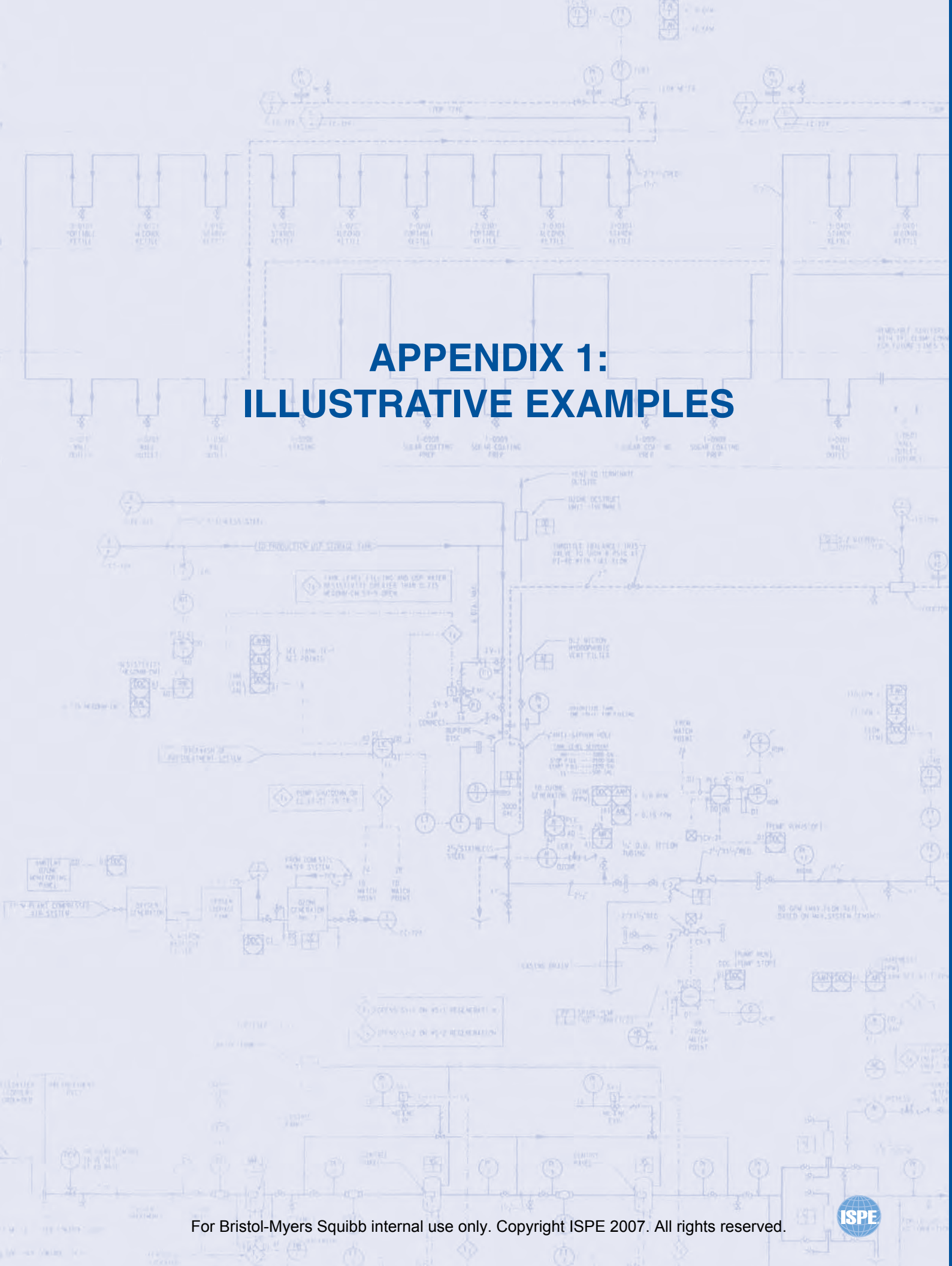
11.9 REVALIDATION

Revalidation can be thought of as the validation of a previously validated system that has been changed or modified. A program to assess the need for revalidation should be established, in conjunction with the organization's change control system.

Revalidation can be performed as the result of an event-based or time-based assessment. The event-based assessment is driven by a change made to the system that is outside the scope of the original validation. Performing validation again, i.e., revalidation, is necessary to ensure that the system can perform reproducibly in its new state. Time-based revalidation is driven by a system assessment at a defined interval, to ensure that the sum of incremental changes made within the scope of the current validation, have not pushed the system outside the scope of the original validation. These time-based assessments also should include a review of historical system performance. It is important to maintain adequate in-process monitoring and control, to detect changes that may occur which could cause validated processes to go out of control. In this way, revalidation efforts can be focused on those processes that truly require revalidation, not just in accordance with a predetermined time frame.

When justified by the magnitude of changes made, or historical changes in system performance, performing validation again (i.e., revalidation) is necessary to ensure that the system can perform reproducibly in its new state, and re-establishes the beginning time-point of the next time-based assessment.

APPENDIX 1:
ILLUSTRATIVE EXAMPLES



12. APPENDIX 1: ILLUSTRATIVE EXAMPLES

The following illustrative examples provide one interpretation of how the key concepts of this Guide can be applied in preparing for commissioning and qualification activities. Depending upon company policies or the intended use of the equipment listed, there may be additions or deletions to the listed activities.

