

# Baseline

## PHARMACEUTICAL ENGINEERING GUIDE

A GUIDE FOR NEW FACILITIES

VOLUME 5: COMMISSIONING AND QUALIFICATION

EXECUTIVE SUMMARY

JUNE 2000

A DOCUMENT DEVELOPED IN PARTNERSHIP BY:







## ISPE PHARMACEUTICAL ENGINEERING GUIDE

## COMMISSIONING AND QUALIFICATION

## FOREWORD

As noted in the Baseline® Guides, Volume 1, the pharmaceutical industry has experienced a ratcheting effect in the cost of new facilities. This increase in cost has 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, architectural and HVAC. The absence of a consistent and widely accepted interpretation of 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). That first discussion allowed for the creation of 10 facility engineering guides, now known as the *Baseline®* Pharmaceutical Engineering Guides. These guides are intended to assist pharmaceutical manufacturers in the design, construction and commissioning of facilities that comply with the requirements of the FDA. Volume 1, covering Bulk Pharmaceutical Chemicals (BPC), was published in June of 1996. This Guide, for Commissioning and Qualification, is the fifth volume in the series.

As with the BPC Guide, the Commissioning and Qualification Guide, has been sponsored by ISPE's Pharmaceutical Advisory Council, made up of senior pharmaceutical engineering executives from owner companies, the FDA 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 BPC Guide. The Commissioning and Qualification Guide itself was produced by a task force of around 60 individuals who expended a great deal of their own time in its preparation and development.

## Editors' Disclaimer:

<p>This guide is meant to assist pharmaceutical manufacturers in the design and construction of new facilities that 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 FDA.</p>
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COMMISSIONING AND QUALIFICATION

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This guide was developed by an integrated US-European team under the co-leadership of Alan Philips of Pfizer and Christopher Wood of Glaxo Wellcome.

The **Core Team** on the guide was comprised:

Alan Philips	Pfizer
Christopher Wood	Glaxo Wellcome
Bob Myers	Kvaerner
Georgia Keresty, Ph.D.	Bristol Myers Squibb

The **Extended Review Team** was comprised the **Core Team** plus

Jan Gustafsson	Novo Nordisk
Graham Shewell	SmithKline Beecham
Todd Troutman	Kvaerner
Simon Shelley	Glaxo Wellcome
Gene Yuan	Hoffman LaRoche

The **Chapter Credits** are as follows:

Introduction	Alan Philips	Pfizer
	Georgia Keresty, Ph.D.	Bristol-Myers Squibb
Key Concepts & Philosophy	Chris Wood	Glaxo Wellcome
	Georgia Keresty, Ph.D.	Bristol-Myers Squibb
Impact Assessment	Bob Myers	Kvaerner
	Simon Shelley	Glaxo Wellcome
	Todd Troutman	Kvaerner

Good Engineering Practice	John Fadool Graham Shewell	Glaxo Wellcome SmithKline Beecham
Commissioning	Mark E. Miller <sup>1</sup> Chris Wood Graham Shewell	Genentech Glaxo Wellcome SmithKline Beecham
Qualification Practices	Jan Gustafsson Gene Yuan Sue Bacso	Novo Nordisk Hoffman LaRoche Merck
Enhanced Design Review	Graham Shewell Chris Wood	SmithKline Beecham Glaxo Wellcome
Installation Qualification	Bob Myers Bob Adamson Todd Troutman	Kvaerner Foster Wheeler Kvaerner
Operational Qualification	Bob Myers Todd Troutman	Kvaerner Kvaerner
Performance Qualification	Chris Dell Cioppia	Kvaerner
Related Programs	Georgia Keresty, Ph.D. Todd Troutman	Bristol-Myers Squibb Kvaerner
Illustrative Examples	Bob Myers	Kvaerner

The guide co-team leaders would also like to acknowledge the contributions made by the following part-time members of the guide team:

Flemming Steen Jensen (then of) Novo Nordisk

Steve Heidel Merck

Cecilia Luna Novartis

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Tony deClaire APDC Consulting

FDA Reviewers:

We would like to thank the following FDA review team for their input to this guide:

