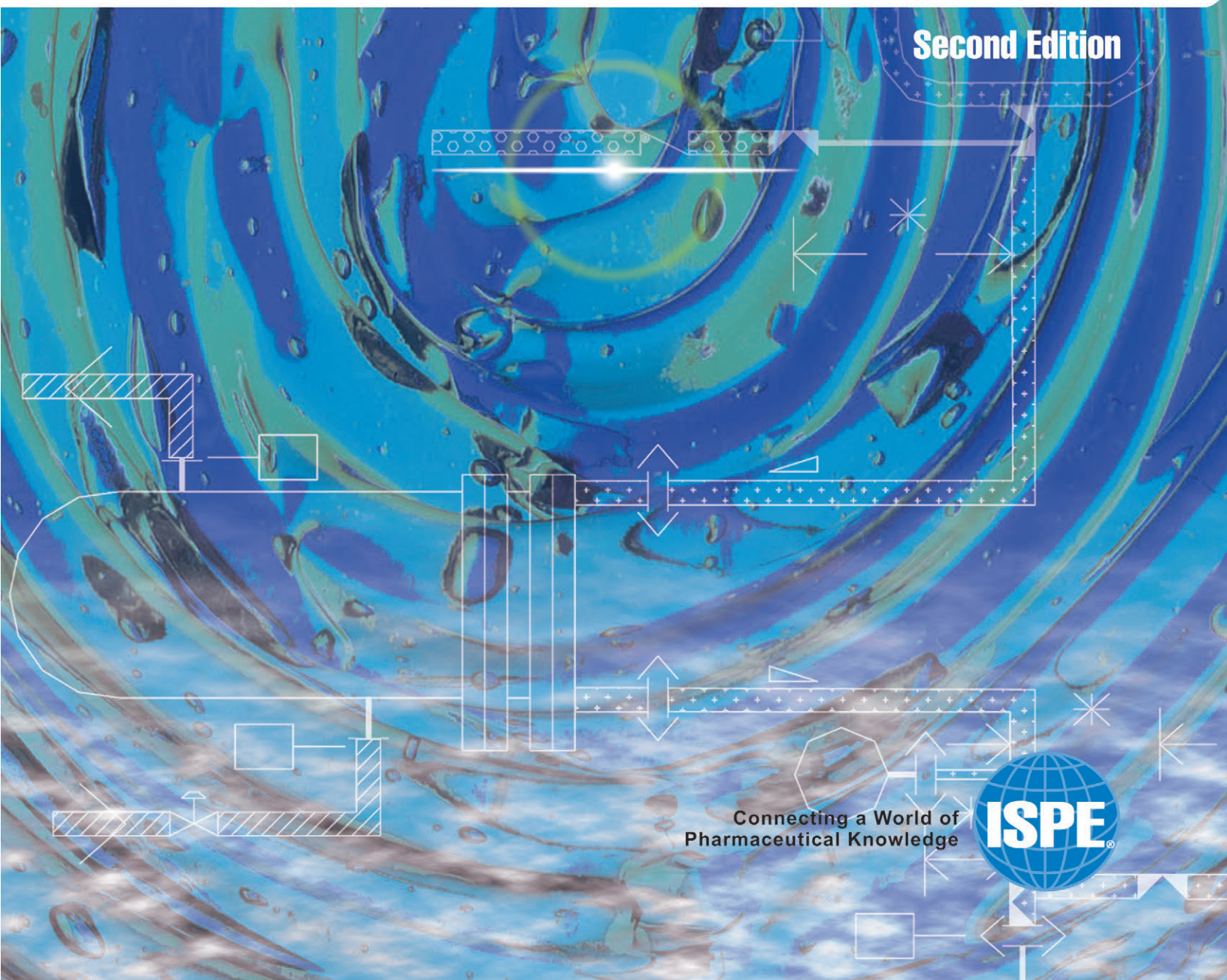




**Good
Practice
Guide**

Approaches to Commissioning and Qualification of Pharmaceutical Water and Steam Systems

Second Edition



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Pharmaceutical Knowledge



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Disclaimer:

This Guide is meant to assist pharmaceutical companies in managing the commissioning and qualification of pharmaceutical GMP water and steam systems. ISPE cannot ensure and does not warrant that a system managed in accordance with this Guide will be acceptable to regulatory authorities. Further, this Guide does not replace the need for hiring professional engineers or technicians.

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Preface

The ISPE Good Practice Guide: Approaches to Commissioning and Qualification of Pharmaceutical Water and Steam Systems focuses on the engineering approaches and practices involved in providing cost effective water and steam systems in a timely manner that are specified, designed, installed and operated to meet their intended purpose. Specifically, this Guide addresses the lifecycle process of designing, constructing, commissioning, and qualifying water and steam systems regulated by international healthcare authorities.

This Guide describes how a capital project delivers process, commissioning and qualification (verification) activities, and on-going monitoring work together through the validation lifecycle for GMP water and steam systems.

The main benefit of this Guide is that it describes a project execution, commissioning and qualification (verification) approach for GMP water and steam systems based on process understanding. The required quality of water or steam is achieved without unnecessary project expense due to duplication of effort and non-value adding activities.

This Guide describes current, established, good practice, and references other guidance documents published by ISPE, where applicable. The focus is on achieving cost-effective compliance with existing regulations and associated guidance.

Acknowledgements

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Pharmaceutical Water and Pure Steam Systems

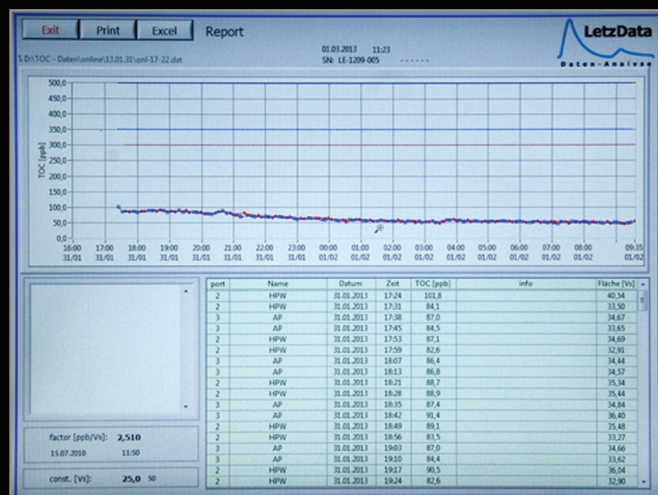
- 316 L
- DIN 11864
Aseptic Couplings
- Anti Rouging Concept
- Green Planet Concept



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1 Introduction

1.1 Overview

Water and steam may be used in cleaning operations, laboratory activities, and the manufacture of pharmaceutical or biopharmaceutical products. Water and steam may come into contact with product or process contact surfaces, or may be used in the testing of products.

Good Manufacturing Practice (GMP) processes may produce drug substances or drug products. Water also may be used as a final product, e.g., as US Pharmacopeia (USP) packaged waters or other pharmacopeial equivalent, or as a combination drug product, including:

- Sterile Water for Injection
- Sterile Water for Irrigation
- Sterile Water for Inhalation
- Sterile Purified Water
- Bacteriostatic Water for Injection
- Water for Hemodialysis

Systems that generate and distribute pharmaceutical water and steam are subject to commissioning and qualification or verification practices.

Commissioning and qualification or verification is intended to bring a pharmaceutical water or steam system into operation, as part of design and construction. The water or steam systems (i.e., equipment and controls) are subject to GMPs. Commissioning and qualification or verification should verify that these systems create water and steam (i.e., product) of a consistent and repeatable quality. Qualification also should verify that supporting quality systems have been integrated into the validation lifecycle in order to maintain the validated state of the system.

Historically, the qualification model has consisted of an independent confirmation of the entire system installation and operation after the engineering commissioning has been completed.

The ISPE Good Practice Guide: Approaches to Commissioning and Qualification of Pharmaceutical Water and Steam Systems, along with the ISPE Good Practice Guide: Applied Risk Management for Commissioning and Qualification [1], changes this focus based on the use of a risk assessment to determine the process steps and controls that ensure the system output meets the quality requirements.

1.2 Purpose

This Guide addresses both a traditional commissioning and qualification and a science and risk-based approach to the commissioning and qualification of pharmaceutical water and steam systems.¹ This Guide aims to assist in the integration of the capital project management process, the commissioning and qualification process, and the on-going operation into the Quality Risk Management (QRM) validation lifecycle.

¹ Note: other approaches also may be used for commissioning and qualification.

The purpose of this Guide is to describe how a traditional approach or the principles discussed in the ISPE Guide: Science and Risk-Based Approach for the Delivery of Facilities, Systems and Equipment [2] and the ISPE Good Practice Guide: Applied Risk Management for Commissioning and Qualification [1] can be applied to GMP water and steam systems. Ultimately, the goal is to increase understanding of GMP water and steam systems in the pharmaceutical and biopharmaceutical industries. It should be recognized that there are a number of ways of achieving this goal; this Guide describes examples of how to implement a traditional approach or a science and risk-based approach.

The main emphasis of this Guide is on high purity water and pure (clean) steam. Discussion and information on other pharmaceutical waters and steam are also provided. The United States Pharmacopeia (USP) [3], European Pharmacopeia (EP) [4], and Japanese Pharmacopeia (JP) [5] define different types of compendial high purity water, including:

- Water for Injection (WFI)
- Purified Water
- Highly Purified Water
- Pure Water (purification train water feed to a pure (clean) steam generator)

The type of water used for a specific pharmaceutical and biopharmaceutical process is dependent on a technical evaluation of which water is appropriate for that process.

Different compendial pharmaceutical waters have different specifications. The commissioning and qualification practices to create and preserve water quality, in generation, storage, and distribution systems, may vary according to the type of compendial water. Harmonization of pharmacopeial mandates for WFI and purified water classifications between the USP [3], EP [4], Chinese Pharmacopeia (ChP) [6], Brazilian Pharmacopeia [7], and JP [5] is an ongoing endeavor. At the time of publication of this Guide, there are still differences between these pharmacopeias.

The intended audience for this guidance is both corporate and local within an organization and in the following disciplines:

- Critical Utilities
- Facilities
- Engineering, Process and Project Management
- Business Process Owners
- Process Analytical Technology (PAT) and Validation Team
- Quality Control
- Quality Assurance

1.3 Objectives for this Guidance

This Guide has seven principle objectives:

1. Provide understanding on the importance of Commissioning and Qualification (C&Q) (verification) and how it fits into both a validation lifecycle and a project lifecycle

2. Explain and demonstrate an example of a science and risk-based risk management process for water and steam systems and what are typical system boundaries and critical aspects
3. Discuss Critical Aspects (CAs), Critical Quality Attributes (CQAs), and Critical Process Parameter (CPPs)
4. Discuss business essential parameters – key business considerations for design, construction, commissioning, and qualification. Some of these relate to non-product quality items like Health, Safety, Environmental (HSE) considerations, Information Technology (IT), or other “commissioning only” project scope items
5. Provide identification of and discussion on project scope activities included in the qualification of water and steam systems in the context of full project delivery
6. Provide information on the User Requirements (URs), Functional Specification (FS), and how a Quality by Design (QbD) approach may be implemented
7. Ultimately, provide an alternative “science and risk-based” method that can be applied to the qualification of GMP water and steam systems

1.4 Scope

The scope of this Guide is to cover practices and activities associated with the commissioning and qualification or verification of pharmaceutical water and steam systems. Discussion is centered on those items which directly affect water or steam CQAs during production, storage, and distribution.

This Guide can be used as a standalone document as well as in conjunction with the ISPE Baseline® Guide: Water and Steam Systems (Second Edition) [8], the ISPE Good Practice Guide: Applied Risk Management for Commissioning and Qualification [1], and the ISPE Guide: Science and Risk-Based Approach for the Delivery of Facilities, Systems and Equipment [2].

This Guide aims to provide an example of how risk assessment can be used to determine the critical aspects, the definition of CQAs and CPPs, and the identification/appropriate execution of quality indicating verification activities applied throughout the validation lifecycle.

This Guide provides an approach for commissioning and qualification and how they correspond to:

- The validation lifecycle
- Risk management
- Process analytical technology
- Quality by Design (QbD) concepts

Those critical aspects that assure water or steam quality over the life of a system should be identified and documented. These items should be subject to both commissioning and qualification processes. Other Good Engineering Practice (GEP) related requirements (H/S/E/Business), which have impact on water or steam system performance, should be commissioned only. Appropriate system lifecycle operating and maintenance programs should be identified and implemented.

The risk assessment and risk mitigation processes used during design and qualification is fundamental to ensuring product quality, and in allowing system designers and operators to gain process understanding of those product CQAs and process CPPs which affect water or steam quality.

GEP commissioning is intended to provide documented evidence confirming that a system is installed and operates to meet the specifications traceable to user requirements.

The approach to commissioning and qualification described in this Guide uses the following process to complete qualification:

- The system requirements, CQAs and CPPs are defined.
- The risks to the CQAs are identified, and the associated controls/critical aspects are defined (these may be design controls or procedural controls).
- The means of detection if the risk occurs are defined.

These are then scored considering:

- Severity of the risk – if it occurs.
- Likelihood of occurrence – with the controls defined in place.
- Probability of detection – this has to be effective prior to release of any product associated with the system output.

Installation Qualification (IQ) and Operational Qualification (OQ) should confirm that:

- The design qualification was satisfactorily completed.
- The system commissioning was completed confirming that the installation and operation complied with the design specification.
- Engineering change management was done with quality engagement - the installation is still considered “design qualified” with the installation and operation meeting the final revision of the specifications.
- The risk controls identified in the risk assessment are in place and operating as specified.
- The commissioning is completed following agreed GEPs (see the ISPE Good Practice Guide: Good Engineering Practice [9]), with defined deliverables; qualification can now focus on those critical aspects that can directly affect the quality of system output.
- The scope of the engineering testing and inspection covers requirements for business, safety, and compliance with specifications (from a contractual and quality perspective).

Typical documents delivered would include:

- Installation Verification
- Operational Verification
- Commissioning/Verification Summary Report
- Turnover Package

1.4.1 Regulatory Aspects

This Guide addresses compliance with international regulations and guidelines for water and steam systems, and considers:

- New systems and extensions to existing ones
- Existing validated systems

A wide range of healthcare requirements related to water and steam system compliance have been taken into account, including:

- GMPs
- ICH Q7A [10], ICH Q8(R2) [11], ICH Q9 [12], and ICH Q10 [13]
- ASTM E-2500 [14]

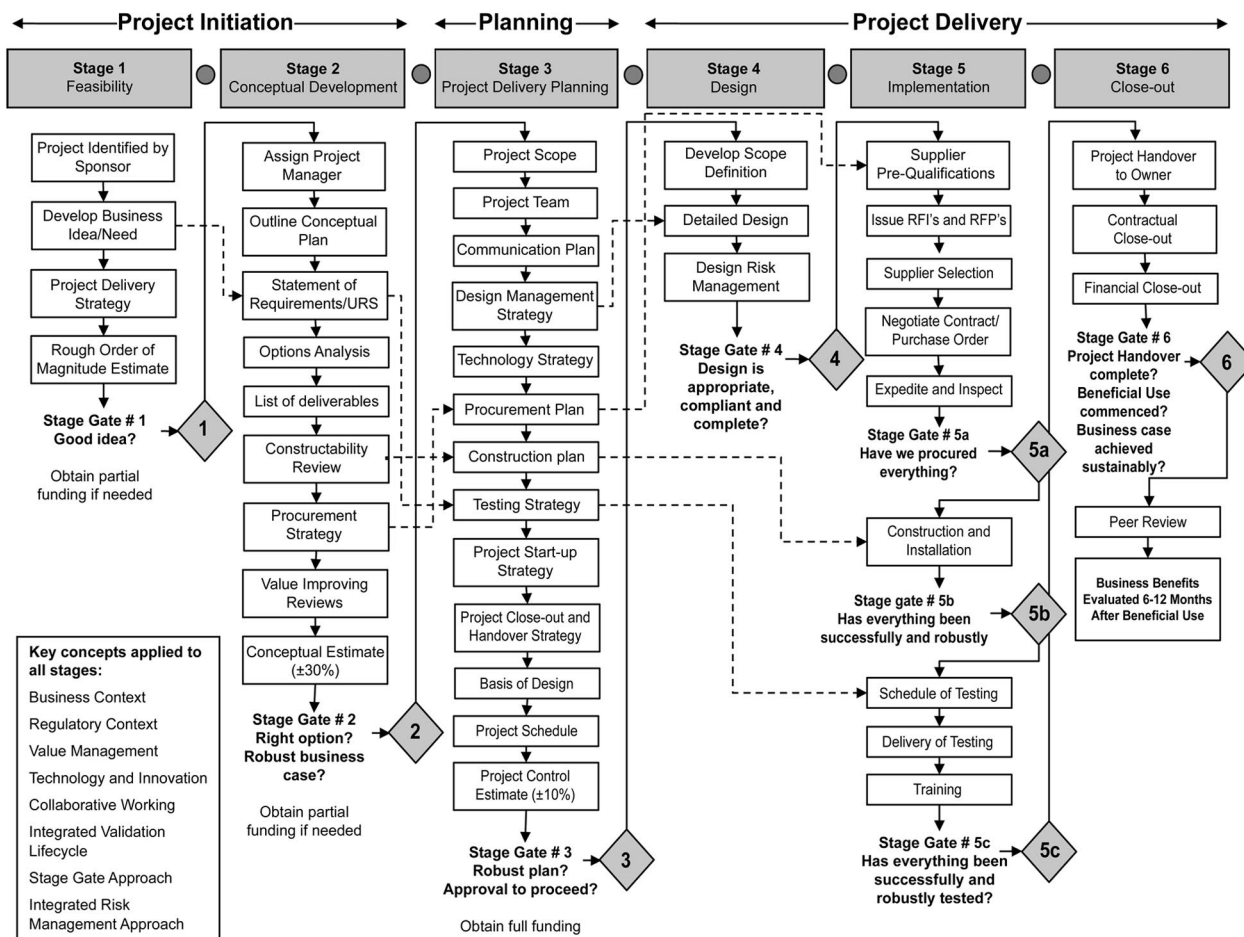
The following regulations and guidelines have been specifically considered in developing this document:

- FDA regulations, Compliance Policy Guides, and “21st Century Initiatives” [15]
- Relevant sections of EU GMPs, e.g., Annexes [16]
- USP [3]
- EP [4]
- JP [5]
- ChP [6]

The commissioning and qualification of such a system would typically be considered a part of an overall project to provide this system.

A typical project lifecycle is shown in ISPE Good Practice Guide: Project Management for the Pharmaceutical Industry – Figure 1.7 [17]; aligned terminology is used in this Guide.

Figure 1.1: Project Management Flowchart



1.5 Benefits

This Guide provides alternative approaches to commissioning and qualification (verification) practices and activities associated with GMP water and steam systems. Benefits and attributes of this approach include:

- Risk assessment to identify aspects that are “critical to quality.” This provides a focus for the quality related activities during design, construction and qualification with a supporting rationale.
- A streamlined delivery model minimizing duplicate testing, utilizing engineering documentation to provide the documented record that the installation and operation meets the specification. This approach utilizes the Subject Matter Experts (SMEs) in the most effective manner.
- Risk-based approach to the qualification of GMP systems is employed as compared to the traditional approach that repeats the engineering work, delivering separate, often voluminous IQ and OQ documents.
- The risk assessment provides a useful tool to reference when considering the potential impact of proposed changes.
- The approach described impacts IQ and OQ; Performance Qualification (PQ) follows the traditional approach, providing operational data on the system that will support long term operation.
- Integration of project management good practices

This Guide can be used by industry professionals involved in the design, construction, commissioning, and qualification of new or newly renovated water and steam systems, which are regulated by the international healthcare authorities.

Other benefits of a quality centric qualification approach include:

- Efficient and cost effective use of resources and minimum overlap in either commissioning and traditional validation or the use of PAT in lieu of traditional validation
- Effective focus on objectives and deliverables through the entire lifecycle
- Minimal duplication and overlap in documentation
- Efficient handling of audits, inspections and assessments

1.6 Structure of this Guide

This Guide is presented in three main sections:

1. Introduction
2. Validation Lifecycle
3. Appendices

The main section of the Guide, the validation lifecycle, focuses on high purity water systems.

The Guide describes two approaches to the commissioning and qualification of pharmaceutical water and steam systems. The two approaches share common activities until the completion of the C&Q stage, where the validation lifecycle is divided into two tracks:

- Track 1 describes a traditional qualification approach
- Track 2 described a QRM approach

The two tracks recombine at the sampling stage of the validation lifecycle, from which commissioning and qualification activities are again common to both approaches.

Information and references are given (mainly in Appendices) on lower grade process water and types of pharmaceutical steam.

The Appendices provide additional material and guidance in order to assist in the identification of regulations, issues, and topics that should be considered.

1.7 Key Concepts

Key concepts and principles of a global implementation as used within this Guide include:

Critical Aspects

Critical aspects of manufacturing systems are typically functions, features, abilities, and performance or characteristics necessary for the manufacturing process and systems to ensure consistent product quality and patient safety.

Critical Quality Attribute (CQA) (ICH Q8(R2))

A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure product quality.

Attribute of the water or steam product which usually relates to the identity, purity, or quality of the water or steam product. Some attributes for water and steam are contained levels of Total Organic Carbon (TOC), conductivity, microbial activity, etc.

Critical Process Parameter (CPP) (ICH Q8(R2))

A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces desired quality.

Qualification (ISO)

The process to demonstrate the ability to fulfill specified requirements.

Verification (ISO) (1) (ASTM) (2)

(1) Confirmation, through the provision of objective evidence that specified requirements have been fulfilled. (2) A systematic approach to verify that manufacturing systems, acting singly or in combination, are fit for intended use, have been properly installed, and are operating correctly. This is an umbrella term that encompasses all types of approaches to assuring systems are fit for use such as qualification, commissioning and qualification, verification, system validation, or other.

Quality (ICH Q6A)

The suitability of either a drug substance or drug product for its intended use. This term includes such attributes as the identity, strength, and purity (from ICH Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances) [18].

Quality by Design (QbD) (ICH Q8(R2))

A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.

Quality Risk Management (QRM) (ICH Q9)

A systematic process for the assessment, control, communication, and review of risks to the quality of the drug (medicinal) product across the product lifecycle.

System

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

Commissioning

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

The term commissioning is used within this Guide to describe the GEP activity used to provide documented evidence that a system is installed and operates to meet the specifications.