12.1 WATER FOR INJECTION ILLUSTRATIVE EXAMPLE

System Description

A storage and distribution system that delivers Water For Injection (WFI) at a given flow rate, to a certain number of use points, meeting criteria for microbial limits, total organic carbon, conductivity, pH, and endotoxins. The loop is continuously circulating and is hot. The System Impact Assessment has been performed. Based on this, the critical equipment and components have been determined and are included in the scope of the qualification documents. However, all system components (critical and non-critical) are included in the commissioning scope of this system.

Commissioning

- Loop Checks
- Verification of the proper operation of the unit operations, (pretreatment and final treatment), including test sequences, shut-down, and start-up
- Alarms and Interlocks Testing
- P&ID walkdown, resulting in an “as-built” P&ID
- Generation of as-built isometrics
- Instrument Calibration
- Cleaning and Passivation
- Hot alignment of pumps
- Pressure Testing
- Flushing and blowing of circuits, and system drainage
- Feeding fluid into the system
- Feed water flow rate verification
- Utilities Check
- Electrical Power Tests
- Motor Run Tests
- Lubrication Checks
- Isometric Drawing Checks

- Safety Checks (relief, emergency shut-down, continuity, etc.)

Installation Qualification

- Critical instruments are still in calibration
- Documentation Review and Check, including:
  - P&ID check of critical components
  - Welding documentation checks
  - Passivation documentation check of Storage tank and distribution loop
  - Loop check documentation verification for critical components
  - PLC Documentation
- Installation check of critical components
- Sample valves are installed properly and accessible
- Check for proper pipe slopes, free of dead legs and air breaks in drain lines

Operational Qualification

- Critical instruments are still in calibration
- Critical Alarms and Interlocks Testing
- WFI Still Operational Check
- WFI Storage tank check (pressure hold, temperature control, etc.)
- Distribution loop (pressure, temperature, conductivity, TOC, etc.)
- Steam Sterilization Test
- Use Point Verification
- Integrated system testing of normal operating parameters
- Capacity Test
- Control System Operational Test for critical functions
- Power Failure Test
- RFI Test
- SOP Review

Performance Qualification

- Intensive sampling program for an extended period, for
  - pH/Conductivity/TOC
  - Bioburden
  - Bacterial Endotoxin
- A reduced sampling program over an extended period of time

NOTE: A final report can be written here

- Accumulation of one year of WFI sample test data

12.2 HVAC ILLUSTRATIVE EXAMPLE

System Description

A system that supplies air through sheet metal ductwork, pre-filters, hot water coil, chilled water coil, centrifugal fan, and HEPA filters, with pre-filtration. The system works on the principle of constant volume, varying the temperature of the supply air, with a fixed fresh air and recirculation volume. For this process, and depending on the application, the critical parameters are differential room pressure, temperature, relative humidity, and particulates. The System Impact Assessment has been performed. Based on this, the critical equipment and components have been determined and are included in the scope of the qualification documents. However, all system components (critical and non-critical) are included in the commissioning scope of this system.

Commissioning

- Hydronic Balance Testing
- Sound Measurement Testing
- Vibration Testing
- Alarms and Interlocks Testing
- Air Flow rate testing in ductwork
- Air Volume Supply and Return, testing and balancing
- Fan RPM and Amperage
- Temperature, humidity (coil duties) and static pressure testing (duct leakage)
- Differential pressure testing and balancing
- Loop Checks
- HEPA Filter Integrity Testing
- Verification of the proper operation of air coils, air handling units, fans and air filters, including test sequences, shut-down, and start-up

- P&ID walkdown, resulting in an “as-built” P&ID
- Utilities Check
- Instrument Calibration
- Electrical Power Tests
- Motor Run Tests
- Lubrication Checks
- Isometric Drawing Checks
- Safety Checks

Installation Qualification

- Critical instruments are still in calibration
- Documentation Review and Check, including:
  - Testing/Balancing Report
  - P&ID check of critical components
  - Loop check documentation verification for critical components
- HEPA filter Integrity testing data review
- Installation check of critical components

Operational Qualification

- Critical instruments are still in calibration
- Critical Alarms and Interlocks Testing
- Temperature, Relative Humidity, and Differential Pressure Testing under static and dynamic conditions
- SOP Review

Performance Qualification

- Monitoring and Testing for particulate levels (Surface and Airborne)
  - Static (non-viable) Particulate Monitoring
  - Static (viable) Particulate Monitoring (sterile areas)
  - Dynamic (non-viable) Particulate Monitoring
- Dynamic (viable) Particulate Monitoring (sterile areas)

12.3 VIAL BARRIER ISOLATOR ILLUSTRATIVE EXAMPLE

This HEPA filtered unit is a sealed enclosure used to aseptically fill and stopper parenteral product. The vials enter into the barrier isolator from the discharge end of a glass sterilization-depyrogenation unit. Stoppers enter through a rapid transport unit. The inside of the barrier enclosure is cleaned and sterilized prior to production start-up.

This sealed enclosure is a barrier between a sterile and a non-sterile area, and provides complete segregation between personnel and product. Strategically located glove ports provide operator access to filling and stoppering operations. A production isolation enclosure is made of stainless steel with glass doors that open. When the doors are closed, a sealed environment is created.