Robert Sharpnack Investigator

Eric S. Weilage NDA/ANDA Pre-approval Inspection Manager

Robert Coleman National Drug Expert, DEIO

Brian Nadel Compliance Officer, CDER

We also appreciate FDA support from the following representatives:

Sharon Smith-Holston Deputy Commissioner for External Affairs

Susan Setterberg Regional Director, Mid-Atlantic Region

Joe Phillips Deputy Regional Manager, Mid-Atlantic Region

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Mel Crichton Eli Lilly

Bruce Davis Astra Zeneca

Paul Lorenzo (Retired)

# 1. INTRODUCTION

## 1.1 BACKGROUND

The design, construction, commissioning and qualification of manufacturing facilities regulated by 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 Food and Drug Administration (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 the 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 these standards, 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 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 cGMP's. 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 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 FDA and other authorities and for which substantial guidance documentation exists.

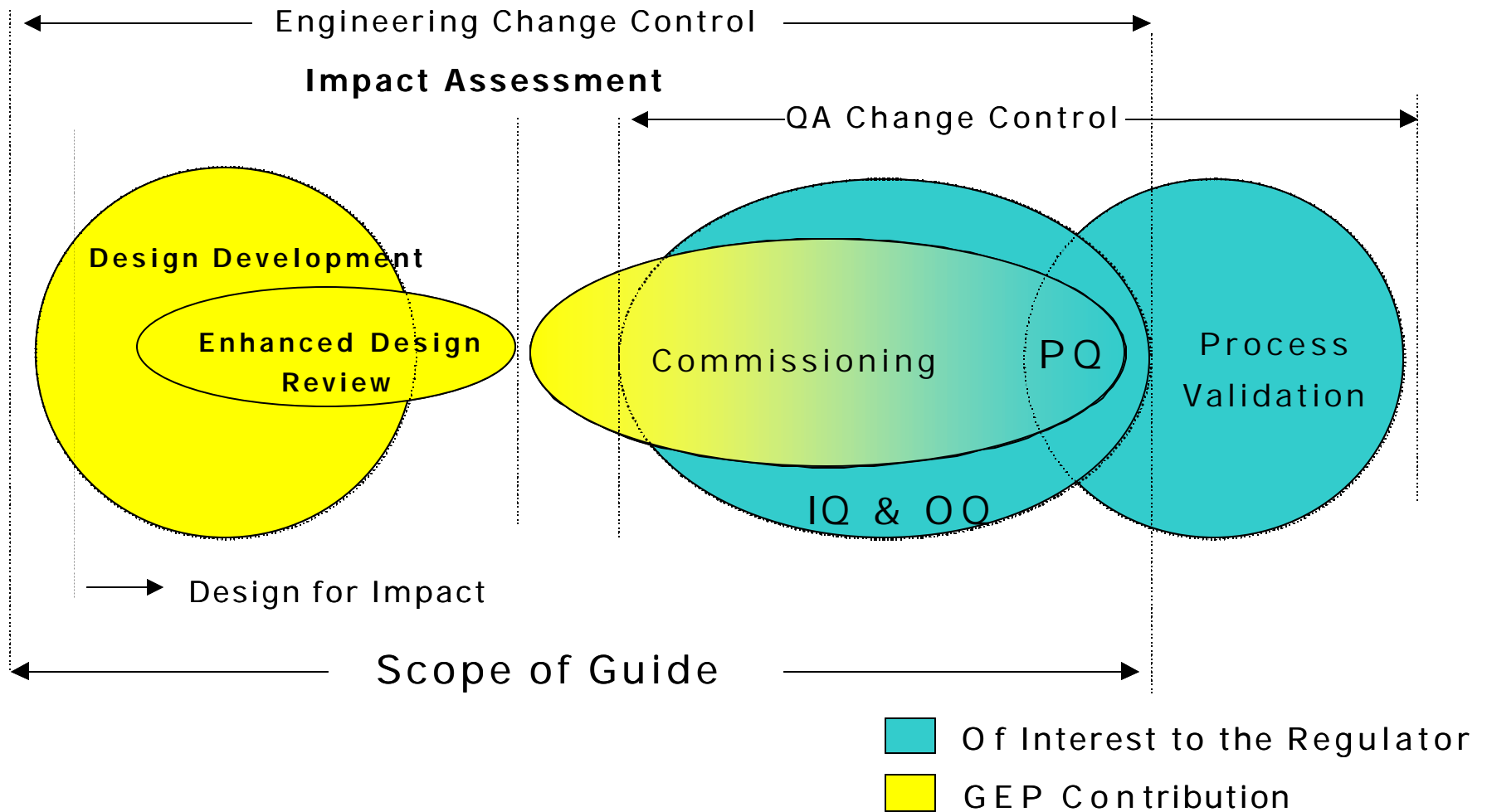
It must be recognized, however, that *Commissioning* and *Qualification* activities are the foundation upon which Process Validation is built. Furthermore, these activities play a crucial role in delivering operationally effective, safe and efficient facilities, utilities and equipment. Therefore, it 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 meeting regulatory requirements to supply the United States (US) market and is aligned with US standards and references. The Guide may also be helpful to manufacturers needing to meet European requirements.