Validation Lifecycle

Listing of a series of events within the life of a direct impact manufacturing system which are identified as important to create or maintain product quality over the life of the direct impact system when using traditional C&Q methodology.

User Requirements Specification (URS)

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.

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.

2 The Validation Lifecycle

Water and steam systems usually start off as capital construction projects.

Many tasks in a validation lifecycle and a project lifecycle are similar in timing and scope. The phases within a project lifecycle and the interdependencies and interrelationships between lifecycle components need to be understood in order to understand the concept of a validation lifecycle.

Both cycles are optimized when activities are appropriately coordinated in an approved manner to eliminate unnecessary duplication of testing efforts and reporting.

One of the key elements of science and risk-based management is the determination of CQAs and CPPs. This also has been proposed for traditional C&Q.

The primary focus of this Guide is on commissioning and qualification, or verification with discussion of the major phases, including:

- Project Initiation (Feasibility and Conceptual Development)
- Requirements Definition
- Project Delivery Planning
- Initial Risk Assessment
- Specification and Design
- Procurement and Construction
- Commissioning and Qualification, or Verification
- On-Going Operations
- Maintaining the Qualified State over the System Lifecycle

Further details of these phases are given in Table 2.1. In general, the following sections are arranged in order of the validation lifecycle elements for direct impact water and steam systems.

Table 2.1: Typical Validation Lifecycle for Water or Steam Systems

Engineering and Validation Project Requirements Defined Tasks	Project Initiation (Feasibility and Conceptual Development)	Design (Basis of Design and Detailed)	Procurement and Construction	Commissioning, Qualification and Project Closeout	On-Going Operations
Project Delivery Planning - Project Team Organization - Responsibilities - Cost Controls and Schedule - Design Management, Procurement, Construction and Testing Plans - Project Validation Plan	X Preliminary planning	X Full project delivery plan by end of basis of design	X Procurement and construction plans tracked and managed	X C&Q and close-out plans tracked and managed	
Process User Requirements Definition Initial Critical Quality Attributes and Critical Process Parameters	X				
Design Phase Items - URs - Design (conceptual and detail) FDS - DDS - Safety Review - System Level Impact Assessment - Component Level Impact Assessment - Final CQAs and CPPs - Quality Risk Assessment/Critical Aspects List - Design Review (DR) (DQ for Q7A Facilities or as defined in Annex 15 to the EU Guide to Good Manufacturing Practice)	X Feasibility and conceptual design	X Basis of design and detailed design	X Early procurement activities linked to detailed design completion		
Commissioning and Qualification Plan Project Commissioning and Qualifications Plan Development (Verification Plan)		X			
Procurement and Construction - System Fabrication and Construction - Supplier Documentation/ Generation of Turnover Packages (TOPs) - Supplier Documentation and Material Certificate Review			X Procurement and construction plans delivered		
Commissioning - Factory Acceptance Test (FAT) - Start-Up Activities - Commissioning Activities (IV/OV) - Standard Operating Procedure (SOP) and Maintenance Development - Sampling - Training				X C&Q plan delivered	

Table 2.1: Typical Validation Lifecycle for Water or Steam Systems (continued)

Engineering and Validation Project Requirements Defined Tasks	Project Initiation (Feasibility and Conceptual Development)	Design (Basis of Design and Detailed)	Procurement and Construction	Commissioning, Qualification and Project Closeout	On-Going Operations
Qualification - Qualification Protocol Development (IQ, OQ, PQ) - IQ Execution - OQ Execution - PQ Execution (may be negated by PAT) - Qualification Final Reports - Verification Testing and Performance Testing Replace C&Q for QRM				X C&Q plan delivered	
Project Completion and Document Delivery - Project Handover and Closeout - Project Learning Review				X Project close-out plan delivered	
On-Going Quality Monitoring - Water Chemistry - Micro - Endotoxin - Facility Specific Quality and Business Parameters - Continuous Improvement					X
Periodic Performance Evaluations					X
Maintaining the Qualified State over the System Lifecycle - Determine Need Based on Project Change Level or Periodic Performance Evaluation - Depending on Situation; may go back to URs					X

2.1 Project Delivery Planning

Project delivery planning activities incorporate initial key tasks which can affect the success of a project to install a pharmaceutical water or steam system. These key tasks include:

- Project team definition
- Responsibilities of project team members, including Engineering and the Quality Unit (QU)
- Engineering and QU change controls
- Planning of each part of the project lifecycle
- Schedule development and project cost controls
- Documentation requirements

- Approvals both within and external to the project team
- Project risk assessment and management

For pharmaceutical water and steam systems, project teams may include:

- In-house engineers and system operators
- Contracted Architect and Engineer (A&E (the design authority))
- Equipment suppliers
- Third-party inspection personnel
- QU personnel
- Construction contractors
- Commissioning and qualification consultants
- Maintenance personnel

The project delivery strategy should define the need for active participation by project team members throughout the project lifecycle, typically through the use of Responsible, Accountable, Consulted, Informed (RACI) Charts or a similar responsibility matrix. The roles, responsibilities, and effective communication of project team members should be understood.

Change management programs should be established at the start of a project. Elements of conceptual design and the basis of design (also called front end design), may be managed under change control. Detailed design engineering activities are, typically, under engineering change management. Although Design Review (DR) can occur throughout the design process with compliance to QbD, approval of Enhanced Design Review (EDR) usually signifies the transition from Engineering Change Management (ECM) to QU change management.

The ISPE Good Practice Guide: Project Management for the Pharmaceutical Industry [17] describes the typical activities during project delivery planning and typical tasks in each of the stages of the project lifecycle.

The ISPE Baseline® Guide: Commissioning and Qualification [19] and the ISPE Good Practice Guide: Applied Risk Management for Commissioning and Qualification [1] describe typical commissioning and qualification documents, roles, and responsibilities that may be appropriate for many systems. Information provided in this Guide is based on these ISPE documents, but adds additional information that relates more specifically to water and steam systems.

The role of the QU is to ensure that an organization's quality system is established and appropriately utilized in the management of GMP activities. The role of the QU includes ensuring that staff is qualified for their roles, and that the appropriate reviews are used. The QU should review and approve, as a minimum:

- Requirements that influence product quality, and/or the assurance of product quality, and acceptance criteria
- Plans to demonstrate the above requirements have been achieved.
- Results that demonstrate the above requirements have been achieved and a conclusion that systems are fit for intended purpose and ready for next steps (e.g., process validation)

2.1.1 Documentation

This Guide provides guidance on the types of documents normally created during a water or steam project. The possible role of QU approvals on specific documentation during the commissioning and qualification portions of the project is also discussed. When referencing documentation from one project phase to another (e.g., commissioning work being referenced in qualification), the QU's approval may be sought for the specific test case being referenced.

There also should be QU involvement whenever any document that the QU previously approved should be changed. For all other changes, the project team should have an established project document change management procedure.

Turnover Packages (TOPs)

A risk analysis should be completed early in a project to determine the documentation requirements for equipment, components, or systems. Based on this risk analysis, facility owners should approve the turnover requirements. The turnover requirements document should detail the TOP requirements and responsible personnel. Each project may have unique requirements for TOP documentation.

A sample turnover package is in Appendix 7.

TOP requirements should be included with the equipment or system procurement documentation. Equipment or system suppliers should submit a plan for execution of a TOP for approval by the facility owner.

Information TOPs are typically created for facility owners by project personnel; these documents contain information generated during project execution, which will be used to commission, qualify, validate, and maintain the facility. Projects may consist of multiple systems, which could be commissioned and qualified at separate times.

2.2 Design Phase Items

The design phase of either a water or steam project should follow a project information development process and be appropriately documented. These documents may include the URs, the Functional Design Specifications (FDSs), and the Detailed Design Specifications (DDSs). Depending on the proposed project execution strategy and size of project, these documents may be combined.

Technical requirements which are identified by users, but which are not related to water/steam quality generation or maintenance should be tested as needed. HSE considerations, IT, or other non-product quality related items should be documented to meet local requirements. This may occur as part of the turnover packages, commissioning test plans, or reports.

2.2.1 User Requirements (URs) or User Requirement Specification (URS)

URs should describe requirements of the pharmaceutical water or steam system in terms of product to be manufactured and distributed. The URs should describe the source of the feed water, the output quality and quantities required, and operating and maintenance requirements.

URs should specify what the GMP water or steam system is required to do. Items recorded in the URs should be verified.

URs are usually brief documents; revisions to the URs should be made through a formal change management system to help to ensure that the project team is aware of any changes.

URs should provide a briefing document² to the system designer. The URs should be maintained as lifecycle documents. The URs should be approved by appropriate parties to ensure agreement on project needs. Where possible, URs should be finalized prior to the start of detailed design. Revisions to the URs should be avoided once the detail design has started to avoid costly and time-consuming changes.

URs should be used as a reference during the design review/design qualification process to ensure that the design satisfies user expectations. The results of the design review/design qualification process should be summarized in a DR (design qualification) summary report.

2.2.2 **Functional Design Specification**

The FDS should specify **how** the GMP water or steam system will perform required functions. The FDS may be one or more documents. Typically, the FDS is preceded by procurement and installation. The FDS should be tested or verified during commissioning.

The FDS should include requirements such as:

- Specific capacity and flow of the water or steam system
- High purity water generation system feed water quality
- Alarms and messages
- Point of use: water flow, temperature, and pressure
- Sanitization techniques to be used in the storage and distribution system
- General Human-Machine Interface (HMI) layout
- Process control system strategy including input/output and interlock configurations
- Electronic data storage and system security

(For further information, see GAMP® 5 (Appendix D2) [20]).

2.2.3 **Detailed Design Specification (DDS)**

The DDS is a set of documents that specify a system, and includes the component and construction specifications and associated drawings for the GMP water or steam system.

It is considered good practice to define which drawing will be used as the compliance reference document – usually a Process Flow Diagram (PFD) or Process and Instrumentation Diagram (P&ID); other drawings may then be categorized as engineering reference drawings, e.g.:

- If sloping of pipework is defined as critical to quality, the isometric drawing also may be considered a compliance reference drawing.
- The mechanical floor layout drawing may be considered a compliance reference drawing.

The DDS should describe the construction and required control logic to ensure that the design can produce a system that will provide a reliable delivery of water or steam to end-users. The DDS may include:

² i.e., a “brief” description of the proposed water system enabling discussion of the future system.

- Materials used to build the water or steam system that will ensure continuous quality water or steam³
- Pump, heat exchanger, storage vessel, and other field component/device specifications, including critical instruments
- The definition of the installation requirements for equipment⁴
- Documentation requirements for the system:
 - Materials/construction specifications
 - Construction inspection requirements
 - TOPs requirements
 - Documentation requirements
 - System commissioning requirements
- Storage vessel vent filter operation (e.g., electrically heat traced versus steam heat traced)
- Treatment system description (i.e., process flow sheet, etc.) in relation to source water quality and seasonal variations
- Electrical drawings; these drawings should allow both a construction check and fault diagnosis throughout the system
- Hardware specification; architecture and hardware of the control system (see GAMP® 5 [20])
- Redlined P&IDs

Depending on the quality of the system feed water, water generation systems usually require unique items to meet the user requirements completely.

2.2.4 Quality by Design (QbD) Considerations

The FDA has encouraged QbD based on using PAT as the means to control the production of a product. TOC and conductivity measurements can be used for online monitoring, but are not typically used on control loops. Online microbial detection instruments are available. These instruments can count the microbial colony forming units, but cannot capture and save the microbial colony forming units. USP Standards for pharmaceutical grades of water require that the colony forming units found in the water sampled are incubated and that the colony forming units are identified. Therefore, pharmaceutical water systems cannot constitute a fully PAT system at time of publication.

Water systems should be designed by specialist designers, as the quality of a water system design is critical. The designs should include only items that are known and developed by system users, such as types of instruments, methods of microbial control, or methods of chlorine removal.

Through design qualification, quality has agreed that the proposed design is fit for its intended use. Quality has approved the commissioning and qualification plan, confirming agreement with the process, personnel, and documentation standards expected results and acceptance criteria. The work is conducted following GEP, associated documentation standards, and change management processes.

³ Were alternative materials to be used, problems with contamination, corrosion, or leachables could occur.

⁴ Incorrect installation of equipment, such as reverse osmosis units or other de-ionization equipment, could lead to damage or problems with equipment performance.

At the completion of the operation verification a brief commissioning summary report should be produced by an independent engineer (i.e., not the engineer responsible for the commissioning) to confirm that the documentation is acceptable and demonstrates that the system is installed and operates to meet the specifications; any changes from the agreed design should be managed through the management system. Approval of this document by quality releases the system to have the qualification summary report completed.

2.3 Commissioning and Qualification Plan

The C&Q plan may be generated at the conclusion of (or concurrent with) the project design phase. There may be benefits in defining the commissioning and system validation strategy prior to the start of detail design.

The approach used may influence the content and structure of the detail design documents – for example, the specifications may incorporate the supply, construction, as well as the commissioning and qualification requirements for the system.

The C&Q plan should define the activities and responsibilities that make up the commissioning and qualification of a system (or components of a system) within its operating environment. It should include the:

- Project scope definition and/or system boundaries
- The approach to be used and the document deliverables
- Minimum required documentation deliverables and personnel/SME responsibilities
- TOP requirements
- Identification of the group which should receive documentation (validation, facilities, engineering, manufacturing, etc.)

The C&Q plan should focus on the transition from commissioning to Performance Qualification (PQ) in order to maintain the system in a satisfactory state for qualification, e.g., maintenance and sampling. The C&Q plan may be divided into two separate documents.

Frequently, an overall validation master plan describes the validation strategy for a complete process facility. The C&Q plan is generated and used to describe commissioning and qualification for a specific system (i.e., WFI system, process nitrogen system, etc.)

C&Q plans should be cost effective. The development of C&Q plans for pharmaceutical water or steam systems should be considered to ensure that responsibilities are clearly defined and activities, which impact final water or steam quality, are included and commissioning activities are not unnecessarily repeated during qualification.

The QU should be involved with development of the commissioning and qualification plan.

The design of pharmaceutical water systems is usually based on the average and instantaneous quantity and quality (or different qualities) of water required by an end-user. Sampling (whether on-line using PAT or off-line) of the generation and distribution system should be dictated by the design and address any risks identified through applied risk management for C&Q and also address any regulatory expectations. It is considered good practice to sample the system as soon as it is made operational in order to obtain an understanding of its operating characteristics.

2.4 Procurement and Construction

Procurement activities should ensure that purchased equipment complies with the specifications created during the project design phase with any variations from the specifications reviewed and accepted or rejected by the design authority⁵ and organization.

A user/an owner/user that has a lot of experience with local installations can add a lot of value during the procurement and construction stage – suggesting changes/improvements based on that detailed experience.

The most efficient process will not repeat tests, unless there is a logical reason to do so – e.g., reconfirming control wiring is correct after it has been disconnected for shipping purpose, then reconnected.

In addition to the traditional approach of purchasing, installing and operating a water and steam system, organizations also can contract for the supply of water from a third party that installs, operates, and maintains the system, generally charging based on the utility consumption. The utility consumption should be discussed prior to the Project Delivery Strategy Phase which is the first stage in procurement planning. This is a risk based decision function. Refer to the ISPE Good Practice Guide: Project Management for the Pharmaceutical Industry [17] for general procurement principles, if needed.

A generation system can be purchased from a specialist supplier and the procurement, installation, and quality control of the storage and distribution system project managed within an organization. Alternatively, a complete installation of the storage and distribution system can be purchased from a specialist contractor.

An assessment of supplier Quality Management System (QMS) can allow organizations to use appropriate supplier data to support commissioning and verification, potentially reducing the scope of FATs/Site Acceptance Tests (SATs).

The commissioning strategy should incorporate the results of any supplier assessments, and define both the receipt and installation verification approaches, and the calibration strategy to be used within a project.

Procurement specifications should define:

- Roles and responsibilities for a construction
- Related quality control activities during construction
- Performance and/or timeline based payment schedule

Installed systems should have documentation that is acceptable to the owner or the owner's representative.

Installation verification should provide documented evidence that installed equipment complies with design specifications and incorporates agreed engineering changes.

The completion of procurement and construction is usually identified through the review and acceptance of construction TOPs.

2.5 Commissioning and Qualification

This section of the Guide is intended to indicate project activities or items typically included in the commissioning of compendial water and steam systems.

⁵ For example, the project designer's representative and the organization's representative.

The process of commissioning should provide documented evidence that will ensure that the system owners or systems users receive a system that can produce or deliver a supply of water or steam in a manner that is consistent with the system owner's requirements.

Once the commissioning process has started, an approved change management system should be established in order to control, capture, and document changes to compendial water and steam systems.

2.5.1 Start-Up Activity

A system release memo should be prepared and submitted before beginning start-up, commissioning, or validation. The memo should include the pre-start-up safety report.

Before starting the main activities for commissioning, a walk down inspection (possibly via a check list) of a system should be performed. Responsible personnel should be notified of any problems observed in:

- General cleanliness
- Visibly sagging or unsecured piping/tubing especially of indirect impact system utilities
- Disconnected piping/tubing
- Improper air breaks to floor drains
- Disconnected wiring/pneumatic lines
- Disconnected/broken instruments
- Disconnected/broken valves
- Disconnected/broken pumps
- Leaks
- Threaded fittings in hygienic piping/tubing systems
- Lack of identification for process piping or system components
- Dead legs

2.5.1.1 Safety Reviews and Checks

Prior to system start-up, several safety reviews and checks should be performed on the compendial water or steam system, including:

1. A safety review of ports to be sampled to ensure that sampling technicians have the appropriate Personal Protective Equipment (PPE) needed to safely take samples.
2. A safety review of the equipment to ensure that the mechanical associates have the appropriate PPE needed for the safe operation of the equipment. The owner and/or owner's representative should provide authorization before turning on the utility supplies to the system (electricity, water, compressed air).

3. A documented check that the system is in a safe condition. The procedures and scope of this check usually depends on the project, but would typically include a safety focused document check, e.g.,
 - Hydraulic or pneumatic pressure testing completed satisfactorily
 - System valves in the specified condition, i.e., open or closed
 - Warning labels and signage is in place
 - Insulation review
 - Relief devices check

A walk down of the electrical connections should be performed by an SME or authorized person to ensure that they are acceptable to the owner or the owner's representative and that fuses/overload ratings are as specified.

2.5.2 Commissioning Activities

The commissioning process usually begins when construction of a water or steam system nears completion. System components are put into operation through a series of engineering activities. This work is usually defined in a documented commissioning plan.

Throughout the commissioning process, the principles of GEP (see the ISPE Good Practice Guide: Good: Good Engineering Practice [9]) should be applied when putting system components into operation. GEP principles include:

- Compliance with pressure vessel codes
- Electrical codes
- Plumbing codes
- Other local building codes and practices

Pharmaceutical water and steam systems require commissioning prior to operation.

The following is a representative list of typical commissioning activities that bring pharmaceutical high purity water systems into operation:

- Walking down and checking that P&IDs, general arrangement, and isometric drawings are representative of the installed system.
- Checking system for maintainability, e.g.,
 - Verifying that components (such as pumps, vent filters, gasket replacement, gauges, and sensors, etc.) that will require maintenance and/or calibration have sufficient room for mechanics to safely service components.
 - Checking that all the parts to be replaced during preventative maintenance are clearly identified.
- Checking that installation records (i.e., construction turnover packages, etc.) for the system equipment and components have been created. In addition, check vessel internals for items such as sprayballs and vortex breakers.
- Checking that the water system has been installed in accordance with the design, installation drawings, and that planned backflow prevention (including air breaks for drains) equipment has been adequately installed.

- Checking that the pipe flushing with soft or de-ionized water to remove construction debris, or use of mechanical cleaning methods, as necessary, and have been verified as complete and documented properly. **Note:** in-line filters and/or strainers that had been installed during the flushing phase, but are not part of the permanent installation should have been removed after the flushing phase and this should have been documented.
- Checking that the pipe system pressure (i.e., hydrostatic or pneumatic) tests and have been verified as complete and documented.
- Checking that the cleaning and passivation of stainless steel equipment and piping systems and have been verified as complete and documented.
- Checking that a documented and approved material joining program (e.g., welders certificates, procedures, isometric drawings, and non-destructive tests including joining of metals used on “product/process contact surfaces”) has been used during construction of the system and that appropriate joints have been examined/inspected (e.g., per ASME BPE [21]).
- Checking that specified piping/tubing material was received and installed, as specified.
- Checking heat numbers of materials (if applicable). Polymer materials, such as PVDF and PP, should be documented by conformity declarations, which would be joined by welding.
- Checking received materials of construction versus materials specifications for components (e.g., instruments), which will be in direct contact with the compendial water or steam.
- Checking that the piping/tubing system specified to be sloped and drained was constructed to achieve drainage to low points. High purity water systems should be sloped to aid in drainage of the systems. It may not be possible to slope some sections of piping/tubing. These sections should be identified on the drawings. Alternative methods (i.e., blowing with air or removable spool pieces) may be used in these areas of piping to achieve required drainage.
- Checking that instrumentation loop checks have been performed.
- Checking that instrument inspection and calibration was performed per the specification and according to the manufacturer’s recommendations.
- Testing “usability” of each sample point, by use of correct sample bottles (size and volume).
- Confirming that area ergonomic conditions (i.e., acceptable ventilation, sample point access, etc.) are suitable to conduct sampling. Inadequate area ventilation can lead to water sample contamination. Samples should be taken in the same way that the port is going to be used.
- Checking that a master list was created between non-critical and critical instrument components, see elsewhere in this section of the Guide or the ISPE GAMP® Good Practice Guide: A Risk Based Approach to Calibration Management (Second Edition) [22].
- Performing start-up and checks of support utilities, electric power, pump motor run, and pump hot alignment and lubrication checks.
- Checking for adequate pressure and fluid flow per design within the system, including sprayballs operation.
- Checking the high purity water generation system feed water flow, quality, pressure, and temperature.

- Performing tests to confirm specified operation of the unit operations in pretreatment and final treatment, including shutdown, start-up and alarming. Included in these tests are specific automation system tests, e.g., valve sequencing, interlocks, loop tuning, and connections between water systems and process systems (i.e., connection to glass washer or other processing pieces of equipment). This data can be compared to the FAT to determine system performance.
- Performing tests to confirm the operation of heating and/or cooling exchangers that may exist within the water or steam system (i.e., run hot water sanitization cycle and cool down for operation after sanitization).
- Performing system safety tests (i.e., relief, emergency shutdown, continuity, etc.)
- Checking that applicable construction codes (pressurized equipment, electrical, mechanical codes, etc.) and building permit conditions have been followed including seismic and electrical/electromagnetic fields (EMF) requirements.