Commissioning

- P&ID walkdown, resulting in an “as built” P&ID
- Utilities Check
- Alarms and Interlocks Testing
- HEPA Filter Integrity Testing, Air Balancing, and Differential Pressure Testing
- Loop Checks
- Leak Detection (enclosure and gloves)
- Test to demonstrate that entire isolator can be sterilized without compromising isolator integrity
- Test to confirm that contaminants cannot pass from transfer device(s) to isolator interior
- Confirm that glove ports are located properly for personnel to perform filling functions
- Functional testing of equipment, including operational sequence, alarms, and controls

Installation Qualification

- Critical instruments are still in calibration
- Documentation review and check, including:
    - P&IDs
    - HEPA Filter Certifications, Air Balancing Reports
    - Equipment Specifications
    - Utility Requirements
    - Calibration Certifications
    - Weld Certifications
    - PLC Documentation

    - Sample Valve Locations
- Installation check of critical components

Operation Qualification

- Critical instruments are still in calibration
- Critical Alarms and Interlocks Testing
- Training Program and Operational/Preventive Maintenance and cleaning SOPs
- Functional Testing including alarms and interlocks
- Determine Sterilization Parameters (Time, concentration, temperature, etc.)
- Qualify Sterile Material Transfers (Components and Product)
- Compatibility of Materials of Construction with cleaning and sterilizing agents
- Glove Leak Testing (could have received a pinhole since commissioning)
- Enclosure Leak Testing
- Filling Line Integration with the isolator
- Handling of Interventions Procedure
- Relative humidity/temperature checks
- Airflow pattern and velocity checks
- SOP Review

Performance Qualification

- Manual Cleaning and Sterilization of Barrier Enclosure, with media
- CIP and SIP of Product Path
- Product Simulation Fills (Media Fills)
    - Growth Promotion Studies
- Container Closure Studies of the Vial
- Toxic Decontamination
- Environmental Monitoring of the Isolator and the Room Isolator is in
    - Non-viable Particulate Monitoring
    - Viable Monitoring

12.4 PROCESS VESSEL SYSTEM ILLUSTRATIVE EXAMPLE

System Description

A process vessel used for preparation of batch product. This includes a pressure rated jacketed vessel, agitator, pump, utility ties-ins, and transfer piping.

Commissioning

- Loop checks
- Verification of the proper operation of the unit operations, including test sequences, shut-down, and start-up
- Alarms and Interlocks Testing
- P&ID walkdown, resulting in an “as-built” P&ID
- Instrument calibration
- Documentation check and certification of vessel and jacket pressure rating
- Hot alignment of pumps
- Cleaning of vessel
- Flushing and blowing of circuits, and system drainage
- Feeding fluid into the jacket
- Utilities check
- Electrical power tests
- Verify utilities
- Agitator run tests
- Lubrication checks
- Safety checks

Installation Qualification

- Critical instruments are still in calibration
- Documentation Review and Check, including:
  - P&ID check of critical components
  - Welding documentation checks
  - Loop check documentation verification for critical components
  - Material certifications for product contact parts

- Installation check of critical components

Operational Qualification

- Critical instruments are still in calibration
- Critical alarms and interlocks testing
- Integrated system testing of normal operating parameters (i.e., agitator speed, mixing, heating, cooling, discharge, etc.) using water
- Spray Ball pattern testing and coverage
- Pressure Hold Test (for sterile process)
- Vacuum Hold Test (if applicable)
- Transfer testing
- Empty vessel temperature distribution during a SIP cycle (for sterile process)
- Batch weighing, using water (if applicable)
- SOP Review

Performance Qualification

Company definitions of PQ vary widely. Many firms define PQ of a process vessel as cleaning or sanitization validation. Within the context of this Guide, Cleaning Validation (CV) is referenced as a separate related program, covering all CV requirements of the process or the facility, and is not within the PQ of a process vessel system. Some companies, for sterile vessels or manufacturing using sterile techniques, may define sterilization/sanitization validation under the scope of PQ.

12.5 AUTOCLAVE ILLUSTRATIVE EXAMPLE

System Description

An autoclave is a pressure chamber used for sterilization via steam under pressure. Generally, plant steam is delivered to the jacket, while clean steam is delivered to the chamber. In this example, the cycle would involve a ramp up to sterilization temperature, a specified sterilization hold time to achieve the required F_0, and then a temperature/pressure ramp down period. The autoclave has a fixed cycle program based on process temperature, exposure time and chamber pressure exhaust rate.

Commissioning

- Loop checks
- Verification of the proper operation of the unit operations, including test sequences, shut-down, and start-up
- Alarms and Interlocks Testing
- Documentation check and certification of vessel and jacket pressure rating

- P&ID walkdown, resulting in an as-built P&ID
- Instrument calibration
- Hot alignment of pumps
- Pressure/Vacuum testing
- Drainage
- Feeding fluid into the jacket
- Utilities check
- Electrical power tests
- Lubrication checks
- Safety checks

Installation Qualification

- Critical instruments are still in calibration
- Documentation Review and Check, including:
    - P&ID check of critical components
    - Welding documentation checks
    - Passivation documentation check of Storage tank and distribution loop
    - Loop check documentation verification for critical components
    - Material certifications for product contact parts
    - PLC Documentation
- Installation check of critical components

Operational Qualification

- Critical instruments are still in calibration
- Critical alarms and interlocks testing
- Empty Chamber/Temperature Uniformity checks
- Vacuum leak testing
- Control System Operational Test for critical functions
    - Printouts

  - Cycle step through/Timer verification
  - Cycle programming verification
  - Control System Security
- Bioseal Integrity Testing
- Clean Steam Generation (if self contained clean steam generation)
- Power Failure Test
- RFI Test
- SOP Review

Performance Qualification

- Loaded Chamber Temperature Distribution and Mapping
- Heat penetration and BI challenges (3 consecutive runs for each load pattern)

12.6 CLEAN-IN-PLACE SYSTEM (CIP) ILLUSTRATIVE EXAMPLE

System Description

This system is used to automatically clean in place and rinse process equipment. In this example, the CIP system provides cleaning solution at a controlled temperature and pressure. A concentrated cleaning agent is mixed with deionized water to achieve the required concentration and is delivered with static spray devices.