Figure 1-1 The scope of the Commissioning and Qualification Baseline® 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.

The determination of a system as either 'Direct Impact' or 'Indirect Impact' is critical. It is this differentiation between system types that determines the degree of effort and level of resources required for each system. **System Impact Assessment** provides the thought process and 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, and by the right people (e.g. QA Departments).

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.

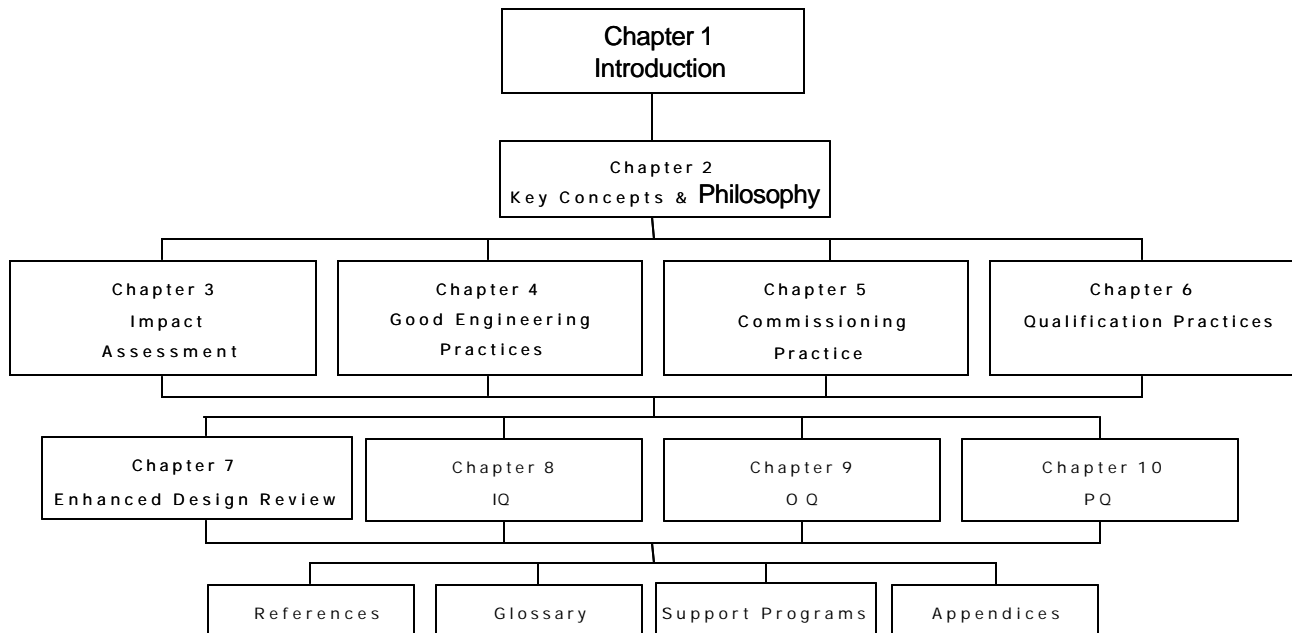
It will also be seen that throughout the Guide, the application of **Good Engineering Practice** is essential to the commissioning and qualification activities. Good Engineering Practice, commonly referred to as GEP, is proven and accepted, cost-effective, engineering methods and practices that ensure 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**” 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 FDA or other regulatory authorities. The design review activities are part of GEP and are unregulated by FDA, i.e. these are good engineering practices, not regulatory requirements.