A TOP should be created so that initial system operating and maintenance tasks may be performed.

TOPs may be created on a “by system” basis to allow systems to be commissioned in an organized fashion within a larger facility construction project. **Note:** in Europe, a technical dossier, describing the system/equipment, is required to cover the same items recommended in this chapter of this Guide. If the technical dossier is not present, the system is of “less” use.

Typical items, which contribute to product quality are confirmed during commissioning or qualification may be:

2.5.2.1 “As-Built” Drawings

Drawings can depict flow of materials, critical features, or sampling locations. Drawings issued for construction may include submittal drawings (for approval), P&IDs, equipment drawings, and PFDs.

Approved “as-built” drawings should verify features which may be relevant to product quality or maintenance. Components shown on the drawings should be physically inspected (field verified) to confirm that the drawings accurately reflect features such as:

- Appropriate installation
- Tagging
- Location
- Direction of flow
- Sample Point of Use (POU) location
- On-line quality monitoring devices or other instrumentation in the process flow

Typically, an organized set of “as-built” drawings which include isometric drawings is created for high purity water or steam systems. Where modifications are planned for a system, “as-built” isometric drawings can be used to determine the correct technique to drain the system. “As-built” designated drawings should be signed-off by the owner or owner’s representative and made available to the owner or owner’s representative.

Example 1: Sample POU Drawing

A drawing should show sample points and all POU’s in a system. It should show all sampling points and their designation/identification for the purpose of commissioning the system and so that the chemists or microbiologists know where to collect the samples.

Example 2: P&ID Drawing

A P&ID drawing should show the sequence of equipment, which can directly impact product (water) quality, and key piping and instrument characteristics, such as:

- Materials of construction
- Line sizes
- Valve types
- Nozzle orientations
- Piping “unique identifier” labeling
- Materials of construction
- Insulation
- Flow direction

2.5.2.2 Equipment or Piping Component Installation

Water and steam generation and distribution equipment should be installed so that the equipment functions per design. Checks should be performed to confirm whether equipment (e.g., reverse osmosis units, stills, pure (clean) steam generators, and continuous de-ionizers) is installed per design. The installation should be compared to construction drawings and specifications. Any discrepancies between the design and the installation of water and steam generation and distribution equipment should have a documented assessment to determine the impact on the water or steam quality and/or the need for modifications based on the assessment.

For equipment and piping components, as-found conditions should comply with installation drawings and specifications.

2.5.2.3 Welding and Other Material Joining Procedures and Documentation

Welding or other material joining techniques, such as (ASME BPE [21] section on material joining) and documentation is required. The weld procedure should be pre-approved by the system owner or the owner’s representative (e.g., the third party inspector) before execution of the weld procedure.

Appropriate welding or other material joining methods and procedures and documentation practices should be established and used for all applicable piping/tubing components.

Many high purity water and pure (clean) steam systems are largely constructed of 316L stainless steels (DIN 1.4435 and/or DIN 1.4404). Where appropriate, plastics and other metals may have been used for these systems.

An appropriate welding or material joining program should be defined prior to construction activities and as a minimum, include:

- Routine inspections by qualified or certified SMEs throughout installation to verify that requirements are being met.
- A defined weld or material joint inspection program. This should be performed for all applicable piping and tubing in the high purity water or pure (clean) steam system.

For example, for high purity water distribution systems constructed of 316L SS, weld joint quality is typically determined based on internal and external features of completed welds. (See Section MJ of the ASME BPE [21], or the EN ISO 3834 standard [23], to determine documentation requirements. See BS EN ISO 9712 standard [24] to determine third party requirements).

Examination of all external welds (both manual and automatic machine) is normally performed by the installer of the piping/tubing system. Examination reports should be completed by the installer on weld log sheets. Internal welds may be inspected by indirect visual methods (i.e., borescopic or using mirrors) by the system owner or the owner's representative at a typical minimum of 20% of total daily completed welds for automatic machine welds and 100% of daily completed manual welds. For welds produced by an automatic machine, the number (or percentage) of daily internal welds inspected may be increased based on the number of rejected welds. See the European Pressure and Machinery Guidelines (EU PG) [25] for pressure and x-raying of welds for pure (clean) steam lines which may require special safety requirements.

- Labeling of welds or other connections and appropriate inspections during construction. Inspection reports should be included with supplier documentation.
- A weld map drawing showing weld locations. The heat numbers of metals joined on either side of a weld should be included in weld logs. The heat numbers should be traceable to material certificates of analyses. (The "heat number" corresponds to the chemical composition of the material (i.e., 316L SS or similar grade such as DIN 1.4435 or DIN 1.4404) used to construct the system. The "heat number" map should include product/process contact surfaces of tubing, valves, fittings, etc.)
- Review of the qualification records of welders. The qualification records of a welder should be adequate prior to the welder performing any work. The qualification records should be included in TOPs. EN 287-1 [26] and EN 1418 [27] can be used as a guide to determine welder certification requirements.
- Verification should be obtained that approval signatures (including installation contractors, owner, or owner's representative) have been provided on weld documentation, including the weld maps.

2.5.2.4 Materials Certification

Materials used to construct water systems should preserve the quality of the water or steam product. Materials should be used that are "not reactive, additive, or adsorptive" to the water or steam product. Engineers that design systems may specify materials, e.g., metals, plastics, or elastomers, which should ensure the quality of water or steam products.

316L stainless steels and non-leaching plastics/elastomers are typically specified for high purity water and pure (clean) steam systems. Other materials also may be used. Although the surface of these materials is usually included in a piping component material specification, material surface finish is not, typically, critical to water quality maintenance.

2.5.2.5 Line Slope

Line slope in water and steam systems is a GEP activity. (See Section SD of the ASME BPE).

The usefulness of line slope can vary depending on the type of system, e.g.,

- In pure (clean) steam distribution systems, sloping of distribution lines is intended to prevent "cold spots" (where condensate may collect) or preserve the physical properties of pure (clean) steam delivered to a point of use.
- In one-way high purity water distribution systems where pure (clean) steam is used for sanitizations, sloping is intended to achieve adequate system sanitizations.

- In re-circulating high purity water distribution systems, slope verification documentation may be “non-value added,” because the system is continuously recirculated.

Line sloping is usually intended to:

- Aid in system drainage to low points for future system shutdowns
- Assist in the removal of passivation chemicals

Re-circulating high purity water distribution systems are not usually drained, but if they are, air can be used to supplement the system drainage procedure. Where re-circulating high purity water distribution systems are shut down and drained, they are usually flushed and sanitized before being put back into service.

For the Detailed Design Specification (DDS) development, engineers should make a determination whether line slope verification should be included in the project, based upon requirements and risk assessment. The line slope verification can be verified using a calibrated level device and documented on the isometric drawings. Slope verifications should be performed prior to the addition of any insulation.

For systems where commissioning has been deemed necessary, the acceptance criteria are that “as-built” isometric drawings that indicate the slope are available and that an approved slope measurement procedure has been used. Suppliers and engineering departments should produce slope information.

If line sloping is for GEPs, commissioning should be performed to verify the extent of line sloping included in a project. Organizations may choose to install piping/tubing level and plumb, e.g., where line sloping has been determined to be non-value added in relation to water quality.

2.5.2.6 *Hydrostatic Pressure Test*

Water or steam systems should be free of leaks, which can lead to contamination of the water or steam. From a system operating consideration, hydrostatic pressure tests should be performed and documented. Water (e.g., softened water) used for hydrostatic testing of high purity water systems should be of appropriate quality to avoid the introduction of contamination, which could cause problems during construction or start-up.

Hydrostatic pressure tests may be conducted in selected sections of the system, such as sections of piping that can be isolated and pressurized at varying times during construction. Tests can be performed by making reference to a particular section of the system P&ID. For further information on the requirements for hydrostatic pressure tests, see ASME B31.3 [28].

2.5.2.7 *Cleaning and Passivation*

Product contact surfaces should be maintained in a passive condition (by passivation) in high purity water and pure (clean) steam systems to help to maintain the quality of water or steam.

Passivation usually involves introducing an acid solution into the system to remove elemental iron and to maintain or enhance the chromium to iron ratio of a weld and produce a passive layer on the surface of the metal. Completed welds should undergo passivation procedures. The first step of a passivation procedure is usually a chemical cleaning process to prepare the metal of the completed weld for passivation. Specified cleaning and passivation procedures should be followed and documented. Documentation usually includes:

- Cleaning and passivation procedures
- Cleaning agents used
- Cleaning temperature and times

- Passivating chemical solutions used
- Temperature and contact times
- Identification of line sections
- Components passivated
- Approval signatures

Cleaning and passivation activities may be delayed to:

- Prevent the need to repeat cleaning and passivation steps if piping or tubing modifications are needed during start-up and commissioning
- Provide a chemical sanitization just prior to the start of water quality testing

The project team should plan when to perform the system cleaning and passivation, which may be performed sequentially on specific segments of equipment or piping/tubing sections.

Cleaning and passivation of a system should be performed only on an as need basis.

For further information on passivation, see ASME BPE [21] and ASTM A380 [29].

2.5.2.8 Vent Filters

Vent filters are used on high purity water storage vessels as a particulate and microbial barrier between the surrounding environment and the water. Pressure safety devices (i.e., rupture discs, etc.) should be used to protect against vessel over-pressurization.

A method should be identified for replacing vent filter cartridges (e.g., Steam-In-Place (SIP) with pure (clean) steam or autoclaving the filter in its housing prior to installation so that it does not contaminate the system). The process should be documented.

Vent filters (e.g., 0.2 µm) are suitable for microbial retentive gas filtration. Areas of concern for gas filtration are blockage of the filter caused by condensed water vapors or leakage caused by improper filter installation or defective filters.

Control measures to avoid accumulation of condensate vapors in the vent filter housing include:

- Electrical or steam heat tracing
- A self-draining housing orientation
- Placement of the housing at a distance far enough from the tank such that vapors do not accumulate

Where heat tracing⁶ (such as electric jacket or steam) is used, the temperature should be set above the normal operating temperature of the water in the storage vessel so that the temperature is above the dew point temperature and below the manufacturer's maximum temperature rating for the vent filters.

⁶ Heating by flexible electric heating elements.

Vent filters should be constructed of specified and verified materials. They should be integrity tested in the housing prior to initial use and periodically thereafter. Regular visual inspections and testing procedures should be performed, including post integrity testing in the housing after removal.

Post integrity testing can be used to verify that the filter is not plugged or has not been leaking at the time the filter is removed from service. Post integrity testing can provide assurance that preventative maintenance schedules and procedures are appropriate. Filter integrity testing methods include:

- Bubble point
- Diffusion
- Water intrusion

Filter integrity testing methods can vary, depending on the filter manufacturer, application, and type of filter.

Vent filter integrity testing equipment may not be available at some “non-sterile” product manufacturing sites. Acceptance of a supplier certification of vent filter integrity may be considered sufficient based on an audit of the supplier’s manufacturing site and QMSs.

Commissioning documentation should contain information that confirms that the method selected for avoiding condensation is appropriate, that the filter orientation allows for drainage and that the filter integrity testing has been performed and successful results have been obtained.

2.5.2.9 *Support Utilities*

It should be determined whether support utilities are critical or non-critical systems. These utilities (i.e., instrument air, drains, power, cooling water, plant heating steam, etc.) should be commissioned. These systems should be connected to critical components in accordance with specifications (i.e., the URs).

Other system utilities (i.e., compressed air blow, N₂ blanket, etc.) may be required for use in the compendial water or pure (clean) steam system.

2.5.2.10 *Loss of Utility*

This test can be specifically planned for systems based on the likelihood of occurrence and potential water or steam quality risk. A risk assessment on the loss of utilities should be performed at the beginning of the project and documented. This should include the proposed testing to be performed or why testing does not need to be performed. The risk assessment should be approved by the system owner. The commissioning plan should include a strategy on how the system will be restored to service after loss of utilities, such as whether the system will need to be drained, flushed, sanitized, steam sanitized, or passivated, how it will be released for use, and who will release it for use.

The system’s response to loss of support utilities to the generation equipment and distribution system should be investigated. Response to loss of electrical power should be considered. This includes retention of critical data, as well as safe equipment and system response.

Equipment and system responses to loss of other utilities (e.g., compressed air, hot/cold process water, glycol, and nitrogen) should be documented to ensure that adequate protection is provided in the equipment and system design.

For short down times (i.e., due to loss and resumption of a given utility), equipment and system behavior should be adequate to prevent contamination of the system. Except for system specific extended downtime periods, a procedure for loss of electrical power should be developed, including the steps to perform in the event of a power loss. Upon power being restored, the system should automatically return to the service mode/cycle.

A procedure should be developed based on the loss of a utility. The procedure should identify the time period for which a system may go above or below CPPs without experiencing water quality issues. For example, a high purity water system where temperature (which was deemed to be a CPP) decreases for a short time (minutes or few hours); water microbial quality is not affected.

Sampling is a way to determine the effects on the system if support utilities are lost for any period of time. Water quality risk should be considered, when determining sampling requirements to put the system back into operation after loss of utilities.

Loss of utility tests may be combined with initial PQ activities in an effort to finalize system SOPs.

Loss of utility tests, such as electrical power or instrument air, may take into consideration its impact on water quality and a requirement to sanitize the system in the event of loss of a utility.

2.5.2.11 Automated Control System

Each component required for the control system should be installed and commissioned according to specifications. Verification testing for the control systems for computerized or PLC automated equipment/systems is governed by guidelines, which are specific to the type and manufacturer of the controlling system. For further information, see the ISPE GAMP® Good Practice Guide: A Risk-Based Approach to GxP Process Control Systems (Second Edition) [30].

2.5.2.12 Automated Control System Operation

Performance testing of the automated control system is an important part of the OQ and/or commissioning phase of the controls. In most cases, the testing is specific to the type of automated control system (i.e., Programmable Logic Controller (PLC) based or computer based). Typical tests to be performed in this section include:

- Alarm is generated for a particular defined alarm condition situation and message is provided.
- “Hard-wired” alarms and switches are functional and appropriately connected. Note: life safety systems are not part of the water and steam systems and are tested and qualified separately.
- Automated control system and set points are adequately guarded by password access or procedural method.
- Automation system has a procedure for generation of critical data and storage, as well as recovery of data.

CPPs should be developed for field devices (including field control panels) to determine whether they are functional. CPP alarms and interlocks of the control system are functional and appropriate password security level or procedure is present.

For further information on the operational verification of the automated control system, see the GAMP® Good Practice Guide: A Risk-Based Approach to GxP Process Control Systems [30].

2.5.2.13 Instrumentation Calibration

All instrumentation being assessed should be assigned an instrument category. This should be determined using one of the four criticalities defined in this section. These should be clearly understood by the representatives before any assessments are made.

Product Critical Instruments

- A product critical instrument is an instrument whose accuracy/failure may have a direct effect on product quality.

Process/System Critical Instruments

- A process/system critical instrument is an instrument whose accuracy/failure may have a direct effect on process or system performance, without affecting final product quality, or safety.

Safety/Environmental Critical Instruments

- A safety/environmental critical instrument is an instrument whose accuracy/failure may have a direct effect on safety/environment.

Non-Critical Instrument

- An instrument whose accuracy/failure is deemed to have no effect on product quality, process/system performance, safety, or the environment.

It should be verified that all critical instruments have national standards (i.e., National Institute of Standards and Technology (NIST), National Accreditation of Measurement and Sampling (NAMAS)), traceable calibration records on file, and that the instruments are calibrated within the appropriate ranges (design, allowable operating, and normal operating) in which they are to be operated.

Calibration should be documented as part of the qualification program. Calibration documentation should include verification that calibration has been completed. Instruments are usually tagged with a calibration date and calibration due date. Critical instruments should be calibrated at the factory and “stress” field/loop calibrated on site.

Non-critical instruments may not be subject to the same calibration frequency and reference standards as critical instruments. However, non-critical instruments should have at least one verified calibration at the beginning of their use, as reference of their condition.

For additional information, see the ISPE GAMP® Good Practice Guide: A Risk-Based Approach to Calibration Management (Second Edition) [22].

2.5.2.14 Sequence of Operation

Sequence of operation testing should verify that the automated control system, software programming, Standard Operating Procedures (SOPs), and equipment and instrumentation operate according to intended design sequences.

Normal functional and cycle testing is intended to confirm and document the ability of system components to function together as a system in a successful manner which simulates normal operation.

The system functionality and sequencing of various modes of operation is dependent on the design of a specific installation. The functional specification or the supplier design specifications should be referenced to determine the functionality and sequencing of the system.

There may be several different automation systems containing sequence of operations that need to be tested (e.g., generation system PLC, storage and distribution control system).

The concept of when these systems will be tested and the documentation needed should be outlined in the commissioning plan. For example, during commissioning the sequence of operations may be completely tested. If the sequence of operations was tested successfully during a SAT or FAT and the test was documented, verification that the test was completed may be all that is needed according to an approved project commissioning plan.

2.5.2.15 Water Generation

Testing should be performed to ensure the ability of a water generation system to:

- Provide high purity water meeting required specifications under peak demand conditions
- Continuously generate acceptable quality product water in a flow range defined in the system URs

The testing should be performed prior to PQ to ensure that the water generation equipment is capable of producing water to meet the required specification. The testing can provide early assurance that extended operation at minimum and maximum demand conditions will not have an adverse effect upon the quality of the product water. Extended water quality testing should be performed during PQ.

2.5.2.16 Water Distribution

The ability of a water distribution system to provide quantities of product water (of a quality specified in the URs), under the variety of demand conditions to POUs, while maintaining specified pressures in the system, should be tested to ensure proper turbulent flow in the system. System design calculations should be checked during the engineering design review (or Design Qualification (DQ)) or design review by an approved system owner representative. The system should be tested during commissioning to verify the calculations.

During these tests, the goal is to gain assurance that the defined worst case usage scenario will not result in potential contamination of the distribution system during minimum and maximum water demand, due to conditions such as:

- Backflow
- Unacceptable pressure differentials across system components (e.g., heat exchangers)
- Distribution water flow which falls below minimum acceptable rates
- Pressures which fall below minimum values

The water distribution system should be capable of maintaining a minimum pressure at all points within the distribution system piping during the peak water demand for the system. Confirmation of turbulent flow in the recirculating loop may be verified during this testing and should include documented verification that the flow rate in the system does not drop below the minimum turbulent flow rate required to prevent bio-film growth at peak demands.

The time periods for heat up, maintenance, and cool down (the time the system is unavailable for use) should be agreed and documented in the URs specification.

During the commissioning, qualification, and TOP phases, plans that define how long periods of inactivity or delays (planned or unplanned) in the different phases will be addressed should be included to monitor the water system quality to ensure that the system is not compromised.

2.5.2.17 Temperature Maintenance

High purity water distribution systems may be designed to remain hot to maintain continuous sanitization of the piping and storage vessel networks. Other systems may be heated on a validated frequency to sanitize the system on a regular basis, allowing the water system to operate at a lower temperature. This lower temperature may be either controlled or uncontrolled.

A system should be able to maintain desired temperatures (hot/cold) at defined sensing points on the distribution system.

Appropriately located temperature sensors should be used to prove that when heat sanitization is required, the water system network can be brought up to the sanitization temperature for the required interval of time. Where pure (clean) steam is used for sanitization, a system temperature mapping test may need to be developed.

Verification that the temperature, frequency, and duration of sanitization are adequate should be confirmed through water quality testing during PQ.

2.5.2.18 Ozone Level Generation and Maintenance

Distribution systems may use ozone (either continuous or intermittent ozonation) as a method to maintain specified microbial levels below appropriate alert levels within the distribution system. For additional information, refer to the ISPE Good Practice Guide: Ozone Sanitization of Pharmaceutical Water Systems [31].

The ozone generation, distribution, and destruction system should maintain required ozone levels, as required for distribution system normal operation and sanitization.

Verification that the ozone levels, frequency, and duration of sanitization are adequate for microbial growth control should be confirmed through water quality testing during PQ.

2.5.2.19 Standard Operating Procedure Development

Approved SOPs for the functioning (including use, maintenance, calibration, sanitization, etc.) of the water system are required. These documents should be developed (in draft form as a minimum) before the commissioning stage so that they can be executed, verified, and updated during the commissioning phase. Approved SOPs are usually required for PQ.

2.6 Track One – Traditional Approach to Qualification

2.6.1 System Level Impact Assessment

This section summarizes the traditional approach to commissioning and qualification described in ISPE Baseline® Guide: Commissioning and Qualification [19], for water generation, water storage and distribution, steam generation, and steam distribution systems.

Note: if the product is compendial water, the system output is typically used to clean manufacturing equipment, or is product ingredient water; therefore, the system will require validation (i.e., has to be verified/qualified with ongoing performance qualification).

The system assessment may follow the process described in ISPE Baseline® Guide: Commissioning and Qualification [19].

A System Level Impact Assessment (SLIA) should be completed before commissioning/qualification to determine if the system is to be validated, i.e., whether it is a direct impact system.

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., pure (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, Distributed Control System (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.

The compliance drawing should define the system boundary and indicate what is included in the system.

Typically, water and steam systems include:

- The entire high purity water generation equipment train with potable (drinking) water as an input
- Storage and distribution piping loops
- A steam generator, which produces pure steam

In a non-GMP application a system would provide support to GMP systems. Examples of these systems include:

- Plant steam fed to a heater used in the GMP system
- Chilled water to a cooler

Potable water (drinking water), along with associated water quality documentation, is required for the feed water to a high purity water generation train. The location in the quality system, i.e., where this feed water quality is documented on an on-going basis, should be identified.

Systems may be identified as no-impact systems or indirect impact systems within the system impact assessment, i.e., system operation does not affect the final water product quality. Examples of no impact systems include:

- Offices
- Elevators
- Building fire protection systems
- Cooling towers
- Sanitary water systems

Examples of indirect impact systems, i.e., those systems that support the operation of a compendial water system, but do not impact the final system product quality (i.e., the quality of the compendial water) include:

- Potable water systems
- Electrical energy systems, which supply power to the GMP pharmaceutical water generation train
- Compressed air systems (used to actuate valves, etc.)

Generally, indirect impact systems are commissioned, but not validated.