Commissioning

- Loop checks
- Verification of the proper operation of the unit operations, including test sequences, shut-down, and start-up
- Alarms and Interlocks Testing
- P&ID walkdown, resulting in an “as-built” P&ID
- Generation of ‘as-built’ isometrics
- Instrument calibration
- Cleaning and passivation
- Hot alignment of pumps
- Pressure testing
- Flushing and blowing of circuits, and system drainage

- Utilities check
- Electrical power tests

Installation Qualification

- Critical instruments are still in calibration
- Documentation Review and Check, including:
  - P&ID check of critical components
  - Welding documentation checks
  - Passivation documentation check of Storage tank and distribution loop
  - Loop check documentation verification for critical components
  - Material certifications for product contact parts
  - PLC Documentation
- Installation check of critical components

Operational Qualification

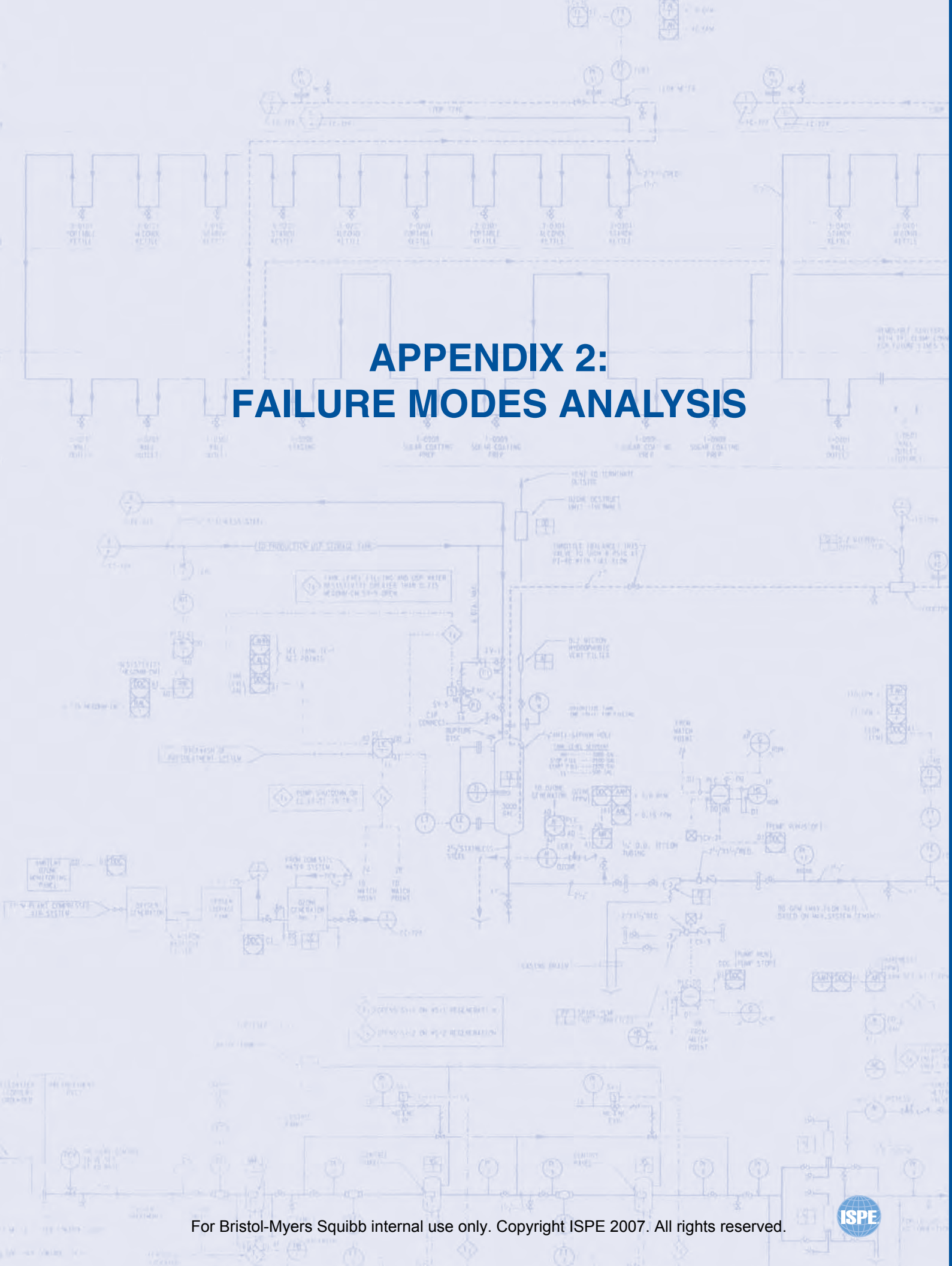
- Critical instruments are still in calibration
- Critical Alarms and Interlocks Testing
- Cleaning Sequence Verification, including:
  - Valve sequencing tests for filling and mixing
  - Valve sequencing tests for flushing and draining
- Operating Test, demonstrating:
  - Flow rate
  - Pressure
  - Temperature
  - Conductivity/pH/detergent concentration
- System capacity test, including adequate pressure at appropriate use points
- Power Failure Test
- RFI Test
- SOP Review