**Installation Qualification (IQ), Operational Qualification (OQ) and Performance Qualification (PQ)** are activities that 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 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

## 2. GUIDE PHILOSOPHY AND KEY CONCEPTS

This Chapter describes the purpose and philosophy of the Commissioning and Qualification Baseline® Guide, and the differences between the commissioning and qualification processes in the context of this Guide. 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.

The key terms used in the Guide are defined, including:

- Direct Impact System
- Indirect Impact System
- No Impact System
- Design for Impact
- Good Engineering Practice
- Enhanced Design Review
- Commissioning

An overview of Qualification Practices is given, including Enhanced Design Review, Installation Qualification, Operational Qualification, and Performance Qualification. V-models are provided for both Direct Impact systems and Indirect Impact systems and the role of Quality Assurance is discussed.

## 3. IMPACT ASSESSMENT

Impact Assessment is the process of determining which systems and/or system components should be subject to Qualification Practices in addition to Good Engineering Practices (GEP). Impact Assessment assists in defining the Commissioning and Qualification scope of a project.

This Chapter considers the Impact Assessment process. Terms specific to Impact Assessment are defined. 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.

## 4. GOOD ENGINEERING PRACTICE

This Chapter provides an overview of the various project phases and sequence, from inception through commissioning, qualification, and operation. Concepts associated with “Good Engineering Practice” (GEP), the types of activities that occur, and documentation that is created through GEP are discussed. Overviews are provided of both effective project controls, and project team concepts and organization.

The Requirements phase is considered in detail, including:

- Project Purpose and Justification

- User Requirements Brief
- Requirements Specifications
- Project Execution Plan
- Maintenance and Technical Support Requirements
- Compliance Requirements
- Deliverables

Stages in the design process are described with specific consideration of Piping and Instrumentation Diagrams, Specifications, and Construction drawings. Construction involves several elements, which are crucial to every project, including project site logistics and project quality control. This Chapter details typical requirements and elements of construction.

The information given in the Chapter aims to demonstrate how GEP, as applied throughout the project lifecycle, provides a basis for effective qualification.

## 5. COMMISSIONING

This Chapter defines the term “commissioning” in the context of the Guide and describes the organization and content of the Commissioning Plan document. Commissioning is positioned within the context of the Qualification effort and guidance is provided in the management and execution of the commissioning activities. Typical commissioning deliverables and the associated commissioning team responsibilities are considered.

Commissioning activities described include:

- Inspection
- Setting-to-Work
- Regulation and Adjustment
- Testing and Performance Testing
- Training
- Turnover
- Commissioning Plan Close-Out

## 6. QUALIFICATION PRACTICES

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. The Validation Master Plan and Qualification Rationale are described in detail. This Chapter contains detailed consideration of Enhanced Documentation.

## 7. ENHANCED DESIGN REVIEW

*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*.

This Chapter gives the regulatory perspective on EDR and relates EDR to the V-Model for Direct Impact systems. The EDR process is detailed. A structured design review method and a failure modes analysis method are suggested for evaluating designs.

## 8. INSTALLATION QUALIFICATION

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

The primary objectives of this chapter are to:

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

## 9. OPERATIONAL QUALIFICATION

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 primary objectives of this chapter are to:

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

## 10. PERFORMANCE QUALIFICATION

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.

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

## 11. RELATED PROGRAMS

This Chapter provides details of 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', 'Indirect' and 'No Impact' systems and their components. 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. Related programs considered include:

- Safety
- Standard Operating Procedures
- Training
- Preventative Maintenance and Calibration
- Computer Systems Validation
- Cleaning Validation
- Analytical Method Validation
- Process Validation
- Revalidation

## 12. GLOSSARY

Terms and concepts used throughout the Commissioning and Qualification Baseline® Guide are defined and cross-referenced.

## 13. ILLUSTRATIVE EXAMPLES

The illustrative examples given in this Chapter 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.

## APPENDIX

The Appendix provides detail and references for Failures Modes Analysis.