2.6.2 **Component Level Impact Assessment**

Components should be shown on piping and instrumentation drawings as “tagged” or uniquely identified items. Typically, components include machinery or apparatus associated with operations or process steps, and instruments.

2.6.2.1 *Commissioned Components*

The approach described in this section of the Guide considers the process steps and proposes documentation and testing approaches based on the potential for a component to impact water CQAs.

Components should be commissioned following GEP. Components which directly impact the system output quality or provide supporting data should also be qualified. Components should be qualified where:

- The process step generates or maintains a system product CQA.
- The instrument produces data that is used to accept or reject the system product.
- The process step preserves system product quality (as defined by the system product CQAs).

Installation and operation should be confirmed to be as specified in qualification documents. Installation and operational qualification documents may be separate documents or may be combined in one installation and operational qualification document.

Critical and Non-Critical Instruments

Instruments can be categorized as critical or non-critical. The level at which non-critical instruments are tracked, maintained, and calibrated (or verified) is typically less stringent than that for critical instruments.

Typical activities and considerations for non-critical instruments include:

- Engineering reviews of instrument application, technology, materials of construction selections, and configuration
- Programs for calibration and maintenance management
- Programs for inspection, tracking, and replacement
- May or may not require a failure analysis of each failure
- Importance of reliability varies depending on function

The maintenance and calibration approach will vary depending on the instrument function. Where an instrument contacts the system product, the materials of construction should be considered.

Instruments should be categorized as critical where:

- The instrument monitors or controls a critical process operating parameter.
- Failure or alarm (and the failure or alarm is not detected by another component downstream in the system) of the instrument will have a direct effect on quality of the system product.
- The instrument is used for the adjustment or calibration of critical components, such as secondary/working test standard.
- Information from this instrument is recorded as part of the product batch record or lot release data.

Qualification Documents

The qualification is meant to ensure and verify that all project activities or components, which can effect water or steam quality, have been:

- Adequately documented during commissioning
- Included in the project scope
- Executed appropriately

A well-developed commissioning plan for a water or steam system, developed with the approval of the quality unit, can make the qualification process more of a verification activity (rather than duplication) of already executed and documented activities.

IQ or OQ protocols can be used to verify (via documentation) that all project activities or items that contribute to water or steam quality have been executed or performed and have been adequately documented during commissioning. If they haven't been verified during commissioning, a separate exercise (qualification) should be undertaken to complete the verification that installation and operation has been completed according to approved design specifications traceable to user requirements.

The QU should be involved in the development of the commissioning and qualification plan to help to ensure that the qualification requirements will be met during commissioning. The commissioning and qualification plan should clearly define documentation standards, acceptance criteria, and expected results.

Qualification activities can be executed during FATs and/or SATs.

For small modifications or changes to a system, it may be possible to eliminate commissioning and capture all of the requirements in the qualification protocol. If this is done, the qualification package should be written such that there is flexibility to make minor changes and adjustments as long as there is QU approval and agreement for the approach that will be taken.

The documents delivered as part of the approach provided in ISPE Baseline® Guide: Commissioning and Qualification [19] include:

- Commissioning and Qualification Plan
- Commissioning Report
- Commissioning Summary Report
- Installation Qualification
- Operational Qualification
- Qualification Summary Report – used to release the system for PQ

2.7 Track Two – The Quality Risk Management Approach

2.7.1 *Good Engineering Practice*

An essential element of quality risk management approach is the use of engineering to provide the documented evidence that the system is installed and operates according to the specification. There are many ways of implementing a quality risk management approach; this Guide provides one example.

Quality oversight of the process is a requirement; in this example, it has been achieved through the definition of good engineering practices in a series of procedures:

- Good Documentation Practice
- Design Review and Qualification
- Engineering Quality Systems
- Commissioning Planning and Execution
- Engineering Change Management
- Automation

2.7.2 *Defining the Commissioning Deliverables*

The commissioning deliverables should be clearly defined in the commissioning plan with the intent of the deliverable and the associated roles and responsibilities. Commissioning plans also should define acceptance criteria and expected test results. These documents may be created by an organization SME or by a specialist supplier. The commissioning plan should be approved by the QU.

Typical commissioning deliverables may include:

- Receipt Verification
- Installation Verification (IV) Document
- Safety Inspection/Walk Down
- Operational Verification (OV) Document
- Transfer of Custody
- Stage Summary
- Science and Risk – Development and use of the Risk Assessment
- Defining the Risk Assessment Process
- Critical Quality Attributes
- Critical Process Parameters

2.7.3 Receipt Verification

This can be a simple process of a visual inspection of the equipment for damage before accepting delivery or a detailed check of components and functional testing/calibration of instruments.

This inspection also can be used to add instruments onto a calibration database.

2.7.4 Installation Verification Document

Usually the first field effort for commissioning is the Installation Verification (IV). This document should provide evidence that an installation complies with approved design specifications, and that instruments are calibrated in accordance with those specifications.

It should be noted that instruments may be categorized for calibration requirements:

- Some instruments may be acceptable with a manufacturer's certificate of conformity.
- Some instruments, such as variable area flowmeters, do not require routine calibration, just an inspection for wear.
- Instruments critical to product quality (system output is considered the product in this instance) are usually calibrated on site to ensure that they were not damaged during shipping.

Other items generally covered in IV are the engineering quality checks carried out during construction to confirm that:

- The "as built" drawing (or red line drawing if the "as built"/record drawing was not yet available) accurately reflects the installation.
- The correct data defining the spare parts is available to put into the maintenance management system from which a bill of materials including component documentation is produced.
- Instrumentation check-out had been completed (point to point wiring checks and functional loop checks).
- The system has been cleaned and passivated per specification (this may be in IV or OV).
- Fuse ratings and overload settings are as specified.
- Tags and labels are installed according to a component list.
- Pipework contents and flow directional labels have been added as specified.

2.7.5 Safety Inspection/Walk Down

Before a new or modified system is energized, and power made available, it is considered good practice to perform a safety walk down; the scope of this is generally defined in an organization's procedures and can include electrical safety, valve orientation, safety warnings, etc.

2.7.6 Operational Verification (OV) Document

This OV document should provide documented evidence that a system operates to meet the specification.

The scope of work may include:

- Sequence of operation testing

- Determination of adjustable set points, e.g., level settings
- Tuning of control loops and verification of controller action
- Determination and verification of control module parameters and constants
- Testing of interlocks including indication and response actions
- Verification of alarm functions
- Power loss and recovery test
- Emergency shutdown verification (confirmation that there is no stored energy in the system)
- Testing at the specification limits, e.g., system design peak usage

This OV document may include a commissioning summary, or there may be an independent commissioning summary report. The summary report should include a summary of any changes made, and issues experienced during commissioning, so that the history is available to the system owner.

The summary report should be reviewed and approved by an independent SME to provide a level of quality assurance within engineering.

Completion of the summary report signifies completion of commissioning of the system.

The information contained in the operational verification document is also typically repeated in the qualification summary report, which also may be reviewed and approved by the QU.

2.7.7 *Transfer of Custody*

Prior to the transfer of custody, work should be performed by the engineering department or project team; quality oversight should be obtained by:

- Quality Unit approval of the commissioning and qualification plan
- The procedures followed to do this work, the commissioning and qualification plan, and related acceptance criteria should be approved by quality, i.e., follow a quality system.
- The Quality Unit may review documents or witness a test, but would generally not pre- or post- approve individual documents. Acceptance criteria used in commissioning documents should be defined in a C&Q plan or the system specifications.
- TOPs should be provided to appropriate parties for review, revision (if required), and approval.

Generally once the commissioning has been completed the responsibility for operating and maintaining the system is transferred from the project team to the system owner.

2.7.8 *Stage Summary*

Through the system design review (or DQ), the QU should have agreed that, from a quality perspective, the design is fit for purpose.

The QU should have approved the:

- Commissioning and qualification plan
- Confirming agreement with the process
- Personnel
- Documentation standards
- Expected results
- Acceptance criteria

IV and OV have been completed providing documented evidence that the system is installed and operates to meet the specifications.

It is expected that these activities would be completed with a level of quality unit engagement and oversight to ensure confidence in the deliverables.

At the completion of the OV, a brief commissioning summary report is produced – this should be approved by an independent engineer (i.e., not the engineer responsible for the commissioning) to confirm that the documentation is acceptable. The report should confirm that the system is installed and operates to meet the specifications, and that any changes from the agreed design have been managed through the engineering change management system.

The work is conducted following GEP, and the associated documentation standards, and change management processes.

Approval of the commissioning summary report by the QU releases the system to have the qualification summary report completed (see relevant section same heading).

2.7.9 Science and Risk – Development and Use of the Risk Assessment

The process described here uses a risk assessment to determine the risks to system product quality due to the equipment – and defines the associated risk controls that must be in place in order to provide an acceptable risk profile for a system.

2.7.10 Defining the Risk Assessment Process

In order to define the scope, and align it to that of traditional IQ/OQ, or combined IOQ, this Guide uses the following assumptions:

- The output of the system is considered to be the “product.”
- The inputs to the system are considered to be “qualified,” i.e., meet specification.
- The aspects that are reviewed are those within the system boundary.
- The focus is on product quality (patient safety).
- To avoid the assessment becoming a very detailed Failure Mode and Effect Analysis (FMEA) – which would not achieve the program goal – the maintenance and calibration quality systems are considered to be in place and effective.

Information used for the risk assessment includes:

- CQAs
- CPPs
- Potential risk to product quality (system product)
- Source of the risk
- Risk controls (design/procedural)
- Means of detection of the risk should the controls fail

An initial draft risk assessment may be generated by a small number of SMEs, in order to make the process more efficient. The information generated should include a system description and control strategy to ensure that there is a clear definition of the scope of the assessment and a clear understanding of how the system operates.

The initial draft risk assessment and supporting information can be reviewed and scored by a larger team of SMEs led by an experienced facilitator, to help to ensure that the operating knowledge and experience of site personnel is captured. The larger team should be composed of the small number of SMEs and additional representatives from quality/validation, operations, and engineering groups/departments.

The following actions are usually predefined:

- Low risks are accepted.
- Medium risks can be accepted by the team or the team can elect to add additional controls to reduce the risk.
- High risks should have additional controls added to become medium or low risks (tables provided in this section of the Guide show recommended scoring values). The risks are scored using the tables below based on the design and the planned content of the operational and maintenance procedures.

Note: these tables are examples and are not exclusive. Various high risk assessment gauges and tables are available.

Table 2.2: Risk Assessment Chart

Rating	SEVERITY of the effect of failure	Likelihood of OCCURRENCE	Ability to DETECT the failure
9	Severe – serious impact to a critical quality attribute of the output of the system/equipment. Impact to final product critical quality attribute.	Frequent – failure is almost inevitable. Consistent failures observed (e.g., once a week or several times a month).	Absolutely uncertain – existing controls cannot detect the failure. No controls are in place.
7	Major – significant impact to a critical quality attribute of the output of the system/equipment. Possible impact to final product critical quality attribute.	Likely – failure is likely and will occur in most circumstances. Repeated failures observed (e.g., once a month or several times a year).	Remote – remote chance that controls will detect the failure. A control may be in place but is untested or unreliable.
5	Moderate – possible impact to a critical quality attribute of the output of the system/equipment. No Impact to final product critical quality attribute.	Occasional – failure is probable at some time and has been observed (e.g., once every 1 – 2 years).	Moderate – a moderate chance that the control will detect the failure.
3	Minor – minor impact to a critical quality attribute of the output of the system/equipment. No impact to final product critical quality attribute.	Unlikely – failure could occur at some time. Only isolated incidents observed (e.g., once every 3 – 5 years).	High – very likely that the control will detect the failure (e.g., a procedural control).
1	Insignificant – no impact to QA of the output of the system/equipment. No impact to final product critical quality attribute.	Remote – failure is extremely unlikely. No history of failure.	Almost certain – the control will detect the failure in almost every instance (e.g., an alarm or automated function).

Scoring the Risk Assessment

Table 2.3: Scoring for Severity and Likelihood of Occurrence

		Severity of Risk				
		1 Insignificant	3 Minor	5 Moderate	7 Major	9 Severe
Likelihood of Occurrence	9 – Frequent	Medium	Medium	High	High	High
	7 – Likely	Low	Medium	High	High	High
	5 – Occasional	Low	Medium	Medium	High	High
	3 – Unlikely	Low	Low	Medium	Medium	High
	1 – Remote	Low	Low	Low	Low	Medium

Table 2.4: Scoring for Detection

Risk Classification		Detection				
	<i>Risk Level from Table 2.2</i>	1 Almost Certain	3 High	5 Moderate	7 Remote	9 Absolutely Uncertain
	High	Low	Medium	High	High	High
	Medium	Low	Low	Medium	High	High
	Low	Low	Low	Low	Medium	Medium

Note: an interim result can be determined, based on severity and occurrence, using Table 2.3. That result and the detectability rating are then used in Table 2.4 to determine the final risk level.

The initial draft risk assessment may be performed once the conceptual design is available; this can provide a risk profile for the proposed design.

If the profile is acceptable, the design may be developed as proposed – if the profile is not acceptable, e.g., where there are high risks, the design should be revised and reassessed to determine whether it is acceptable.

To finalize the risk assessment, the design should be reviewed against the issued for construction design specification, and completed with a brief summary report.

The risk assessment provides:

- A tool to determine the overall risk profile for the proposed system design
- A vehicle to identify the aspects of the design that are “critical to quality”

A risk assessment report usually contains the sections:

- A Summary, including:
 - System Description and Control Strategy
 - CQAs
 - CPPs
 - CAs, where applicable
 - Risk Assessment Methodology
 - Risk Assessment Scope
- Results, including:
 - A summary of the results of each assessment, confirming any medium level risks that have been accepted by the team.

- Mitigation Plans:
 - Where applicable
- Communication:
 - Defines where high risks were communicated to senior management for review and acceptance.
- Conclusions

2.7.11 Qualification Summary Report

A Qualification Summary Report is used to accept a system (rather than the traditional IQ and OQ protocols) and release it for PQ.

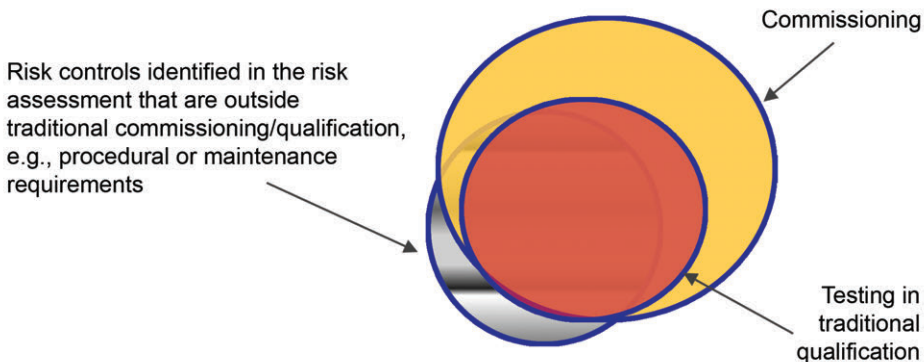
The key sections of the Qualification Summary Report with descriptions of the content where title is not self-explanatory include:

- Summary
- Purpose and Scope
- System Description
- Description of System Modifications/Changes
- Summary of the Verifications Performed:
 - Confirming that DQ, IV, and OV have been satisfactorily completed, providing a documented record that the installation and operation of the system comply with specifications (and approved engineering changes).
- Risk Assessment Qualification Requirement Summary:
 - Confirming the risk controls (that were defined in the risk assessment) which provided an acceptable risk profile were all implemented and satisfactorily tested.
- No testing is repeated.
- The quality risk management approach clearly identifies the risks to system product quality and associated controls.
- Confirmation that the design risk controls have been addressed prior to procurement through design review/ design qualification.
- Confirmation that the system design risk controls are in place and operating as specified confirms the risk profile of the operational system.
- In addition – if the risk controls are procedural, the procedures are checked to ensure that they have the relevant content.
- The risk assessment provides a reference for use during change control to assess if a proposed change impacts the quality controls within the system.

- Component is used to control critical process elements that affect product quality, repeatability, effectiveness, or durability without independent verification of control.
- Component is used to create or preserve quality.

Figure 2.1 presents a diagrammatic illustration of the result of following the Quality Risk Management (QRM) approach.

Figure 2.1: Quality Risk Management (QRM)



An example of this component evaluation process for a typical compendial Water for Injection (WFI) equipment generation and distribution system is given in Appendix 1.

For critical components, a very low risk, high reliability is required. Critical components require a failure analysis for each failure. Critical components should have:

- High reliability
- High maintainability
- Continuous improvement capability

In terms of the deliverables, the documents that will be produced following the ISPE Baseline® Guide: Commissioning and Qualification [19] approach, and the quality risk management approach are very similar.

The quality risk management approach uses engineering documents, IV, and OV to provide documented evidence that the system is installed and operated to meet the specifications. The quality risk management approach includes a quality risk assessment.

The approach described in ISPE Baseline® Guide: Commissioning and Qualification [19] would include the engineering deliverables, and add the IQ and OQ to provide the documented evidence that the system is installed and operated to meet the specifications.

2.7.12 Critical Quality Attributes

The CQAs described in this section are typical examples for a compendial water system.

A CQA is defined as: *“A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.”* (ICH Q8(R2)) [11].

CQAs should be measured with appropriate accuracy; instrumentation accuracy requirements are usually described within the relevant pharmacopeia.

For compendial water systems, CQAs are defined by the specifications within the pharmacopeia that applies to the market being supplied. Where several markets are supplied, the most demanding requirements within the relevant pharmacopeias should be met.

For compendial water systems, alert and action levels should be set for CQAs. Limits for the alert and action levels used should take account of the accuracy of the instrumentation used, as necessary.

System performance data should be trended as part of PQ; analysis of the data and review of the performance trends help to provide evidence that the system is operating in a state of control, i.e., the water from the system reliably meets the specifications.

Unusual or undesirable trends should be investigated and a corrective action initiated, e.g., upward trends in the system microbial levels may indicate that more frequent system sanitization is required.

Example CQAs include, e.g.:

- TOC
- Conductivity
- Microbial levels
- Endotoxin levels
- Nitrate concentration
- Heavy metals concentrations

TOC

Where a TOC measurement is used for compliance purposes (e.g., release of water), the TOC measurement may be taken on-line or in a sample which is analyzed in a laboratory.

Where an on-line TOC measurement is for “in-process” control, upset indication, or information, rather than as an indication of compliance to a CQA, the on-line TOC instrument would not be considered critical.

Conductivity

Where a conductivity measurement is used for compliance purposes (e.g., release of water), a non-temperature compensated conductivity measurement (on-line or laboratory value) can be used to record a CQA. Where temperature compensation is used, it should comply with the relevant pharmacopeial requirements.

Where the conductivity measurement is for in-process control or information, and is not an indication of compliance to a water specification attribute, an on-line conductivity measurement may not be considered a critical component.

Samples may be taken to measure compliance with water specifications and should be measured in a laboratory.

Temperature

Temperature is usually considered a CPP; however, when temperature is used or reported with conductivity for water release, it may be considered a CQA.

Microbial

Where microbial tests are required, water is usually sampled and analyzed off-line in a laboratory. Microbial quality is a USP requirement (and, therefore, a CQA). Test results may be used to demonstrate conformance to the USP requirement.

Endotoxin

In the US, a USP Bacterial Endotoxins Test (BET) is normally required for WFI water distribution systems at POUs.

Nitrate

Where tests for nitrates are required, water is usually sampled and analyzed off-line in a laboratory.

Heavy Metals

Where tests for heavy metals are required, water is usually sampled and analyzed off-line in a laboratory.

Other Example CQAs for a Clean Steam System

Other properties or characteristics of a compendial water and steam system may be CQAs, depending on the water or steam specification, including:

- Superheat (Steam)
- Dryness (Steam)
- Non-Condensable Gas (Steam)

For further information on CQAs, see the ISPE Baseline® Guide: Water and Steam Systems (Second Edition) [8].

2.7.13 Critical Process Parameters

A CPP is defined as: *“a process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality.”* (ICH Q8(R2)) [11].

Typically, CPPs are used to create and maintain water quality. CPPs are characterized at minimum and maximum values, which represent the qualified allowable operating range of values for the particular CPP. If a minimum or maximum value is violated, an investigation may be warranted. For example, where a WFI distribution loop has been qualified to consistently produce “in spec” WFI when operated at temperatures above 70°C (158°F) and there is an alarm if the system temperature drops below 70°C (158°F), there is no need to trend the operating temperature of the system on an ongoing basis.

CPPs, including minimum and maximum operating ranges, should be qualified. The ability of a system to meet these parameters is usually tested during commissioning. The effects on water quality should be demonstrated as part of PQ.

As part of gathering information to improve process understanding, CPPs for a compendial water or steam system should be identified and managed. Example CPPs for compendial water systems include:

- Water Temperature
- Ozone Level

- Flow
- Water Pressure
- Water Level

Temperature

Temperature levels (measured and/or controlled) may be considered:

- Critical (if directly related to a CQA (e.g., on-line conductivity measurement))
- Of process importance to a specific qualified system

The temperature of water (maintained or uncontrolled) may not be considered to be a CPP in some sections of a compendial water system. Examples of where the temperature of water should be considered as a CPP include:

- On-line conductivity measurements (see section on CQAs)
- Continuous sanitization applications where a system is maintained at a specific temperature (e.g., hot or cold) to inhibit microbiological growth
- Sanitization cycle control where the proven sanitization process for a specific system is dependent upon the operation of the system at or above a specific temperature during the sanitization cycle
- Other process applications where temperature levels and therefore, associated control is deemed critical to a specific process

Typically, microbial contamination will not proliferate in high purity water systems above specific temperatures. Decreasing operating temperatures below ambient temperatures in “cold” high purity water storage and distribution systems can retard microbial growth.

Example

For many years, a company operated a qualified purified water distribution loop (storage vessel, pumps, heater, points of use, water return to vessel equipment) at uncontrolled ambient temperatures (15°C to 30°C) (59°F to 86°F). Sanitization of the system included a weekly increase in loop temperature to 80°C (176°F) for two hours.

Based on “process understanding” gained from this existing distribution loop, a new loop was planned. For the similar new loop, the only change was that a cooler was included in the design. The cooler was used to maintain a normal distribution loop operating temperature of less than 15°C (59°F). Water temperature was acceptable to production operations. Based on control of the temperature with subsequent system qualification, the company was able to extend the time between sanitization from one week to two weeks, which was highly desirable from a production operation perspective. Water flow rates in both systems were very similar.