APPENDIX 1: ILLUSTRATIVE EXAMPLES

Performance Qualification

Company definitions of PQ vary widely. If a PQ for the CIP system is performed, this would generally include verification of cleaning efficacy, using equipment soiled with actual product. This process may be included in cleaning validation protocols for the individual pieces of equipment served by the CIP system. In this example, there would be no PQ for the CIP system itself, since CIP performance is verified in cleaning validation, covered in the "Related Programs". (See Chapter 11.)

APPENDIX 2:
FAILURE MODES ANALYSIS



13. APPENDIX 2: FAILURE MODES ANALYSIS

Failure Modes Effect Analysis (FMEA) and *Failure Modes Effect and Criticality Analysis* (FMECA) are probably the most widely used failure mode analysis[9] tools. The principle of FMECA/FMEA is to consider each mode of failure of every component and to ascertain the effects on system operation in turn. However the scope of the study will depend on the perspective taken and the level of analysis required.

The FMECA process produces a quantified measure of reliability. This requires reliability data. In practice, this might be difficult to obtain and will either restrict the assessment to an FMEA or a more qualitative form of FMECA.

However, Table 13-1 provides a brief illustration of how the method can be used in the absence of comprehensive reliability data.

Table 13-1 FMECA Assessment

Function	Failure Modes	Failure Causes	Failure Detection Method	Effect of Failure	Failure Probability	Detection Probability	Severity Factor
One Function	Several failure modes	Several causes for each mode?	Are each of these causes detectable?	Consequence of failure?	How probable is this failure cause?	How sure can we be of detecting the failure cause?	What level of risk does this present?
				A (1-5)	B (1-5)	C (5-1)	AxBxC

It can be seen that a frequent, undetectable failure of severe consequence will score 125 (5x5x5). The severity score will indicate the major risks and suggest the means of addressing them i.e.:

1) Re-design

2) Improved failure detection

3) Compensate for failure and its consequences with procedures

FMECA and FMEA can be performed from different perspectives, such as safety or availability. However as an Enhanced Design Review tool, the perspective taken should be impact on product quality and most importantly, ensuring that defective product will be detected. It is important that this perspective is clearly stated at the outset of the exercise. For example, a component whose failure will seriously affect system availability but not product quality would have a low consequence score when the assessment is performed from the product quality perspective and vice versa.

An effective FMECA process can only be performed by a team, which has a thorough knowledge of the system's design and application. The process will require significant commitment. For specialist systems much of this knowledge will reside with the supplier. Should the complexity and application of the system suggest performing FMECA, (see Section 7.5.3) careful consideration should be given to including FMECA within the supplier's scope of work.

[9] The FMEA/FMECA process is essentially limited to hardware failure; it will not reveal software coding or implementation errors although it can be used to reveal software design and specification errors.

APPENDIX 2: FAILURE MODES ANALYSIS

For a more comprehensive discussion of FMECA and FMEA, refer to:

- IEC 60812 (1985-07) 'Analysis techniques for system reliability - Procedure for failure mode and effects analysis'
- BS 5760-5: 1991 ' Reliability of systems, equipment and components. Guide to failure modes, effects and criticality analysis (FMEA and FMECA).
- US MIL-STD-1629 'Procedures for Performing a Failure Mode, Effects and Criticality Analysis'

GLOSSARY

GLOSSARY

Acceptance Criteria

The predetermined result of a specified test.

Basis of Estimate

Narrative explaining all assumptions or clarifications made in developing the estimate.

Commissioning

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

Commissioning Plan

A plan which defines the facilities, systems, and equipment that will be commissioned based on the agreed to system boundaries.

Commissioning Steering Team (CST)

Usually consists of representatives from the major stakeholder and/or decision-make groups. The CST is responsible for managing changes to the Commissioning Plan and directing the detailed commissioning activities.

Conceptual Design

Design stage, to generate various alternatives for evaluation. The project team then selects the concepts to be taken forward into the functional design stage.

Construction Drawings

2D/3D drawings of all systems, schedules, details, dimensions, notes, references, etc. Many of these drawings are “red lined” during the construction phase and updated at project completion. Many of these drawings are then kept up to date for maintenance, safety or GMP reasons.

Critical Component

A Component within a system where the operation, contact, data, control, alarm, or failure may have a direct impact on the quality of the product.

Design Development

Engineering process by which the generation of the design is managed.

Design for Impact

Design for Impact is used to describe the practice of making conscious design decisions with respect to the impact of the system in operation at the beginning of design development.

Detailed Design

Design stage when the documents required for construction bidding and contracting, as well as system and equipment purchase, fabrication, installation and testing are produced.

Direct Impact System

A system that is expected to have a direct impact on product quality. These systems are designed and commissioned in line with Good Engineering Practice and in addition, are subject to Qualification Practices that incorporate the enhanced review, control and testing against specifications or other requirements necessary for cGMP compliance.

Engineering Change Management

A process by which a qualified representative(s) reviews proposed or actual changes for their impact, approves or denies the requests, and manages and tracks their implementation. Engineering change management is good engineering practice, to effectively manage the project execution and the associated costs and schedule.

Enhanced Documentation

Required for "Direct Impact" systems. Enhanced documentation may involved additional tests, documentation, QA change control and QA review and approval.

Enhanced Design Review (EDR)

A documented review of the design, at an appropriate stage in a project, for conformance to operational and regulatory expectations.

Factory Acceptance Tests (FATs)

Inspection and static and/or dynamic testing of systems or major system components to support the qualification of an equipment system conducted and documented at the supplier site.

Failure Modes Effect and Criticality Analysis (FMECA)

A method of failure mode analysis that produces a quantified measure of reliability.

Functional (or Schematic) Design

The functional design stage generates the key design documents to be used as a framework for the detailed design process. These documents include site plans, floor plans, process and material flow diagrams, air flow diagrams and HVAC schedules, and electrical one-line diagrams.

Functional Design Specification (FDS)

Description of acceptance criteria, in terms of ranges and logic of operation etc.

Good Engineering Practice (GEP)

Established engineering methods and standards that are applied throughout the project lifecycle to deliver appropriate, cost-effective solutions.

Hazard and Operability Review (HAZOP)

The process of systematically reviewing a facility/system/process to determine potential safety concerns.

"Historical" Documents

Documents representing a point-in-time ("snapshot"). These are not updated continuously.

Impact Altering Change

A change that is made to a system which requires that a reassessment be performed to determine if the system type has changed (e.g. an "Indirect Impact" system that becomes a "Direct Impact" system after a change is made to the systems or to another system).

Impact Assessment

The process of evaluating the impact of the operating, controlling, alarming and failure conditions of a system on the quality of a product.

Indirect Impact System

This is a system that is not expected to have a direct impact on product quality, but typically will support a Direct Impact system. These systems are designed and commissioned following Good Engineering Practice only.

Inspection

The process by which the construction and installation is verified as in accordance with the detailed design, specified construction standards and materials and any relevant legal or regulatory demands relating to these areas.

Installation Qualification (IQ)

For "Direct Impact" systems - The documented verification that all aspects of a facility, utility or equipment that can affect product quality adhere to approved specifications (e.g. construction, materials) and are correctly installed.

"Living" Document

Documents maintained throughout the commissioning period as the system or project requirements are modified or updated.

No Impact System

This is a system that will not have any impact, either directly or indirectly, on product quality. These systems are designed and commissioned following Good Engineering Practice only.

Non-Critical Component

A component within a system where the operation, contact, data control, alarm or failure will have an indirect impact or no impact on the quality of the product.

Operating Limits

The minimum and/or maximum values that will ensure that product and safety requirements are met.

Operational Qualification (OQ)

For "Direct Impact" systems - The documented verification that all aspects of a facility, utility or equipment that can affect product quality operate as intended throughout all anticipated ranges.

Pre-Delivery Inspection (PDI)

Inspection and testing of systems or major system components before delivery to site.

Performance Qualification (PQ)

For "Direct Impact" systems - The documented verification that all aspects of a facility, utility or equipment that can affect product quality perform as intended meeting predetermined acceptance criteria.

Performance Testing

The process by which the performance of interdependent systems is demonstrated as within the required tolerances, the output of interdependent systems is demonstrated as delivering the required duty or capacity, the interdependent functions of systems are demonstrated to be as specified and appropriate.

Physical Completion

A project milestone where the installation of a system is complete as per engineering design and the documentation required to support commissioning is available.

Piping and Instrumentation Diagrams (P&IDs)

Primary source of design information for utility systems and process equipment. They are used to depict the process flow, equipment configuration, process parameters, instrumentation, and materials of construction. They also are used to perform overall material and energy balances and pressure balances.

Process Validation (PV)

Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes.

Procurement Plan

A report to identify all bid packages and proposed pre-qualified bidders. The report should list the scope of each bid package along with the contract terms (e.g. lump sum, time and material, not to exceed.)

Project Controls

Control activities used to monitor, report and control cost, schedule, documentation and engineering changes - projects.

Project Execution Plan

A written plan for the project manager to communicate to the user and other stakeholders the approach to be taken for project execution.

Project Logistics

Plan which identifies locations for material/equipment storage, lay-down, staging, temporary offices, dumpsters, break/lunch areas, temporary utilities, etc. The logistics plan should delineate construction personnel, material and equipment access to the project site during each phase of construction. The plan also should incorporate any revised operational personnel and material flows during each phase of the project.

Project Quality Control

Quality control starts with the pre-qualification of the applicable suppliers, contractors and where applicable, the construction management firms and their proposed project teams. Each company's QC program should be reviewed, evaluated and previous project references contacted. The contractor's QC program should include documents and procedures applicable to the specific industry and for potential use to satisfy qualification requirements. If a construction manager is to be used, their QC program should be reviewed for evidence of periodic qualification of potential subcontractors.

Quality Assurance (QA)

The activity of or group responsible for ensuring that the facility and systems meet GMP requirements.

Quality Attributes

Characteristics that define the suitability of a system/process.

QA Change Control

Process by which proposed changes to a qualified system are assessed before implementation to determine the impact on the system. Proposed changes must be approved prior to implementation.