For the older system, there was uncontrolled water temperature in the system, which was acceptable to production operations. The time at temperature for sanitization was considered to be the CPP needed to keep the system in microbial control. In the newer system, however, based on qualification, both the time at temperature for sanitization and the control of distribution loop temperature to less than 15°C (59°F) were found to be CPPs needed to keep system in microbial control.

Ozone Level

The ozone level in water has a similar effect on microbial control as temperature, on both a continuous or intermittent sanitization basis. In a “continuous” ozonation system, there is a continuous sanitizing ozone concentration in the water storage vessel. The ozone is destroyed by UV light before the first POU in the distribution system. The presence of ozone in water is a barrier to microbial growth; however, ozone is a potentially hazardous material. Ozone may be considered a CPP if used to control microbial levels (i.e., CQAs). For further information on ozone in water systems, see the ISPE Good Practice Guide: Ozone Sanitization of Pharmaceutical Water Systems [31].

Flow

Water flow rate (or velocity)⁷ may help to reduce microbial growth and maintain water temperature both in hot and in cold high purity water systems.

In re-circulating portions of a distribution system, fully turbulent flow is usually considered a minimum design requirement. Flow is usually verified upon system start-up and may be monitored during normal system operation. For example, flow may be monitored to determine amounts of water supplied to different users on the water distribution system and to determine that turbulent flow is maintained.

In addition, system flow (including the amount of water stored in a storage vessel) may be monitored and controlled as part of an overall microbial control strategy. For low water usage scenarios and where system flow is used as part of an overall microbial control strategy, water in a system may be replaced with fresh water on a routine basis.

The design flow rate and actual system usage should be demonstrated as providing water meeting the specification as part of Process Qualification (PQ).

Flow rate is not usually considered a CPP, as there is no proven relationship between the flow rate and microbial proliferation.

Water Contaminant Concentration

Water contaminant concentrations can be either expected or unexpected.

Where the ability of treatment equipment to provide a quality product is affected by contaminant concentrations that are above or below the capacity of the treatment equipment to produce product water of a suitable quality, both minimum and maximum contaminant concentrations may be critical.

Example

The treatment device in a vapor compression still is a log reduction (fractional removal) device. If there is too much microbial endotoxin in the feed sent to a vapor compression still, it may impact the quality of pharmaceutical water produced by the still.

In this example, there is no on-line indication of microbial endotoxin compliance for the final pharmaceutical water produced. The concentration of microbial endotoxin in the water sent to the vapor compression still can be considered a CPP. An upper limit to the allowable endotoxin concentration in the vapor compression still feed should be considered. An off-line measurement of this parameter may be required.

Consideration should be given to water treatment capabilities where unexpected events may impact the ability of a treatment system to function adequately.

⁷ The Reynolds number relates back to a specified flow rate that will result in turbulent flow that is the desired state.

Example

Where well water is used to source potable water for a high purity water treatment train, and wells are located primarily in agricultural areas (e.g., where fertilizers and pesticides are used), unusually high rainfall may provide an unexpected challenge to the high purity water generation equipment train.⁸ (Note: local regulations must be complied with for the licensing and use of well water).

For further information on treatment system capability, see the ISPE Baseline® Guide on Water and Steam Systems (Second Edition) [8].

Water Pressure

Where a compendial water system should deliver water to a particular user at a pressure critical to downstream manufacturing operations, pressure may be identified as a CPP.

A compendial water distribution system should maintain positive water pressure relative to the surrounding outside environment at all times of operation, except for where a vessel vent filter is used for vessel breathing.

Where water pressure is critical, the practice typically adopted follows the practice used for a compressed air system; a low supply pressure alarm should be incorporated into the controls of the system that is using the water and which has a critical supply pressure.

Where a compendial water system is susceptible to contamination because of backflow (caused by inadequate pressure differentials), pressure may be considered a CPP.

Pressures in distribution systems may be needed to prevent leaks into the compendial water from the utilities and the surrounding atmosphere and therefore, considered critical. Additionally, adequate distribution loop return pressures may be needed to develop vessel internal spray ball patterns.

Alternative controls include:

- Routine pressure testing of heat exchangers, typically from the process side
- The use of sensitive instrumentation, such as the in-line TOC measurement

These controls should confirm that there is no leakage into the compendial water from utility systems.

Water Level

Water levels in storage vessels may be monitored to control the supply of water into the storage vessels and for the control of mechanical protection and cavitation protection of downstream pumps.

The water level in storage vessels may be a determining factor in the operation of the purification train for demand of make-up and process water, but is not normally considered to be critical to water quality.

2.7.14 Activities and Considerations for the Measurement of CQAs and CPPs

Typical activities and considerations, which are associated with measurement of CQAs or CPPs associated with instrumentation, include:

- Verification of instruments because of the criticality of contact with materials of construction

⁸ Local regulations must be complied with for the licensing and use of well water.

- Engineering and quality review of selection, configuration, and maintenance/calibration requirements
- Generation of Critical Operating Data (COD) – subset of process data (typically, measured values of CQAs) that exists (measured or system generated) in electronic measurement and control systems. These data may depict the identity, purity, or quality of the water product. This data can be used during process validation.
- Strictly controlled system for tracking and replacement of the instrument
- NIST (US) or other national traceable calibration standards
- QU review of critical data
- System for calibration and maintenance of the instrument
- Measurement uncertainty analyses provides information to establish the extent of confidence limits bounding a measurable quantity

2.8 Sampling

The FDA document “*Guide to Inspections of High Purity Water Systems 7/93*” [32] provides guidance for developing a sampling plan and recognizes that more than one approach may be acceptable. Furthermore, USP General Information Chapter 1231 [3] states:

“Water should be monitored at a frequency that is sufficient to ensure that the water system is in control and continues to produce water of acceptable quality ... Established sampling frequencies should be based on system validation data and should cover critical areas, including unit operation sites.”

Sampling and initial testing can commence after water flow has been established through a generation or distribution system. Typically, sampling and monitoring used to build ‘process understanding’ begins during the early stages of start-up of a generation or distribution system.

Monitoring during commissioning is a GEP activity, which can help to:

- Build “process understanding” of the system and each process step
- Define operational and maintenance practices and procedures that will be challenged later during qualification

The results of sampling during commissioning can help to develop plans for sampling during qualification and on-going monitoring. Microbial testing (if required, including coliform or endotoxin) of the incoming potable water through to the end of the treatment chain should begin at a time helpful in enhancing the C&Q process.

Water samples can be taken after each unit operation used to change a characteristic of the water during the pre-treatment and final treatment steps of the generation system.

Typically, sampling of a storage or distribution system is performed:

- At the storage tank and at each POU servicing manufacturing, cleaning activities, or a laboratory facility
- To demonstrate that the quality of water is maintained and meets the requirements of the processes being served

Sampling during the commissioning phase may be used to determine whether a system is functioning as specified. Typically, start-up samples and on-line chemical tests are obtained and tested to compare differences during commissioning. Microbial tests may be performed in a laboratory in order to provide start-up information.

For stainless steel systems, where cleaning and passivation operations are performed to enhance corrosion control, care should be taken to begin sampling **after** these operations are completed, and the system has been rinsed and declared free of acids.

For process engineering projects, the type of analyses performed within pre-treatment steps, final steps, and storage and distribution should be based on the **unit operation** (and regulatory expectations) for the desired product water.

For pre-treatment steps, the typical regulatory requirement is to begin with water that meets the US Environmental Protection Agency (EPA) National Primary Drinking Water Regulations (NPDWR) or equivalent regional (e.g., European or Japanese) or World Health Organization (WHO) requirements for drinking water quality. Each unit operation within the pre-treatment boundary (e.g., filtration, softening, and de-chlorination) should be sampled and analyzed for the process being performed. Sampling should occur at the inlet and outlet of each unit operation to ensure that the anticipated change takes place. Low flow and high flow design conditions may be tested.

Table 2.5 provides examples of typical monitoring for unit operations.

Additional testing may be performed at the outlet of a unit operation to ensure that other attributes do not have an impact on the operation of downstream equipment (e.g., total heterotrophic plate count at the outlet of a carbon filter).

Additional tests also can be applied to final treatment steps, storage, and distribution. Sampling and analyses within the final treatment boundary should be selected in the same manner as the pre-treatment. For example, sampling for total heterotrophic plate count before and after a reverse osmosis step, as reverse osmosis acts as a membrane barrier to micro-organisms.

Further sampling and analyses may be performed to ensure continued business productivity or quality review for the next process step, which is designed for a specific feed water quality (e.g., conductivity being supplied to an EDI unit). Subtle differences in source water quality and the local environment can later manifest as operational and or maintenance issues.

Table 2.5: Typical Sampling Locations in High Purity Water Generation Systems

Generation System Method	Process Step to be Sampled	Monitoring
Distillation (Vapor Compression Still) Multi-Effect Requires Additional RO Pretreatment	Multi Media Filter	Pressure Drop, Particulate
	Softening	Hardness
	Carbon Bed	Oxidation Reduction Potential (ORP) or Free and Total Chlorine, Chloramines, Ammonia, Microbial
	Vapor Compression or Multi Effect Still	Conductivity, TOC microbial, Endotoxin
RO/EDI	Multi Media Filter	Pressure Drop, Particulate
	Softening	Hardness
	pH Adjustment	pH
	De-Chlorination (either/or), Ultraviolet (UV), Carbon, Bisulfite	ORP or Free and Total Chlorine, Chloramines and Microbial, ORP or Free Chlorine
	Reverse Osmosis	Conductivity of Inlet, Outlet, and Flow Rate (to provide % Rejection and Recovery) and Microbial
	Electro Deionization	Conductivity, TOC, and Microbial

2.9 Performance Qualification

2.9.1 Execution of Performance Qualification

The purpose of PQ is to:

- Demonstrate that procedures, personnel, systems, and materials needed for the operation of a water system are integrated.
- Provide evidence that the system can consistently meet the water quality requirements specified in the associated URs

Science- and risk-based assessments can be performed in accordance to ISPE Guide: Science and Risk-based Approach for the Delivery of Facilities, Systems, and Equipment [2].

During PQ, on-line instrumentation and PAT may be employed instead of traditional laboratory water assays to demonstrate compliance to the water specification requirements. The use of on-line instrumentation with delineation for process control limits, definition of upper and lower action and specification limits, with high frequency measurement can be implemented. Integration of statistical process control and/or exponentially weighted process statistical methods can enhance the documentation and data for CPPs, CQAs, and other process parameter measurements. For further information on automation, instrumentation, statistics, and process control, see ISPE Baseline® Guide on Water and Steam Systems (Second Edition) [8], the ISPE GAMP® Good Practice Guide: A Risk-Based Approach to GxP Process Control Systems [30], and the ISPE QLI® Guide: Part 4 – Process Performance and Product Quality Monitoring System (PP&PQMS) [33]. For further information on the application of PAT principles, see ASTM E-2500 [14].

For water systems, PQ should demonstrate that system performance is consistent over an extended period of time. This extended period of time allows for:

- Variations in water use rate
- Initial feed water quality
- Seasonal variations, including differences in surrounding temperatures and variations in feed water quality

The impact of these variations may not affect the water system delivery product; however, dependent on the components installed in the purification system of the water system.

“Process understanding” is needed in order to establish a rationale for the sampling strategy to be used during PQ.

Sampling during PQ may be either on-line or manual (for off-line laboratory analysis). The location and frequency of sampling is dependent upon the system design and the phase of testing. The chemical data collected during PQ may be obtained from on-line instrumentation or manually through off-line laboratory analysis. Microbial and endotoxin testing (if required) should be conducted through laboratory analysis. Sampling locations should be defined in the system design phase. The frequency of the data collection is dependent on the phase of PQ. The attributes measured are dependent upon the applicable pharmacopoeia (e.g., EP, JP, and USP) which is usually determined by the final destination of the drug product.

The sampling strategy for a distribution system should imitate the way in which a system is used during operation. For on-line instrumentation, the measurements should be indicative and comparable to the expected value at the POU.

An example of traditional manual sampling: if high purity water is used from a hose normally connected to the water system, water quality should be sampled from the connected hose. The strategy should have a rationale, which dictates why sampling at a device (such as connected hose) or POU is warranted. The rationale for selecting the points to be sampled and frequency should be justified.

Typically, all water POU's would be sampled for microbial characteristics on some frequency or rotating basis. On-line "end of loop" instrument measurements for compendial attributes, such as TOC and conductivity, can provide accurate depictions of water quality at POU's in a distribution system.

A traditional C&Q sampling program is developed in three phases:

- Phase 1 is to ensure that the system is under control before entering the PQ testing phase, and allow use for production.
- Phase 2 is the first phase of PQ testing.
- Phase 3 is the remaining PQ testing period necessary to have one complete year of testing data (see Table 2.6).

Phase 1 and Phase 2 testing are typically of shorter duration and higher frequency of testing.

The implementation of PAT, risk-based management, and the use of on-line instrumentation should measure the parameters with high frequency, eliminating the need for Phase 1, 2, and 3 regimens. Parameter data should be measured continuously, accessible at all times, and with complete knowledge of the process limits and values. The system can be monitored for any process anomaly or excursion, in real-time, without undue long-term data collection to verify that the process is in a state of control.

The risk-based approach to C&Q may impact the sampling strategy.

A CQA for water at a specific point may be defined as needing to meet a compendial requirement. For example, the point at which conductivity may become a critical measurement would be at the critical component at the end of a purified water generation system (e.g., outlet of a DI mixed bed or outlet of a Continuous Electrodeionization Deionization (CEDI)). Sampling the conductivity at this point should occur during the commissioning and qualification process.

In the case of on-line instrumentation, measurements should be monitored continuously from the inception of the start-up. Any deviations relating to this water CQA should be recorded according to the appropriate deviation procedure.

Non-critical attributes of water should be tested during commissioning, but not necessarily during PQ. Non-critical attributes of water may be tested to meet engineering operational needs, but do not need to be tested for quality purposes. Changes to the system, or the operating procedures should be documented and managed through GMP change management.

Frequency of sampling can be affected by:

- Criticality of POU
- Compendial mandates
- Water quality designation of a system. The robustness of a system design can counteract the need for higher frequency manual sampling.
- Availability of on-line water quality measurement data. The frequency of data recording may be set by the user or it may be dependent on the cycle time of the instrument. On-line instrumentation should be either real-time data or as near to real-time as possible.

- Stability of the sampling results from POU's. For example, during PQ, specific POU's may require extensive sampling. After demonstrating repeated results within the required specification and assessing the risk associated with not have extensive sampling results available for review, it may be justified to reduce the sampling frequency.

Table 2.6: Typical Phases of PQ for High Purity Water Distribution Systems

Phase	Primary Objectives	Typical Duration
1	Finalize appropriate operating ranges on critical process operating parameters. Preliminary operating, cleaning, and maintenance procedures (SOPs) may be further developed, but by the end of Phase 1 they must be finalized and approved. The sanitization strategy for microbial control is tested. Demonstrate production and delivery of water of the required quality. Note: sampling must continue between phases.	Two to four weeks – continuous from start-up initiation
2	Continuously review and trend all available data. Demonstrate consistent operation within established ranges when using approved SOPs. Demonstrate consistent production and delivery of water of the required quality.	Two to four weeks
3	Demonstrate extended performance. Ensure that potential seasonal variations are evaluated and treated. Evaluate effectiveness of the sanitization strategy and make adjustments if necessary.	One year
Note: when using scientific and risk-based management with PAT or advanced monitoring schemes, Phase 1, 2, and 3 are eliminated.		

2.10 Project Completion and Document Delivery

Near the end of a project, suppliers, engineering consultants, third party inspectors, and other personnel should prepare to vacate the facility. Typically, the facility is staged for commissioning, validation, and finally turned over to the owner.

A project TOP summary should be provided to the facility owner summarizing what has been turned over.

After project completion, there should be a project learning review with the project team including key suppliers and end users.

2.11 Performance Qualification Final Reports

Interim PQ reports may be used to provide evidence that a stage has been successfully completed or release a system to the next stage.

PQ final reports should be issued to provide proof and approval of the system validation. Information typically represented in PQ final reports includes:

- All activities identified in the qualification matrix have been completed and verified. In addition, results meet acceptance criteria.
- Good documentation practices have been used.
- All test results met acceptance criteria (e.g., tolerance and range).

- All required SOPs, preventive maintenance procedures, training materials and spare parts requirements have been developed and approved for the components and systems being qualified, or an acceptable action plan has been included to address these documentation requirements.
- Qualification summary has been completed including documentation of any issues identified during the execution of the qualification and corresponding resolution, and an assessment of the state of qualification of the components and systems.

2.12 On-Going Quality Monitoring

During PQ, extensive data is collected to prove that a system can consistently meet specification requirements. The on-going sample plan may be at a lower frequency than that established during PQ, as there is a low risk of a sample failure.

For WFI systems, there is higher risk associated with a sample failure so the on-going sampling frequency may be very similar to that done during PQ. All POU's should be sampled at a predetermined frequency based on the potential risk to product. Daily sampling may be required.

For other water qualities, the frequency should be risked-based or as established by an organization's policies and procedures. It is recommended that samples are taken at a minimum of two different POU's for each CQA so that there are additional data available in the event of an adverse assay result.

A science and risk-based approach should be taken when developing the on-going water quality monitoring plan, continuing the logic used during performance qualification. There is a higher risk of microbial contamination in the high purity water system than there is of chemical contamination. Thus, there should be a rigorous microbial and endotoxin (if applicable) testing plan to assure the system remains in a state of control. There is less potential for chemical contamination of a water system so the monitoring plan may be less rigorous. The use of on-line monitoring for chemical CQAs (e.g., TOC and conductivity) should be considered.

An ongoing quality monitoring plan should be documented in an approved SOP.

Sample points and on-line monitoring instrumentation should have unique identifiers that are traceable between the field valves or instruments, the on-going sampling plan, automation system (for instrumentation) and drawings.

The water quality data should be reviewed by the QU and other key operational and technical personnel to determine if there are any adverse trends. This review should include both sample results and the review of on-line water quality monitoring data. The review should be documented. The review also can be used to verify that the sanitization strategy is adequate to reduce the potential for biofilm formation and assure that the system remains in a state of control. The more frequent the review, the sooner action can be taken when an adverse trend is detected that could affect the water quality.

The data collected also can be used to support the data required for a periodic performance evaluation, which should be performed on a system. The outcome of a periodic performance evaluation can be used as justification for changes to microbial alert and action levels.

For further information on process validation, see the FDA PV guidance [34] and ISPE PQLI PV guidance [35].

2.13 Periodic Performance Evaluation or Periodic Review (PR)

Pharmaceutical water and steam systems should be evaluated on a routine bases to assure the system remains in a qualified and validated state. The frequency of evaluation should be determined based on the risk to the final drug product and is usually annually for critical systems.

The periodic performance evaluation should provide an analysis, summary, and consideration of the combined and cumulative effects of items being evaluated.

The periodic performance evaluation (also referred to as PR), may be used in conjunction with Preventative Maintenance (PM) programs. Periodic performance evaluations can include:

- An introductory section that provides information on the scope of the periodic performance evaluation, system boundaries, and the time period for the periodic performance evaluation.
- Description of a sampling plan, including sample point identification, sample frequency, alert and action levels and other data that will assist in the evaluation.
- Summary and analysis of the testing data to determine whether there are any detectable trends that would justify a modification to the existing sampling program or to the maintenance and operation of a system. Systems should be evaluated as a unit and evaluated with respect to control. Individual sample points also should be evaluated to detect trends.
- Identification of microbial organisms. The data obtained should be reviewed and compared to historical data to determine whether the microbial identification data results provide any useful information about the system, the environment, or the sampling technique. This information can be used to determine whether objectionable organisms are present and to detect shifts in the normal flora of the system.
- Review of microbial data to determine whether microbial alert and action limits are sufficient to ensure an adequate response to system abnormalities.
- Listing of all changes performed on the system during the performance evaluation period and a holistic review of the changes that occurred to determine if an individual change or the accumulation of several changes has impacted the system's validated status.
- Listing of all deviation for the evaluation period. Review the deviations to determine whether there are any adverse trends that may not have been detected by an individual deviation investigation or if there are any systemic issues that may have been overlooked that may impact the validated state of the system.
- Review of any corrective and preventative maintenance performed on a system to determine whether:
 - The current maintenance program is appropriate
 - There are any systemic issues that need to be addressed
- Performance of an alarm review to determine whether there are any alarms that indicate that there are system or equipment issues or items that could indicate a potential water quality concern.
- Review of applicable procedures for the systems or equipment to determine whether there are appropriate instructions provided to personnel who operate and maintain the equipment. This may include a review of deviations that were related to not following instructions or inadequate instructions being provided, indicating procedures may need to be revised or new procedures written.
- Performance of a physical inspection of critical components. Signs of degradation that would indicate the equipment is not being properly maintained should be considered. A review of equipment data should be performed to determine if any equipment performance related issues that need to be addressed can be detected.
- Creation of attachments or appendix containing any data used to complete the periodic performance evaluation.

- Provision of a summary of recommendations and action plans. A review of the action plans from prior periodic performance evaluations to verify that all items were completed.
- Performance of a qualification and validation assessment. Based on results from the assessment of data, a conclusion should be made regarding the state of qualification or validation and whether the system is fit for its intended and continued use.
- Appropriate technical and quality reviews and approvals. Approval by the QU is usually required.

This periodic performance evaluation also may incorporate the requirements and results of the associated control software periodic evaluations to alleviate the requirement for a separate document.

Appendices

The Appendices are intended to provide examples of documents such as component classifications, FDSs, URs, etc. The sample documents show the type of information typically included and tasks to be conducted. These examples are not intended to be absolute guidelines that must be explicitly followed. Equipment, processes, temperatures, flows, pressures, and other parameters are examples of current methods; however, other equally effective alternate methods and processes are also in operation.

The thought process is the key objective. Consideration of sanitization temperature, minimum “dead-leg” requirements (refer to ASME BPE), minimum ozone level, or other possible key operating parameters should be noted. The values that are shown are typically effective, but other values also may be effective.

Appendix 1	Typical WFI Generation and Distribution System Component Classification Example
Appendix 2	Process Water, Pure Steam, and Process Steam
Appendix 3	System Classifications at Points of Use (POUs)/Sub-Loop
Appendix 4	Typical Specifications for Water and Steam Systems
Appendix 5	Sampling and Testing Plan
Appendix 6	Sample Turnover Package Requirements
Appendix 7	References
Appendix 8	Glossary

Appendix 1

Typical WFI Generation and Distribution System Component Classification Example

3 Appendix 1 – Typical WFI Generation and Distribution System Component Classification Example

The design of pharmacopeial water systems is based on process steps or unit operations performed by a piece of process equipment; the system is made up of a series of these steps.