Quality Control (QC)

Process of or group responsible for coordinating the activities associated with analytical test planning and execution.

Qualification Protocol

An individual detailed document that describes the system under consideration, the testing plans, the acceptance criteria and the test results that ensure that a system is installed and operates in accordance with predetermined specifications.

Qualification Rationale

An outline of the approach to be taken in assessing the qualification efforts, determining the extent and boundary limits of the qualification effort, and execution and ownership for the project's qualification activities.

Qualification Summary Report

Report summarizing the results of protocol execution.

Quality Impact

The quality of the product can be impacted by a system or systems which meets any of the following criteria: in contact with product, used as an excipient of ingredient, an/or controls or provides information relative to product acceptance or rejection.

Quality Practices

Includes:

- System Impact Assessment
- Active participation of the Quality assurance department
- Enhanced documentation, document management and a structured approval process
- QA Change control
- Greater end user participation
- Training
- Use of Qualifications Rationales to identify what should be checked, how, to what extent, why and by whom
- Deciding what not to check and why.

Quality System

Planned and systematic activities necessary to provide adequate confidence that a product, process, or service satisfies specified quality requirements.

Regulation and Adjustment

The process of adjusting a system, or elements of it, to operate within the required tolerances. This includes activities such as balancing of chilled water and air conditioning systems, and the adjustment of a reject mechanism on a packaging line.

Related Programs

Programs/procedures implemented at a facility to ensure that operations are conducted as per GMP.

Requirement Specifications

A detailed document used to specify the requirements of the client for individual aspects of the facility, item of equipment, utility and systems in terms of function, throughput, operability and applicable local standards.

Revalidation

Validation of a previously validated system that has been changed or modified. Revalidation can be performed as the result of a change to the system, or a time based assessment.

Safety Plan

A plan to incorporate the requirements of both the construction firm and owner with regard to project safety. Construction safety hazard analysis reviews should occur to identify activities that have higher than normal risk to employees and property. Specific plans, procedures and training should be implemented to address the hazards identified.

Sequence of Operations

Prepared for each system. A detailed description of the system start-up, normal operation and cleaning (as applicable), process monitoring, data acquisition and archive, alarm conditions and response, and shut-down.

Shake-Down

Putting a system or systems into operation, knowing inspection, adjustment, regulation, and testing of the system may be less than complete, having first ensured that it is safe and responsible to do so (e.g., the system will not be damaged, or cause damage, or cause death or injury if operated). The purpose of the shake-down is to rapidly reveal and remedy deficiencies prior to commencement of a formal change control regime within a qualification and-or a commissioning effort.

Setting-to-Work

Precedes Regulation and Adjustment, and includes the necessary calibration and preliminary adjustment of instruments, sensors and mechanisms before initial energizing of systems. Prerequisites are satisfactory Inspection, safety/start-up procedures in-place, training given and documented start-up sequences provided. The first stages of setting-to-work can be considered a “shake-down” of the system.

Site Acceptance Testing (SAT)

Inspection and /or dynamic testing of the systems or major system components to support the qualification of an equipment system conducted and documented at the manufacturing site.

Specifications

Documentation which clearly and explicitly defines the system requirements, codes and standards to be followed during fabrication and construction, test requirements, acceptance criteria and the associated deliverables.

Standard Operating Procedure (SOP)

Written and approved procedures to ensure that activities are performed the same way each time. A comprehensive SOP program must be in place in any regulated organization.

Structured Design Review

A design review conducted by identification of the characteristics of a good design to ensure that all relevant and appropriate aspects are examined.

System

An organization of engineering components which have a defined operational function (e.g. Piping, instrumentation, equipment, facilities, computer hardware, computer software, etc.).

System Boundary

A limit drawn around a system to logically defined what is an is not included in the system.

System Description

General description of the system, describing its components, its designed unit operation functional capabilities, critical functions, and the boundaries of the system(s) covered under the protocol.

System Overview

A high-level process narrative including system boundaries based on operational/functional requirements. Generally included in the commissioning plan.

Testing

Process by which adjustments to, and regulation of, individual systems are demonstrated as within the required tolerances, system components are demonstrated as delivering the required capacity or duty, the functions of the system are demonstrated as delivering the required capacity of duty, the functions of the system are demonstrated to be as specified and appropriate.

Turnover Strategy

A plan for “hand-over” or “transfer of responsibility” of the project.

User Requirements (or User Requirements Brief)

A description of the requirements of the facility in terms of product to be manufactured, required throughput and conditions in which the product should be made.

Validation Master Plan

VMP - a high level document, which establishes an umbrella validation plan for the entire project and is used as guidance to the project team for resource and technical planning.

Vendor /Contractor Audit

An evaluation of the supplier’s ability to deliver a quality product/service.