There may be limited value in conducting a full system and component impact assessment, but there is usually value in defining system functions and categorizing them in order to define the key process steps that generate the “system product critical quality attribute” – and hence require qualification, and those that ensure the system feed to those key steps meets relevant requirements to ensure continued reliable operation of the system.

The component impact assessment can provide a useful tool to define system critical instruments, which require calibration, and those used for engineering information, which can be used for reference, and/or calibrated on a less frequent basis.

An example of this approach is provided below based on the system schematic attached.

GEP should be used to produce documentation confirming that the system installation is completed in accordance with the specifications (installation verification), and operates in accordance with the specifications (operational verification).

Initial Assessment

The original challenges used to determine which systems were direct impact (ISPE Baseline® Guide: Commissioning and Qualification, [19]) are:

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., WFI).
3. The system is used in cleaning or sterilizing (e.g., pure 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 (EBRS), 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.

Use of these challenges would make all of the system process steps direct impact.

Adopting a science- and risk-based approach that utilizes GEP documents to confirm materials of construction allows a modified assessment process that can provide the degree of definition required to define which systems should be supported by GEP documentation, and which require additional verification (qualification).

The system shown comprises the following process steps:

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

Table 3.1: Process Steps

Challenge ----- Process Step	Function	The system generates or maintains a system product CQA	The system produces data that is used to accept/reject the system product	The system preserves system product quality (as defined by the CQAs)
Multi Media Filter	Remove particulate from the feed water	No	No	No
Softener	Remove calcium and magnesium salts that would coat the heat exchanger and still surfaces, reducing efficiency	No	No	No
Break Tank	Intermediate storage	No	No	No
Carbon Vessel	Remove chlorine, taste and odor	No	No	No
5 micron Filter	Remove any particle shedding from the carbon filter	No	No	No
UV Lamp	Provide microbial control of the feed water – managing microbial growth resulting from the flow through the carbon filter	No	No	No
Heating Heat Exchanger	Provides the capability to heat sanitize the pre-treatment system – for biofilm control	No	No	No
Cooling Heat Exchanger	Provides an increased cooling rate after heat sanitizing, to prevent microbial growth, and maintains a consistent normal operating temperature – to assist with consistent microbial performance	No	No	No
1 micron Filter	Prevents any particulate from reaching the RO unit	No	No	No
Trailing Softener	Remove calcium and magnesium salts that would coat the heat exchanger and still surfaces, reducing efficiency	No	No	No
Pre-Heater	Improves the system efficiency by recovering heat that would otherwise be lost	No	No	No
Vapor Compression Still	Provides the chemical and microbiological control	Yes	Yes	No

Thus the vapor compression still is considered the item requiring verification for the treatment system.

GEP documentation (installation and operational commissioning records) is considered to provide the documented record that the installation and operation complies with the specifications.

Based on the first question, the storage and distribution system (maintaining a system product CQA) also would require verification.

The instrumentation on the system can be assessed using a similar approach.

Table 3.2: Instrumentation Assessment

Process: Generation Equipment Component Classification P&ID: Owner:				Component monitors or controls critical process operating parameter.	Failure or alarm of the component will have a direct effect on quality of the product and the failure or alarm is not detected by another component downstream in the system.	Component is used for the adjustment or calibration of critical components, such as secondary/working test standard.	Information from this component is recorded as part of the product batch record or lot release data.	Critical (C) or Non-Critical (N) Instrument?
Component Item Title	Component Tag Number	Component Description	Classification Rationale					
Feed Flow Control	FE-1	Drinking Water Flowmeter	Flowmeter confirms system flow, backwash and regeneration rates	No	No	No	No	N
Pressure Indicator	P1-1, 1A	PIs for MM	Indicators are for M-M filter operation	No	No	No	No	N
Temperature Indicator	TI-1	Temperature Measurement	Gives water temperature at point in system	No	No	No	No	N
Temperature Indicator	TI-2, 3	Temperature Measurement	Temperature indicator for softener	No	No	No	No	N
Flow Element	FE-3	Water Flow Measurement	Measures water flow to break tank	No	No	No	No	N
Temperature Control Element	TE-4	Sub-loop Temperature Control Comp	Part of control system to maintain temperature during equipment sanitization	Yes	No	No	No	C
Pressure Indicator	PI-5A, 5B, 5C	Pressure Indicator on Carbon Bed	Pressure indicators for carbon bed	No	No	No	No	N
Temperature Indicator	T1-5A, 5B	Temperature Measurement	Carbon bed temperature indicator	No	No	No	No	N
Ultra Violet Light and UV monitor	UV-1	UV Light for Microbial	Provides microbial control for carbon bed	No	No	No	No	N

Table 3.2: Instrumentation Assessment (continued)

Process: Generation Equipment Component Classification P&ID: Owner:				Component monitors or controls critical process operating parameter.	Failure or alarm of the component will have a direct effect on quality of the product and the failure or alarm is not detected by another component downstream in the system.	Component is used for the adjustment or calibration of critical components, such as secondary/working test standard.	Information from this component is recorded as part of the product batch record or lot release data.	Critical (C) or Non-Critical (N) Instrument?
Component Item Title	Component Tag Number	Component Description	Classification Rationale					
Flow Element	FV-8	Feed Control to VC	Measures feed to vapor compressor (VC) – provides system capacity limit	No	Yes	No	No	C
Pressure Indicator	PT-8A	Control of the VC Operation	Indirect Impact System local plant steam pressure indicator	No	No	No	No	N
Pressure Transmitter	VC-8	Actual Equipment	Measures pressure and provides control of VC	No	Yes	No	No	C
Temperature Transmitter	FV-8A	Steam Control Valve	Measures temperature and provides control of VC	No	Yes	No	No	C
Analyzer Element	AE-8B	TOC monitor	TOC measurement alarm	No	No	No	No	C
Analyzer Element	AE-8B	Conductivity monitor	Conductivity measurement alarm	No	No	No	No	C

Appendix 2

Process Water, Pure Steam, and Process Steam

4 Appendix 2 – Process Water, Pure Steam, and Process Steam

The main text of this Guide concentrates on high purity water. The purpose of this appendix is to give relevant information regarding qualification items to be included in the validation lifecycle for process water, pure steam, and process steam direct impact systems.

4.1 Non-Monographed/Non-Compendial Water

Water may be used for specific early steps in the manufacturing steps of intermediates (e.g., antibiotic fermentation, equipment rinsing) of APIs. URs should be developed in order to understand qualification requirements for a direct impact process water system. Typically, the URs for non-monographed/non compendial water specify that process water meets or exceeds the characteristics of drinking water.

Water meeting US EPA NPDWR regulations, or a regional equivalent, may meet the process needs of some on-site processing operations that may be performed to soften it or ensure that any potential particulate contamination from the storage and distribution system is removed; filtration may be a requirement to meet the URs. Generally, the following items are included in process water generation or distribution projects in order to maintain water quality.

4.1.1 *Typical Design Considerations and Verifications Performed During Commissioning or IQ/OQ for a Process Water System*

- System should be designed so that it does not promote microbial growth, corrosion, or other forms of contamination. This requirement will contribute to the materials, components, and system configuration selection. If specific engineering choices are necessary to meet the process requirement, those choices should be commissioned.
- System should be capable of controlling microbial proliferation in process water generation or distribution steps. Where a sanitization method (i.e., chlorination, ozonation, flushing, or heating) is used, the residual chlorine (ORP), residual ozone (ORP), flushing efficacy, or system temperature increase should be tested/verified during commissioning.
- System should provide backflow prevention, as needed. Backflow protection is usually required, dependent upon mechanical codes; however, sources of potential process water contamination should be assessed as part of a project. The potential for process water contamination may determine requirements for qualification of backflow protection methods or devices.
- Feed water quality supplied to the process water generation train should meet potable water requirements.
- System design should incorporate the capability to sample between unit operations. The system should be documented.

As a minimum, documentation should include:

- “As-built” P&IDs
- System control description
- Operating and maintenance procedures (including system calibration requirements)

4.1.2 Typical PQ for Process Water System

- Critical quality attributes for sampling:
 - Drinking water attributes
 - Total microbial count
 - Absence of coliform
 - Trace elements, if applicable
 - Hardness, if applicable
 - Conductivity, if applicable
 - TOC if applicable
 - Other attributes as defined in the URs
- For a distribution system, a “risk-based” sampling plan to test appropriate CQAs at POU’s should be established. Typically, there would be three phases of PQ and a science and risk-based sampling plan should be developed based on the properties of the water, the distribution system design, environment, and usage pattern.

Where materials of construction do not impact the chemical analysis of the water, the initial sampling can be from a POU having the longest contact time with the water to confirm that the theory is correct. The location can be developed based on the usage pattern.

For example, for a system that uses chlorine as a microbial control, samples could be taken to measure the microbial quality of the water and to measure free chlorine levels to confirm that the microbial control is still effective in the worst case conditions, i.e.:

- Warmest temperatures
- Longest pipe run
- Longest time with the water static

A typical sampling plan could include:

- PQ Phase 1 – one week – sample each POU at least once.
- PQ Phase 2 – three weeks – sample beginning and end POU at least once per week.
- PQ Phase 3 – sample each POU monthly.

Notes:

Where there are multiple POU’s on a system, and only some are used for production use, the POU’s not used could be excluded from the sample plan if they do not present any risk of contaminating the system.

Where the use of water outside specification may be a significant issue, samples could be taken more frequently.

Where microbiological quality is not a process issue; the sampling plan may be adjusted accordingly, although it is recommended that a sample be taken every six months to demonstrate the system remains in a state of control.

4.2 Steam

The steps and guidelines for commissioning and qualification of direct impact steam systems should predominantly be consistent with direct impact water systems due to the close relationship between these systems. However, there are differences in the design, operation, and maintenance of a steam system that impact the commissioning and qualification efforts. For example, microbial growth is not a problem in a steam system.

4.2.1 Types of Steam

The following types of steam are typically used in pharmaceutical manufacturing operations:

- Plant Steam – steam produced by the feed of potable water or equivalent to an industrial type boiler. Corrosion control additives maybe used in the maintenance of the boiler system. Typically, this steam is used for non-direct contact process heating supplied from a commissioned system.
- Chemical Free Steam (CFS) – steam produced from pre-treated water with no volatile boiler additives. Non-volatile boiler additives should meet the FDA Generally Recognized as Safe (GRAS) listed additives or other equivalent international standard where applicable. Typically, CFS is used for humidification and is not used for product/process contact operation, supplied from a commissioned system.
- Process Steam – direct impact steam that once condensed, meets the quality characteristics of potable water. Typically, this steam is used in manufacturing areas for direct injection heating and sterilization, supplied from a system that has been verified.
- USP Pure Steam/Clean Steam – definitions vary – verify the quality requirement for the process – clean steam – condensate is equivalent to purified water; USP pure (clean) steam – condensate is equivalent to WFI. Pure (clean) steam is predominantly utilized for sterilization.

Where applicable steam utilized for international manufacturing also should meet the requirements of European Standard BS EN 285:2006 “Sterilization. Steam sterilizers. Large sterilizers” [36] non-condensable gases for autoclave use. Requirements may not be applicable for equipment SIP.

Superheat

- The temperature of the steam in excess of the boiling point of water at the atmospheric pressure (steam saturation temperature)
- For a steam supply to an autoclave should be less than 25 K for the branch feeding the autoclave

Causes

Typical causes of superheat include:

- Excessive pressure reduction near to the POU – if a pressure reduction of more than 3:1 is necessary; it should be at least 10 ft (3 m) from the point of use, with a separator at the end of the line – with an unlagged elongated interconnecting pipe – to allow the superheat to dissipate.
- Other problems could be related to autoclave load – or jacket temperature too high (pressure too high).
- This is a short term effect, and not relevant when using steam to SIP equipment.

Dryness Fraction

- Dryness fraction is the ratio of the weight of dry steam to the weight of dry saturated steam and the entrained water.
- For steam supplying an autoclave, the target figure is 0.95 to 1; however, 0.9 to 1 is usually acceptable

Causes

General causes of wet steam include:

- Poor distribution system design
- Inadequate drainage, inadequate falls
- High water level in the steam generator
- Insufficient blowdown from the generator
- From an engineering perspective, it is a bad practice for wet air to enter a system – it can cause at best case increased erosion, at worst case damage to control valves. For this reason, it is good practice for steam to enter a system via a separator with a drain trap.
- Dryness fraction is not relevant to equipment SIP as the system will be free draining, and be temperature mapped during commissioning.

Non-Condensable Gases

- Gases which cannot be liquefied at the conditions of temperature and pressure used during the sterilization process.
- Typical gases are – air, carbon dioxide, and less commonly, hydrogen.
- The maximum acceptable level of non-condensable gases is 3.5%.

Result

- Can inhibit sterilization; non-condensable gases act as an insulator – not usually a problem for non-porous loads – gas heavier than steam – porous loads gas can hold the gases.

Causes

Typical causes include:

- Too low a feed water temperature
- Inadequate blowdown
- Poor distribution system design – inadequate venting
- Feed water treatment (if feed is not PW/WFI)

Non-condensable gases are not generally relevant to equipment SIP, as a well-designed system will drain to a fall with suitable steam traps – this will be verified from the temperature mapping carried out during system commissioning.

4.2.2 Typical Design, Commissioning, and Qualification Considerations for Steam Systems

The commissioning and verification process for process contact steam systems generally follow the same documentation requirements and sequencing documented previously for water systems. Audits and verifications for steam systems also follow previously recommended practices for water systems. However, steam systems will have minor variations or additions to the requirements.

4.2.2.1 USP Pure (Clean) Steam

- Pure (clean) steam should be generated by vaporization in a unit specifically designed for the purpose.
- Feed water to the generation unit should be verified to meet the requirements of the manufacturer to ensure that the steam condensate will meet the relevant specifications.

Commissioning should include:

- Confirmation of trap manufacturer's minimum upstream piping length for condensate cooling at the design steam pressure.
- Confirmation that there is a condensate trap immediately prior to pressure reducing valves. (Pressure reducing valves do not handle condensate well especially in the higher flow range. Condensate can cause erratic pressure operation of a pressure reducing valve.)
- Verification confirmation that the specified materials and elastomers have been used.
- Confirmation that the installed piping/tubing system meets the specified slope for condensate removal.
- Confirmation that condensate traps are installed at all low points in the system.
- Component confirmation of valve configuration to assure condensate removal from the body cavity and drainage through the valve.

Maintenance Procedures

- Verification of procedures should include a verification of a maintenance procedure for condensate trap periodic operational check and maintenance program.
- Commissioning of SIP systems should include confirmation of temperature transmitter location. The recommended location of the SIP cold spot temperature transmitter is above the trap manufacturer's minimum upstream piping length for condensate cooling for the design steam pressure.
- Verification of the correct operation of all condensate traps through visual inspection of condensate removal.
- Pure (clean) steam generator capacity testing is recommended; this is typically conducted as part of the FAT, where all of the instrumentation required is available and it is possible to carry out an accurate test.
- Pure (clean) steam distribution system capacity testing is recommended consistent with the generator capacity. This can be accomplished by operating the design maximum loads – e.g., all autoclaves confirming that adequate pressure is available at each use point.

4.2.2.2 Process Steam

- The system should be documented.

- Condensate should be removed from the system to maintain steam quality.
- System should be constructed of materials that are non-additive, non-adsorptive, and non-reactive so as not to impact the quality of the process steam for distribution.

4.2.3 **Typical PQ Considerations for Steam Systems**

The quality testing for USP pure (clean) steam systems generally follow the same testing requirements and sequencing documented previously for water systems. Typically, sampling strategies and programs for new systems or major revisions **and** sampling strategies/programs for minor revisions to existing steam systems will follow the previous recommendations for direct impact water systems. However, due to the sterilizing properties pure (clean) steam systems, the quality testing for minor revisions may be reduced.

4.2.3.1 *USP Pure (Clean) Steam*

- Testing the pure (clean) steam quality is recommended at the generation point and at process critical locations such as autoclaves and SIP applications. However, POUs of lower criticality may not be tested with appropriate justification such as the testing of a down-stream point of use.
- Pure (clean) steam generators typically include a condensate cooler for obtaining samples and continuously monitoring the TOC and conductivity of the condensate. It is recommended to obtain the quality sample of the condensate from the pure (clean) steam generator from the same condensate cooler utilized for the continuous monitoring.
- Where testing of steam to meet ISO 17665 [37] (i.e., dryness, superheat, and non-condensable gases) is required piping should have the appropriate configuration and fittings – details are provided in the USP ISO Standard. Testing should be conducted at the locations as per the standard.
- PQ testing is typically performed in three phases. Condensate chemical quality is usually tested for the same chemical attributes as that of WFI. Endotoxin content also is limited to that of WFI microbial testing is not required – note this does not exclude endotoxin testing.
- The frequency of tests for physical attributes should be based upon potential risk. An example of a testing program is:
 - Phase 1 – (start-up) approximately three days – sample each POU at least once. Sample each pure (clean) steam generator outlet at least once.
 - Phase 2 – (system consistency/stability) approximately one week – sample each POU at least once. Sample each generator more than once.
 - Phase 3 – (deviations) approximately four weeks – sample the system weekly rotating POUs to cover all POUs in a four week period. Sample the generator outlet weekly.

Ongoing Monitoring

Sample the system monthly – from the generator outlet, outlet furthest from the generator, and another outlet – changing this sample point each month – not maintenance activities should include the requirement for an additional test if the routine breaks the system integrity.

4.2.3.2 *Process Steam*

- Typically, process steam (condensate) is tested for compliance with drinking water at a pre-determined interval. However, levels of critical quality attributes, such as TOC and conductivity, may be used as indicators of possible contamination. These levels may be established during PQ and further assessed during ongoing monitoring. Levels of these quality indicators may be tested during three phases of PQ.
- Phase 1 may be considered to be a demonstration phase. Typical levels of quality indicators of possible contamination are assessed in anticipation of Phase 2.
- Phase 2 PQ testing consists of not less than three samples for these indicators from each sampling location. Sampling frequency interval for each sample from each sampling location is not less than 24 hours and not more than seven days.
- For Phase 3 and ongoing monitoring, sample system monthly from rotating sampling locations for the indicators of possible contamination, including the supply and point of use furthest from the point of supply.

Appendix 3

System Classifications at Points of Use (POUs)/Sub-Loop

5 Appendix 3 – System Classifications at Points of Use (POUs)/Sub-Loop

This appendix provides examples of system classifications for a typical high purity water system. The five figures provide examples of typical POU or sub-loop configurations used in high purity pharmaceutical water systems. These examples indicate system boundaries between various direct and indirect impact systems. This section is not intended to be a design guide on POUs or sub-loop design, but the boundaries of systems are shown for classification information purposes.

Figure 5.1: POU Piping Direct Connect to Process Equipment System Classification Example

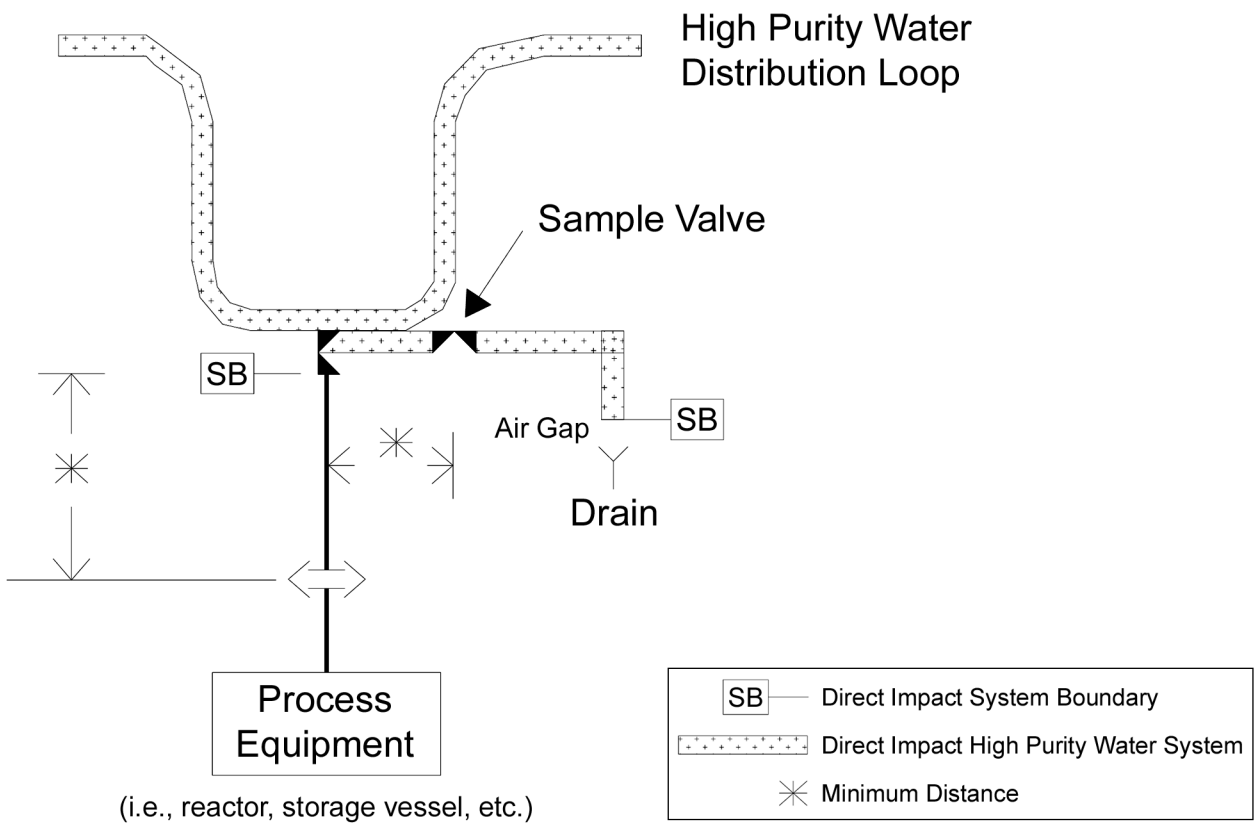


Figure 5.2: POU Hard-Piped to Process Equipment System Classification Example

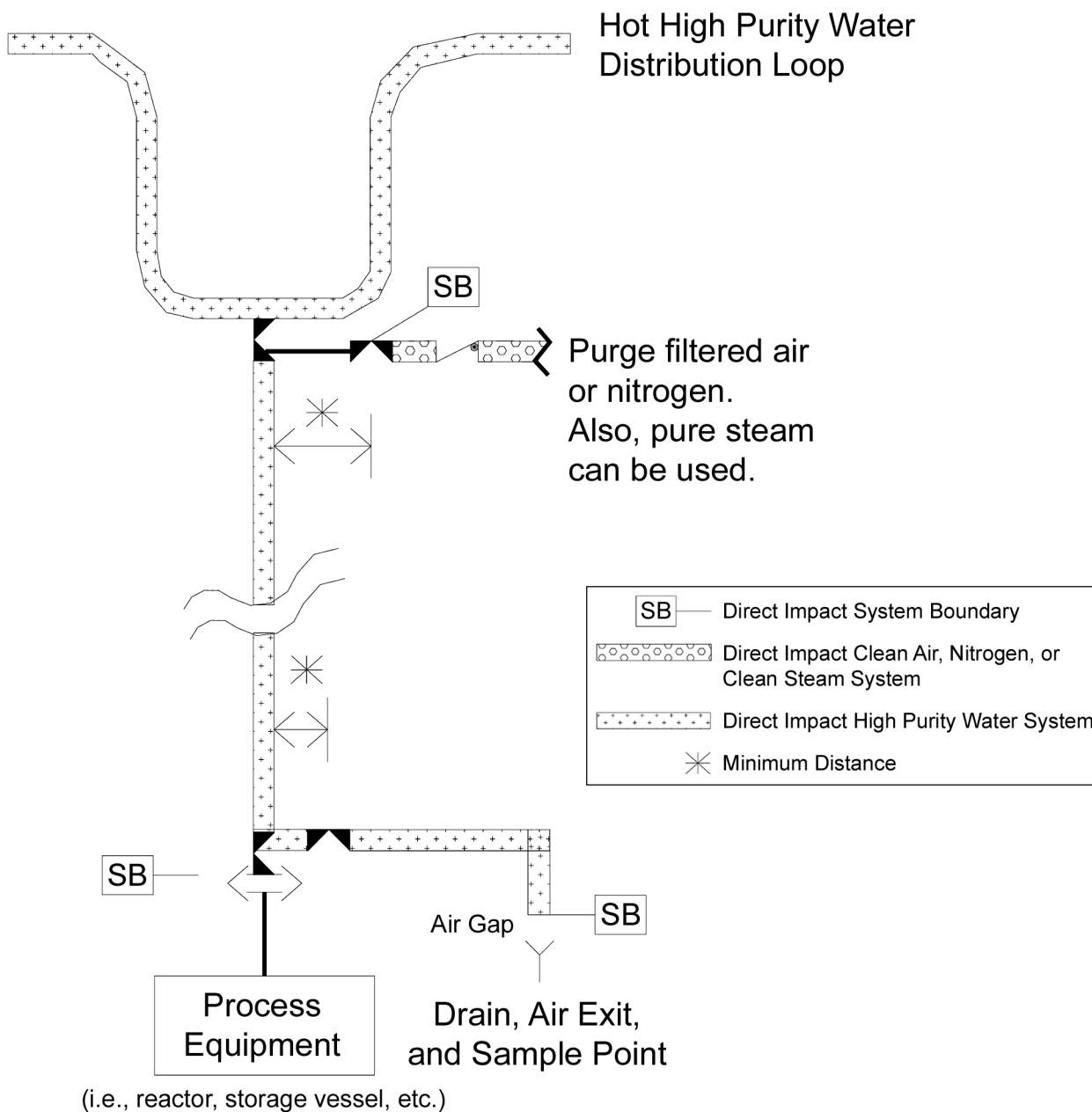


Figure 5.3: POU Piping with Integral Heat Exchanger System Classification Example

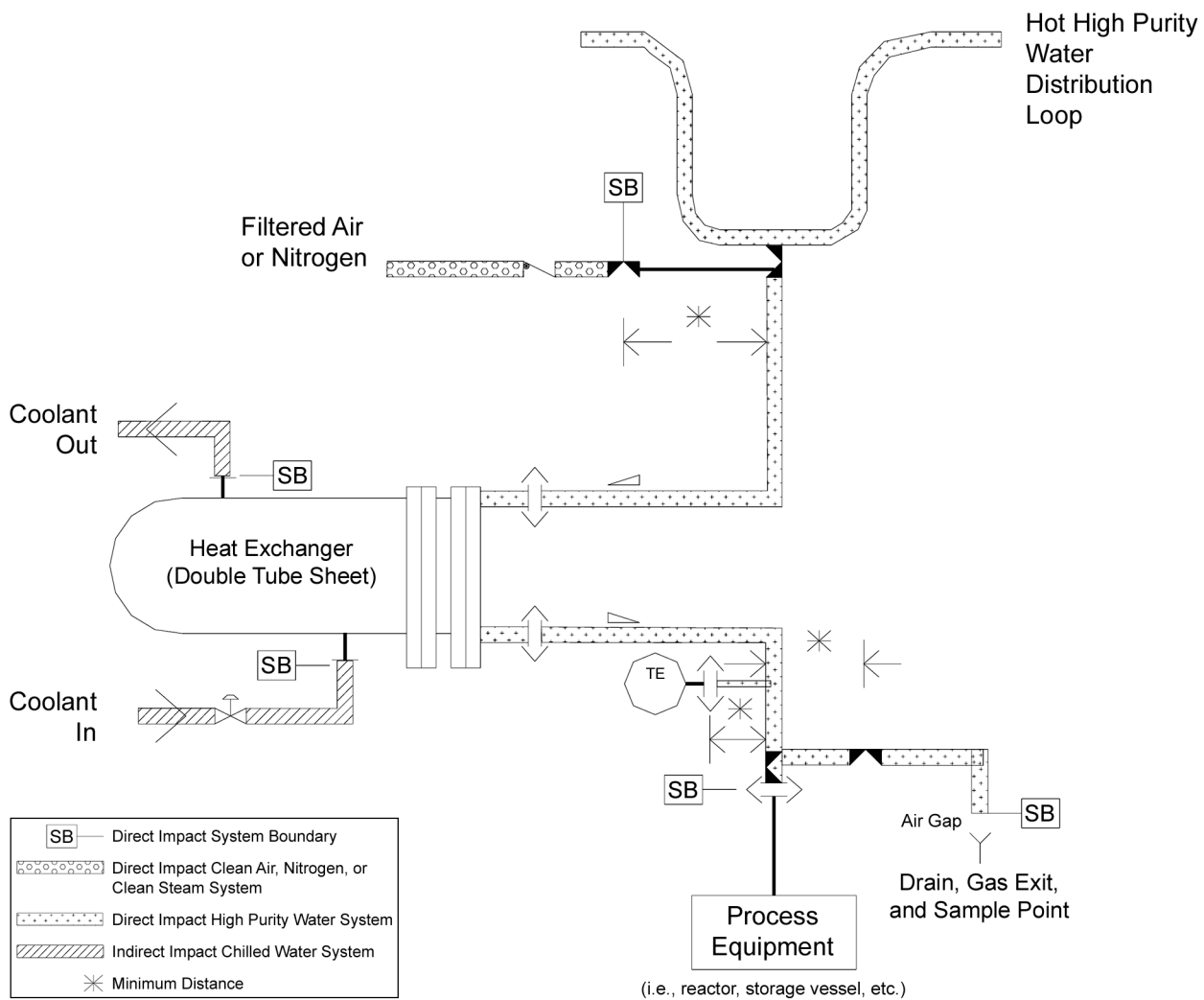


Figure 5.4: POU Piping with Hose System Classification Example

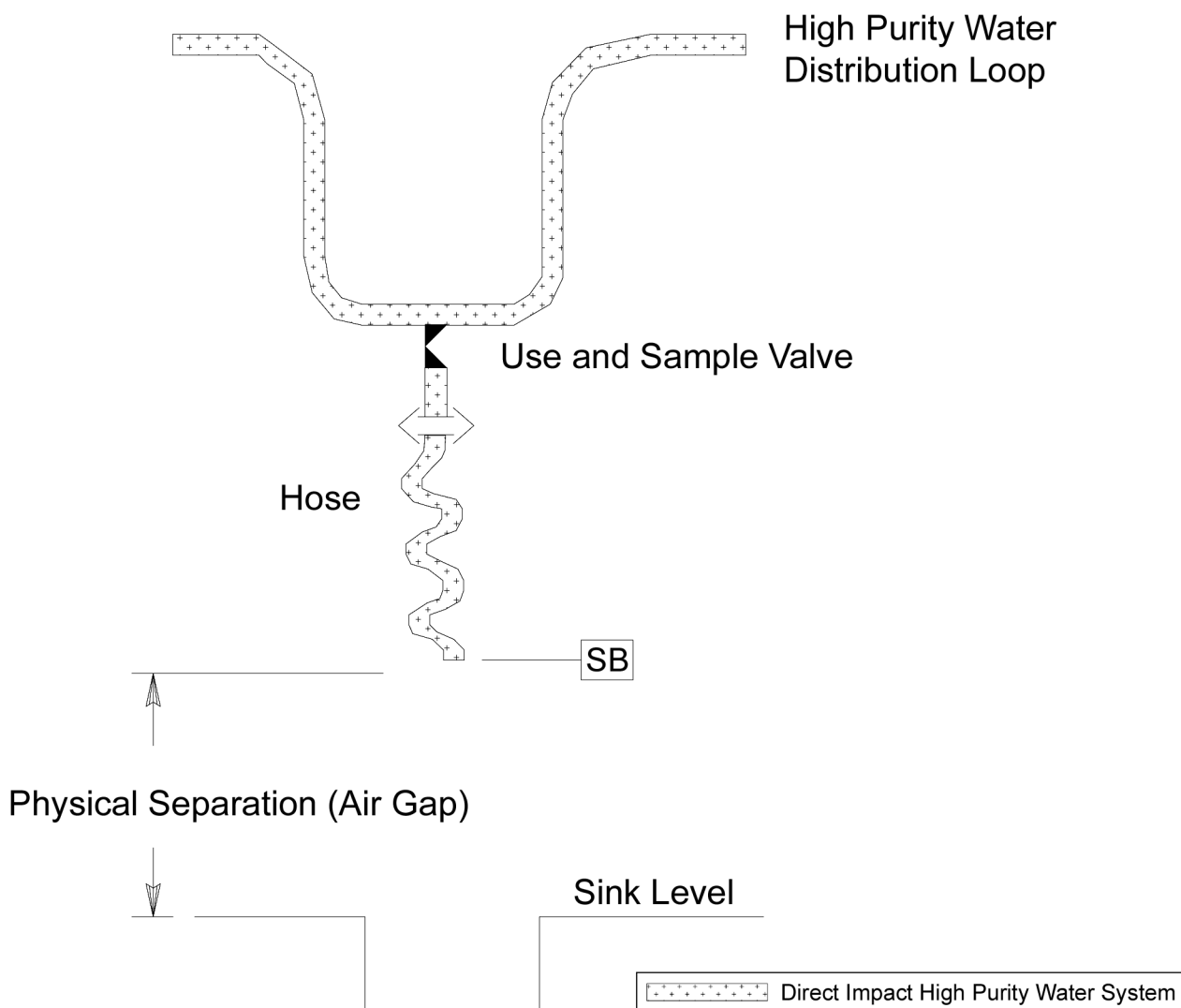
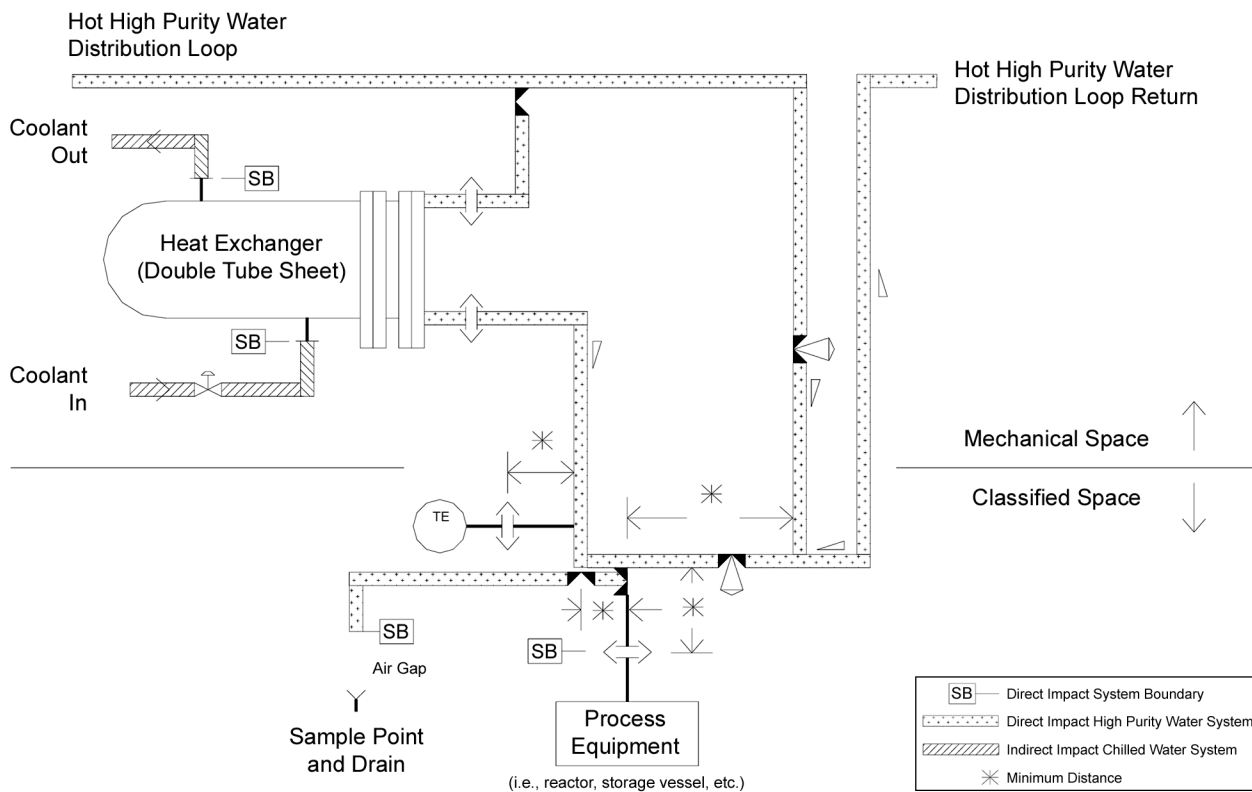


Figure 5.5: Water Distribution System Sub-Loop Example



Appendix 4

Typical Specifications for Water and Steam Systems

6 Appendix 4 – Typical Specifications for Water and Steam Systems

6.1 Introduction

The items requiring verification are generally listed for in the URs, FDS, and DDS. In this section, typical elements for inclusion in these specifications are given. These typical elements are given for demonstration purposes rather than as “absolutes.” In addition, brief descriptions of each specification are given.

Normally, these specifications are developed near the beginning of a project. An adequate level of specification definition should be achieved. Common pitfalls in the creation of these specifications include:

- Not specifying requirements
- Over specifying
- Under specifying
- Specifying requirements in multiple locations

Examples of these pitfalls as they apply to pharmaceutical water and steam systems, include:

- Not specifying requirements:
 - Water type and testing requirements
 - Microbial control methods
 - Critical parameters, including CQAs and CPPs
 - Quantity of water delivered to use point
 - Physical attributes of steam required
- Over specifying requirements:
 - Specific suppliers, other suppliers, manufacturers, or models
 - General hygienic process components and containment specifications rather than just those applicable to water systems
 - How the project should be constructed
 - Including too much construction detail which is likely to appear in another engineering document
 - Basis of design document
- Under specifying requirements:
 - Use of phrases such as “easily cleaned,” “meets current GMP requirements,” “complies with GEP”

- Leaving out designated surface finish for critical system components (e.g., piping/tubing materials, tanks, valves)
- Requirements, not measurable
- Specifications, not measurable

6.2 User Requirements

This specification gives the critical process requirements. The User Requirements (URs) says **what** the water or steam system should do. Items in this specification are tested or verified in PQ and “process validation.” Typical items included in URs for water or steam systems:

6.2.1 Purified Water/WFI

- Distillate from the WFI generation train shall meet the USP, EP, and JP specification for WFI. Product from the purified water generation train shall meet the USP, EP, and JP specification for purified water.
- The treatment train shall be capable of removing ammonia to the detection limit of the measurement instrument.
- TOC and conductivity instruments used for the system shall meet the specifications given in the USP.
- General methods, defined in USP, EP, and JP shall be used for establishing trends in the number of colony-forming units observed in the routine microbiological monitoring of WFI and purified water.
- The distribution system shall provide WFI/purified water quality water at all system POUs.

6.2.2 Process Water

- “Process water,” delivered to POUs, shall meet the quality specification for US EPA NPDWR drinking water or appropriate national drinking water specifications. Additionally, no coliforms are present. Finally, microbial colony forming level shall be less than 500 cfus/ml.
- Water testing methods described in “Standard Methods for the Examination of Water and Wastewater” or the appropriate national drinking water quality testing methods shall be used to determine compliance with the drinking water specification.

6.2.3 USP Pure Steam

- Pure (clean) steam from the generator, upon condensation, shall meet the same chemical and endotoxin quality specifications as WFI.
- Pure (clean) steam from the generator shall have – a dryness value of not less than 0.9 for porous loads for autoclaving, a dryness value of not less than 0.95 for metal loads for autoclaving, superheat content, which does not exceed 25°C (77°F) and non-condensable gas content not exceeding 3.5% by volume. Some steam applications do not require non-condensable gas limits.

6.2.4 Process Steam

- “Process steam,” delivered to points of use and once condensed, shall meet the quality specification for US EPA NPDWR drinking water, or appropriate national drinking water specifications.

- Pressure reducing and de-superheating stations should be fed with condensate or another water source that meets drinking water standards.
- Any additives for boiler operation should be FDA “food” grade additives meeting 21 CFR Part 173.310 [38] or equivalent.
- “Process steam,” delivered to POUs, shall contain superheated content, which does not exceed 20°C (68°F).

6.3 Functional Design Specification

This specification gives the functional design requirements. The Functional Design Specification (FDS) says how the water or steam system will function. Typically, the FDS is tested during commissioning. Here are typical items, which are included in the FDS for water or steam systems:

6.3.1 Purified Water/WFI

- Feed water quality to the purified water generation system shall be of US EPA NPDWR quality and contain no greater than 500 ppm hardness (as CaCO₃).
- In-line TOC and conductivity measurements shall be the primary method to approve WFI quality compliance.
- Reynolds number in the re-circulating piping section of the distribution loop shall be sufficient for fully turbulent conditions at all times of system operation.
- Distribution system will be able to maintain water temperatures equal to or greater than 70°C (158°F) at all times of operation.
- For the purified water distribution loop, system will be able to maintain ozone levels at 0.1 ppm in water in the storage vessel.
- The distribution loop shall be able to deliver 95 L/min (25 gpm) at three points of use, while maintaining 2.8 kg/sq cm (40 psig) at the spray nozzle inlet (return to vessel) during normal operation.
- The distribution system temperature control systems shall maintain 20°C (+/- 2°C) (68°F (+/- 35.64°F)) at all temperature measurement points in the system. Additionally, the thermal capacity of system shall allow temperature to increase and stabilize to 70°C (+/- 2°C) (158°F (+/- 35.64°F)) at all temperature measurement points within one hour from being at 20°C (68°F).

6.3.2 Process Water

- “Process water” pumps shall be able to deliver 3.05 kg/sq.cm. (100 ft.) of head, while delivering 380 L/min (100 gpm) to the piping and point of use network.
- The free chlorine injection system can provide maintenance of 0.5 ppm of free chlorine in the flowing “process water” distribution system.
- Main distribution and branch piping can achieve a “flush to drain” water velocity of 1.5 m/sec (5 ft/sec).

6.3.3 USP Pure Steam

- The pure (clean) steam generator shall provide 454 kg/hr (1000 pounds/hr) of pure (clean) steam at 4.2 kg/sq.cm. (60 psi) at discharge of the generator using USP purified water feed water to the pure (clean) steam generator.

- Generator blowdown shall be between 5% and 15% of generator capacity during normal operation.

6.3.4 Process Steam

- “Process steam” distribution system shall simultaneously provide 45 kg/hr (100 pounds/hr) of process steam at 2.8 kg/sq cm (40 psi) to six (6) use points.
- An on-line TOC meter shall be used to measure the TOC content of the “process steam” condensate.

6.4 Detailed Design Specification

This specification gives the detailed design requirements. The DDS specifies how to build the direct impact water or steam system. Typically, the DDS is tested or verified during commissioning. Here are typical items, which are included in the DDS for water or steam systems:

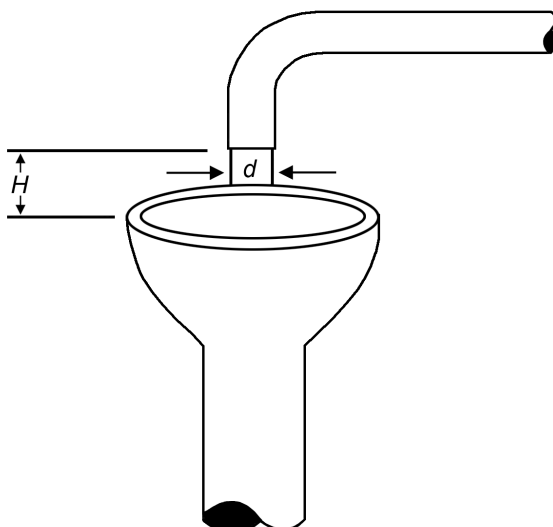
6.4.1 Purified Water/WFI

- Process/product contact surfaces for tanks, piping/tubing, valves, pumps and other components that contact the WFI shall be manufactured from 316L SS and have Ra finishes per Section SF of the ASME BPE Standard.
- All branch valves, which separate branch piping from the main loop, shall be installed per the ASME BPE requirements for “dead legs.”

6.4.2 Process Water

- Drawings or associated documentation for the process water distribution system shall include an “as-built” P&ID.
- The process water piping/tubing materials shall be provided in accordance to owner/user requirements and/or specifications.
- Air gaps will be used to separate (provide back flow protection) process water points of use and drains, as per diagram.