ABBREVIATIONS and ACRONYMS

ABBREVIATIONS AND ACRONYMS

Acronym/ Abbreviation	Description
ASHRAE	American Society of Heating, Refrigeration and Air Conditioning Engineering
BMS	Building Management System
CADD	Computer Aided Design Drawings
CFR	Code of Federal Regulations
cGMP	Current Good Manufacturing Practice
CHW	Chilled Water
CIBSE	Chartered Institute of Building Services Engineers
CIP	Clean-in-Place
COP	Clean-out-of-Place
CST	Commissioning Steering Team
DCS	Distributed Control System
EDR	Enhanced Design Review
EPA	Environmental Protection Agency
FAT	Factory Acceptance Testing
FDA	Food and Drug Administration
FDS	Functional Design Specification
FMEA	Failures Modes Effect Analysis
FMECA	Failures Modes Effect and Criticality Analysis
GAMP	Good Automated Manufacturing Practice
GEP	Good Engineering Practice
GMP	Good Manufacturing Practice
HAZAN	Hazard Analysis
HAZOP	Hazard and Operability Review
HEPA	High Efficiency Particulate Air
HVAC	Heating, Ventilation, and Air Conditioning

ABBREVIATIONS AND ACRONYMS

IEEE	Institute of Electrical and Electronic Engineers
IQ	Installation Qualification
LTHW	Low Temperature Hot Water (for services)
O&M	Operations and Maintenance
OQ	Operational Qualification
OSHA	Occupational Safety and Health Administration
P&IDs	Piping and Instrumentation Diagrams
PDI	Pre-delivery Inspection
PLC	Programmable Logic Controller
PQ	Performance Qualification
PV	Process Validation
QA	Quality Assurance
QC	Quality Control
RFI	Radio Frequency Interference
SAT	Site Acceptance Testing
SIP	Sterilize-in-Place or Steam-in-Place
SOP	Standard Operating Procedure
TOC	Total Organic Carbon
VMP	Validation Master Plan
WFI	Water For Injection

REFERENCES and RELATED READING

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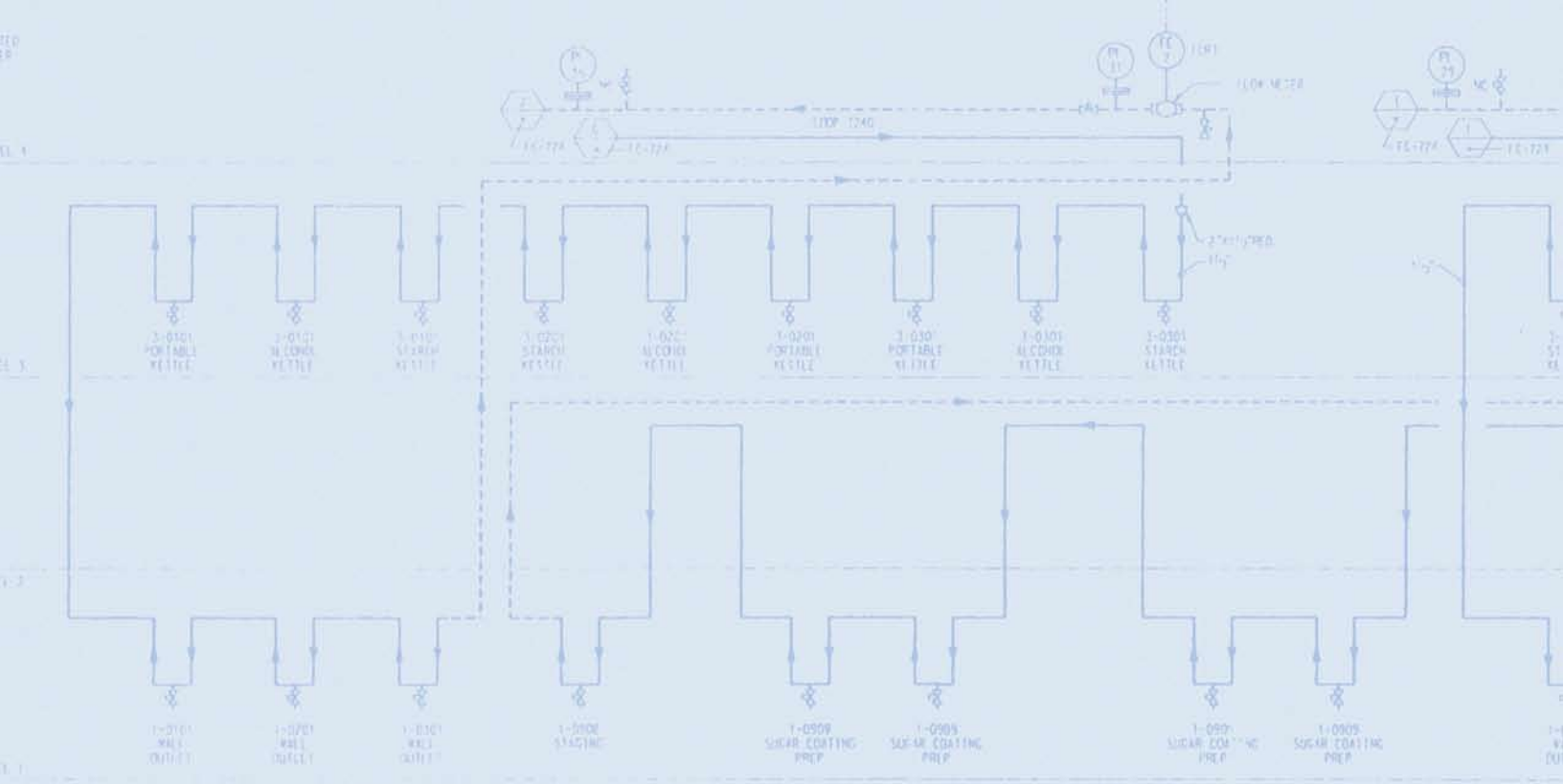

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