Figure 6.1: Drain with Air Break



General Note:

$H = 2 \times d$ or $H = 1$ in. (25 mm) if $d < \frac{1}{2}$ in. (13 mm)

- Distribution piping systems shall be designed without dead-ends (areas of piping where the flow stops and cannot be drained).

6.4.3 *USP Pure Steam*

- Provide isometric drawing for the pure systems.
- Pure (clean) steam piping distribution system shall be constructed of 316L SS.
- All pipework shall drain to low points fitted with steam traps to remove condensate.

6.4.4 *Process Steam*

- Drawings or associated documentation for the process steam distribution system shall include an “as-built” P&ID.
- Provide certified for construction detailed drawing for the portable steam condensate cooler.
- Steam traps are adequately installed to remove condensate.

Appendix 5

Sampling and Testing Plan

7 Appendix 5 – Sampling and Testing Plan

The following is the proposed plan for testing of the purified water generation and distribution systems, covering commissioning, and PQ stages 1, 2, and 3.

Purified Water System – The system has a hot loop, so the POUs will not be individually tested as they are considered a low risk, the higher risk points, i.e., those which are open to the area will be tested, as well as the pre-treatment and “water quality generation” parts of the system (Reverse Osmosis (RO), EDI) system.

Note: The last two sample points are both hot, circa 65°C (149°F).

Table 7.1: Pretreatment and Purification

Location	Commissioning	PQ1	PQ2	PQ3
Pre-softener	X	X	X	X
Post softener sample point/pre-heating heat exchanger	X	X	X	X
Post heating heat exchanger/pre-carbon filter	X	X		
Post carbon filter	X	X	X	T
Post RO pre-filter	X	X	X	
Post RO	X	X	X	T
Post CDI	X	X	X	T
Post 0.45 micron filter	X	X	X	T

Storage and Distribution System – This is a cold loop with weekly heat sanitization.

Table 7.2: Distribution Loop and Point of Use

Location	Commissioning	PQ1	PQ2	PQ3
Distribution Pump Discharge	X		Y1	
Post Heating Heat Exchanger		X	Y	Y
Point of Use Valve	X		Y	Y
Point of Use Valve	X	X	Y	Y
Point of Use Valve		X	Y	Y
Point of Use Valve			Y	Y
Point of Use Valve			Y	Y
Loop Return – Pre UV	X		Y	Y
Loop Return – Post UV		X	Y	Y
Loop Return – Post Cooling Heat Exchanger	X		Y1	Y

Key: X = Daily Sample
Y = Weekly Sample Rotating Locations (1 Pre-Sanitization-Sanitization – Worst Case)
T = Sample Pre- and Post-Sanitization

	Sample Point	Loop Outlet
Pump Discharge	MVDP9	
Level 1 CIP Skid	MV-6715-43	FCV-6715-01
Level 3 Solution Prep. 1	SP-6204-01	FCV-6715-02
Level 3 Solution Prep. 2	SP-6104-01	FCV-6715-03
Utility Panel In Room 356	MV-6715-04	
Feed To Lab Water System		FCV-6715-06
Level 3 IBC Washer	MV-6715-07	
Utility Panel In Room 338	MV-6715-05	
Level 2 Solution Delivery Tank Room 239	SP-6204-02	FCV-6715-08
Level 2 Solution Delivery Tank Room 240	SP-6104-02	FCV-6715-09
Level 1 Girton Parts Washer	MV-6715-41	FCV-6715-10
Level 2 Utility Panel Room 236	V-6715-11	
Level 1 Utility Panel Room 150	MV-6715-12	
Loop Return Pre Heating Heat Exchanger	MVDP10	
Loop Return Post Heating Heat Exchanger	MVDP11	MVCDI10

Outlet/Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
MVDP9	MC							C		M					C	M						C			M			C
SP-6109-01		M	C								M						M									M		
SP-6204-01			M		C							M						M									M	
SP-6104-01				M			C						M						M									M
MV-6715-04					M				C					M						M								
MV-6715-05						M					C				M						M							
FCV-6606-01	M						M						C			M						M						
MV-6715-07		M						M							C		M						M					
SP-6204-01			M						M								C	M						M				
SP-6104-01				M						M									CM						M			
SP-6715-01					M						M									M						M		
MV-6715-11						M						M									C						M	
MV-6715-12							M						M									M						M
MVDP10								M						M									MC					
MVDP11									M						M									M	C			

Key: M = Microbiology C = Chemistry

Appendix 6

Sample Turnover Package Requirements

8 Appendix 6 – Sample Turnover Package Requirements

Typical contents for a turnover package include:

- User Requirements (URs)
- Risk assessments/list of critical aspects
- Functional specification
- “As built” record drawings and specifications
- Parts list
- Spares list – consumables
- Spares list – recommended spares
- Material certification/certificates of conformity
- Construction records
- Quality inspection records
- Calibration certificates

Some of this information may include – supplier recommended instrument calibration and maintenance schedules, pump operation instructions, safety requirements, etc.

Typically construction records or TOP will include:

- Copy of the design specifications
- As built drawings (may be markup copies initially)
- Engineering change records (where applicable)
- Material certification:
 - Heat certificates for metals
 - Certificates of conformity for nonmetallic materials and instruments
 - Surface finishes
- Weld purge gas certification
- Welders certification
- Weld procedures
- Weld coupons

- Weld inspection reports/videos
- Weld Log
- Pressure test
- Cleaning and passivation report/test results
- Calibration certificates for system instruments, the welding equipment and construction QC test instruments

Turnover Package

- a. General information
 - i. Purchase order plus change orders
 - ii. Specifications and datasheets
 - iii. Drawings (P&IDs, supplier-provided, shop, record)
 - iv. Punchlist(s)
 - v. Start-up and commissioning (proposed and executed plans with results and reports)
 - vi. Warranties
 - vii. System release memo before start-up, commissioning or validation, this should include the pre-start-up safety report.
- b. Equipment
 - i. System documentation (surface finish reports, weld procedures and qualification, welder certification, weld map). Consult ASME BPE [21] for more detailed information.
 - ii. System documentation (specifications, datasheets, bill of materials, drawings, performance charts, certifications, inspection and pressure test reports, recommended spare parts list, installation guides and OEM manuals, ASME certificates, test records and calculations, USP VI <87> and <88> documentation [3], 21 CFR Part 177 [39] documentation, and ASME BPE [21].)
 - iii. SAT (proposed and executed plans with results and reports)
- c. Piping
 - i. Piping system documentation (isometric drawings, stamped seismic details, submittals and material test reports and certifications, surface finish tests and certifications)
 - ii. Piping/tubing weld documentation (weld procedures, isometric drawings, weld logs, welder certification, weld inspection, gas certifications)
 - iii. Pipe/tube brazing/soldering documentation (procedures and inert gas certificates)
 - iv. Installation documentation/field verification (piping slope, pressure test, flushing/cleaning, and passivation reports, isometric drawings with slope verification)

- v. Installation documentation/field verification (piping/tube slope and hydrostatic pressure test reports and as-built or record drawings)
- d. Electrical
 - i. Single line drawings
 - ii. Electrical submittals
 - iii. Electrical equipment checkout electronic equipment installation
 - iv. Motor checklist
 - v. Pump operation instructions
- e. Instruments
 - i. Instrument index (instrument list, I/O list)
 - ii. Instrument submittals (specifications, datasheets, loop diagrams, O&M manuals, calibration, control valve field verification reports)
 - iii. Instrument punchlist
 - iv. Instrument field verification
 - v. Supplier recommended instrument calibration and maintenance schedules
- f. Controls
 - i. Control specifications
 - ii. Controls submittals
 - iii. Operator interface
 - iv. Control panel
 - v. Software submittals (software development standards, design description, operator interface panels, screen prints, executed test plans, electronics and hard program copy)
 - vi. Sequence of operation (executed testing procedure)
 - vii. Controls checkout reports (loop check, field power source, input/output, alarms)

Appendix 7

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9 Appendix 7 – References

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Appendix 8

Glossary

10 Appendix 8 – Glossary

10.1 Acronyms and Abbreviations

A&E	Architect and Engineer
BET	Bacterial Endotoxins Test
C&Q	Commissioning and Qualification
CA	Critical Aspect
CEDI	Continuous Electro De-ionization
CFS	Chemical Free Steam
CMMS	Computerized Maintenance Management System
COD	Critical Operating Data
CPP	Critical Process Parameter
CQA	Critical Quality Attribute
DCS	Distributed Control System
DDS	Detailed Design Specification
DI	Deionized Water
DIN	Deutsches Institut für Normung eV (German Institute for Standardization; similar to US ANSI)
DR	Design Review
DQ	Design Qualification
EBRS	Electronic Batch Record System
ECC	Engineering Change Control
ECM	Engineering Change Management
EDI	Electrodeionization
EDR	Enhanced Design Review
EP	European Pharmacopeia
EPA	Environmental Protection Agency (US)
EU	European Union
FAT	Factory Acceptance Test

FDA	Food and Drug Administration (US)
FDS	Functional Design Specification
FMEA	Failure Mode and Effect Analysis
FS	Functional Specification
GAMP	Good Automated Manufacturing Practice
GEP	Good Engineering Practice
GMP	Good Manufacturing Practice
GRAS	Generally Recognized as Safe
HEPA	High Efficiency Particle Assay (filtration)
HMI	Human-Machine Interface
HSE	Health, Safety, Environmental
HVAC	Heating, Ventilation, and Air Conditioning
I/O	Input/Output
ICH	International Conference on Harmonization
IQ	Installation Qualification
IT	Information Technology
IV	Installation Verification
JP	Japanese Pharmacopeia
MU	Measurement Uncertainty
NAMAS	National Accreditation of Measurement and Sampling (UK)
NIST	National Institute of Standards and Technology (US)
NPDWR	National Primary Drinking Water Regulations (US)
O&M	Operation and Maintenance
OQ	Operational Qualification
ORP	Oxidation Reduction Potential
OV	Operational Verification
P&ID	Process and Instrumentation Diagram (Drawing)

PAT	Process Analytical Technology
PFD	Process Flow Diagram
PLC	Programmable Logic Controller
PM	Preventive Maintenance
POU	Point of Use
PQ	Performance Qualification
PW	Purified Water
QbD	Quality by Design
QC	Quality Control
QMS	Quality Management System
QRM	Quality Risk Management
QU	Quality Unit
RACI	Responsible, Accountable, Consulted, Informed
RO/EDI	Reverse Osmosis/Electro De-ionization
SAT	Site Acceptance Test
SIP	Steam-In-Place
SLIA	System Level Impact Assessment
SME	Subject Matter Expert
SOP	Standard Operating Procedure
TOC	Total Organic Carbon
TOP	Turnover Package
UR	User Requirement
USP	United States Pharmacopeia
UV	Ultraviolet
VC	Vapor Compression Still
WFI	Water for Injection
WHO	World Health Organization

10.2 Definitions

Action Level

Levels or ranges (actual attribute values) that, when exceeded, indicate that a process has drifted from its normal operating range. Exceeding an action level indicates that corrective action should be taken to bring the process back into its normal operating range.

Alert Level

Levels or ranges (actual attribute values) that, when exceeded, indicate that a process may have drifted from its normal operating condition. Alert levels constitute a warning and do not necessarily require a corrective action.

Active Pharmaceutical Ingredient (API)

Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

As-Built" Drawings (Record Drawings)

Construction drawings that represent the physical condition of the plant or system at turnover from the designer or installer at satisfactory operation. These documents supplement and compliment the system manuals and protocols.

Calibration

A comparison of an instrument measurement standard or instrument of known accuracy to detect, correlate, report, or eliminate by adjustment any variation in the accuracy of the unknown standard or instrument.

Change Management System

A systematic approach to proposing, evaluating, approving, implementing, and reviewing changes.

Clean or Pure Steam

Water vapor under pressure and free of boiler additives. When condensed, the clean or pure (clean) steam condensate meets the quality specification for WFI.

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 that defines the facilities, systems, and equipment that will be commissioned based on agreed system boundaries. It also defines how they will be commissioned and what the responsibilities for the associated staff personnel are.

Compendial

Official; purported to comply with USP, EP, or JP.

Control Loop

A group of devices that compare the process variable to a required process condition defined as a set point. Should the Process Variable (PV) deviate from the desired Set Point (SP), the controller will perform a control algorithm based on the error between PV and SP that will then adjust a final control device (valve, actuator, heater, motor, damper, etc.) to bring the PV back to the desired SP.

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.

Critical Process Operating Parameter

A processing variable (temperature, pressure, level, pH, etc.), which may influence the final water or steam quality characterization or impurity profile.

Critical Process Parameter (CPP)

A process parameter whose variability impacts a critical quality attribute and therefore needs to be controlled to ensure the process produces the desired quality. A critical process parameter remains critical even if it is controlled.

Critical Quality Attribute (CQA)

Attribute of the water or steam product which usually relates to the identity, purity, or quality of the water or steam product. Some attributes for water and steam are contained levels of TOC, conductivity, microbial activity, etc.

Critical Operating Data (COD)

Subset of process critical operational data (typically, measured values of critical quality attributes) that exists (measured or system generated) in electronic measurement and control systems. These data may depict the identity, purity, or quality of the water or steam product.

Design Qualification (DQ) (*also called Enhanced Design Review*)

Documented verification that the proposed design of the facilities, equipment, or systems is suitable for the intended purpose.

Detailed Design Specification (DDS)

The Detailed Design Specification (DDS) gives the detailed design requirements. The DDS specifies how to build the direct impact water or steam system. Typically, the DDS is tested or verified during commissioning or qualification.

Direct Impact System

A system, which is expected to have a direct impact on final water or steam 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.

Drinking Water (USP)

Drinking water is not covered by a compendial monograph, but must comply with the critical quality attributes of the US EPA NPDWR or comparable regulations of the European Union, World Health Organization (WHO), or Japan. It may be derived from a variety of sources including a public water utility, a private water supply (e.g., a well), or a combination of more than one of these sources. Drinking water may be used in the early stages of chemical synthesis and in the early stages of the cleaning of pharmaceutical equipment. It is the prescribed source feed water for the production of pharmaceutical waters. As seasonal variations in the critical quality attributes of the drinking water supply can occur, processing steps in the production of pharmaceutical waters must be designed for this characteristic.

Electronic Batch Record System (EBRS)

One or more systems/applications that facilitate the creation/revision, approval, distribution, execution, and data collection of electronic batch record elements; a computer system that stores, in electronic format, the batch record information required by healthcare regulations.

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 Test (FAT)

The partial commissioning and qualification of equipment and/or systems prior to their shipment from the fabricator's site.

Final Device Loop

A group of devices that manipulate the process in a manner that affects the process variable.

Functional Design Specification (FDS)

The Functional Design Specification (FDS) gives the functional design requirements. The FDS says how the direct impact water or steam system will perform its function. Typically, the FDS is tested or verified during commissioning or qualification.

Good Engineering Practice (GEP)

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

High Purity Water

Water conforming to USP Monographs or equivalent.

Highly Purified Water (EMA)

Water intended for use in the preparation of products where water of high biological quality is needed, except where water for injection is required. Highly purified water is obtained from water that complies with the regulations on water intended for human consumption laid down by the competent authority. Current production methods include, for example, double-pass reverse osmosis coupled with other suitable techniques such as ultrafiltration and deionization. Highly purified water meets the same quality standards as WFI but the production methods are considered less reliable than distillation and thus it is considered unacceptable for use as WFI.

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

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 requirements 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.

Loop Check

Different than a loop test, loop check is a process to verify that the components of a measurement loop, control loop, or final device loop, not only are wired correctly, but to confirm that they are “operating as designed.” The loop check can include defining the loop performance benchmark and providing a method for monitoring the performance over time.

Loop Test

Procedure to verify that a group of instruments (transmitters, controllers, recorders, alarms, marshalling panels, input/output modules and any other devices) perform together correctly to achieve a process control strategy.

Measurement Loop

A group of devices that are connected together to infer a process variable (e.g., flow, temperature, pressure, level, etc.), and convert this process variable into a process measurement signal.

Measurement Uncertainty (MU)

Data analyses which provides information to establish the extent of confidence limits bounding a measurable quantity.

No Impact System

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.

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 operating ranges.

Ozone

Ozone is a very strong gaseous oxidizing agent. It is used in deionized water systems to kill bacteria and to reduce, by oxidation, the amount of TOC in the water. Ozone is O₃ and due to reaction with other things rapidly becomes oxygen (O₂). Therefore, it has a short but effective oxidizing potential. It can be destructive to ion exchange using membrane filters and other plastic materials in the system.

Process Analytical Technology (PAT) (ICH Q8(R2))

A system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality.

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.

Periodic Review (PR)

A documented assessment of documentation, procedures, records, and performance to ensure that facilities, equipment, and systems continue to be fit for purpose and safety regulatory compliance requirements. The frequency of periodic review is dependent upon the complexity, criticality, and rate of change.

Potable Water

Water that is suitable for drinking.

Pure (Clean) Steam

Pure steam is water that has been heated above 100°F and vaporized in a manner that prevents source water entrainment. It is prepared from water complying with the U.S. Environmental Protection Agency National Primary Drinking Water Regulations, or with drinking water regulations of the European Union or Japan, or with WHO drinking water guidelines. It contains no added substance. The level of steam saturation or dryness, and the amount of noncondensable gases are to be determined by the Pure Steam application.

Purified Water

USP purified water. Prepared from water complying with the critical quality attributes of drinking water with conductivity in accordance with Stage 1, 2, and 3 tests and conductivity tables. Total organic carbon limit is at 0.5 mg/l. typically less than 100 CFU/ml (10,000 CFU/100 ml) for microbiological acceptability.

Process Contact Surfaces

Surfaces of process components that, under normal design operating conditions are in direct contact with, or have the potential to come in contact with raw materials, in-process materials, Active Pharmaceutical Ingredients (APIs), clean utilities (e.g., WFI, pure steam, CIP solutions, process gases), and where there is a potential for a component (e.g., stoppers) surface to impact drug product(s) strength, identity, safety, purity, and quality.

Product Contact Surfaces

Surfaces of process components that are in direct contact with, or have the potential to come in contact with drug product(s) where drug product(s) are defined by owner/user. Examples of product contact surfaces may include the interior surfaces of bioreactors, process tanks, storage vessels, transfer piping/tubing, pumps, chromatography columns, and recirculating segments of CIP systems.

Qualification Protocol

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

Qualification Summary Report

Report summarizing the results of protocol execution.

Quality Control

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

Quality Unit (*also known as Quality Assurance*)

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

Quality System (ICH Q9)

The sum of all aspects of a system that implements quality policy and ensures that quality objectives are met.

Reverse Osmosis (RO)

A process that reverses (by the application of pressure) the flow of water in the natural process of osmosis so that it passes from the more concentrated to the more dilute solution. This is one of the processes used to reduce the ionic TDS, TOC, and suspended materials of feed water through a semipermeable membrane leaving dissolved and suspended materials behind. These are swept away in a waste stream to drain.

Risk (ISO/IEC Guide 51)

The combination of the probability of occurrence of harm and the severity of that harm.

Risk Analysis (ICH Q9)

The estimation of the risk associated with the identified hazards.

Risk Assessment (ICH Q9)

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

Risk Communication (ICH Q9)

The sharing of information about risk and risk management between the decision maker and other stakeholders.

Risk Control (ISO Guide 73)

Actions implementing risk management decisions.

Sequence of Operation

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 shutdown.

Site Acceptance Test (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.

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 define what is, and is not included in the system.

Turnover Package (TOP)

A collection of pertinent design, construction, supplier, and operational documentation. This collection of documentation is used for the qualification and process validation activity, as well as reference and single source information for the life of any particular system, process, or piece of equipment.

User Requirement Specification (URS)

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

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 critical quality attributes.

Validation Master Plan

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.

Validation Lifecycle

Listing of a series of events within the life of a direct impact manufacturing system which are identified as important to create or maintain product quality over the life of the direct impact system.

WFI

USP water for injection. Prepared from water complying with the critical quality attributes of drinking water. Prepared produced by distillation or a process that is equivalent or superior to distillation in the removal of chemical and micro-organisms. Conductivity in accordance with Stage 1, 2, and 3 tests and conductivity tables. Total organic carbon limit is at 0.5 mg/l typically less than 10 CFU/100 ml for microbiological acceptability. Less than 0.25 USP EU/ml.

Water Types

Types of process water used in biopharmaceutical processing, ranging from municipal ("potable") water to Water for Injection (WFI).

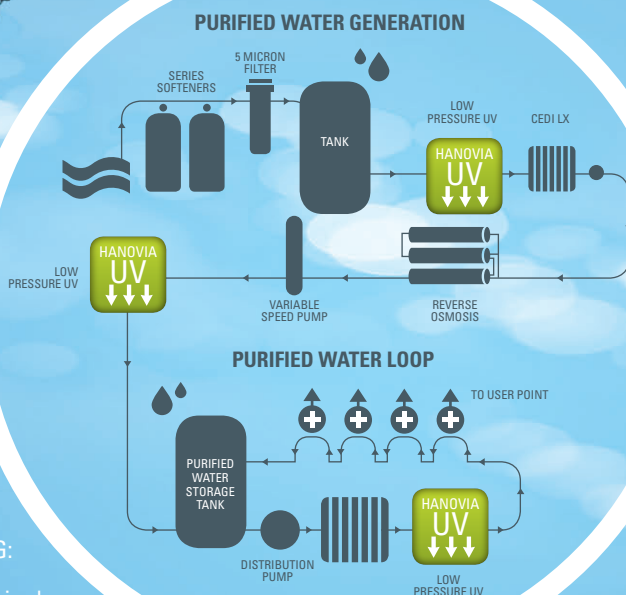
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Bio-assayed, validated independently, disinfection performance to guarantee ultimate process security
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- > **ABSOLUTE DRY UV SENSOR**
DVGW designed, factory calibrated and removal without interrupting water flow
- > **UV OPERATIONS**
Self-adjusting with variable flow and transmittance, maintains optimum disinfection while ensuring energy efficiency
- > **SANITARY DESIGN**
Tri-clamp connections, 0.38um internal surface finish, no ball valves meets latest Pharmaceutical standards
- > **SMART CONTROL SYSTEM**
Informative display, digital / analogue I/O and Modbus communication capability provides flexibility to operators for remote monitoring and control



Pharmaceuticals

Cosmetics
+Toiletries

Medical
+Ophthalmic

Nutraceuticals

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PHARMALINE PQ
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