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Baseline®
PHARMACEUTICAL ENGINEERING GUIDE
FOR NEW AND RENOVATED FACILITIES

VOLUME 4

Water and Steam Systems

Third Edition

ISPE ®

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Preface

The global biopharmaceutical industry and regulators are responding to the challenge of significantly improving the way drug development, manufacturing, documentation, and compliance is managed. New concepts are being developed and applied including science-based risk management approaches, focus on product and process understanding, and quality management systems.

Uncertainty about the requirements for regulatory compliance may discourage innovation and encourage reticence in technological advancement, preventing the cost-effective implementation, adoption, and lifecycle management with new and innovative technologies. ISPE Guides aim to describe current good practices that can help a company develop an effective and cost-efficient approach in compliance with existing regulations and relevant guidances.

This third version of the *Baseline® Guide: Pharmaceutical Water and Steam Systems* describes new variations in the European Pharmacopoeia for the manufacture of Water for Injection by methods other than distillation. Additional changes include discussions on the global harmonization of water quality attributes, comprehensive pretreatment design, rapid microbial monitoring, ozone for ambient sanitization, and membrane technologies.

Acknowledgements

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1   Introduction

1.1   Background

The design, construction, commissioning, qualification, and continued performance of water and steam systems for the pharmaceutical industry represent significant challenges, as these systems need to meet Good Manufacturing Practice (GMP) regulations while remaining in compliance with all other governing codes, laws, mandates, and regulations.

The design, complexity, and cost of these systems are highly variable, compounded by interpretation of regulatory requirements and corresponding design approaches. This Guide is intended to offer a practical and industry-accepted interpretation of regulatory requirements, while providing a broad spectrum of innovative and proven approaches and applications to water and steam system design, construction, commissioning, and qualification.

This Guide has been prepared by ISPE and leading industry experts, with representative feedback from all areas and disciplines of the industry. It reflects ISPE's current thinking related to new water and steam systems and takes into account the FDA's guidelines for *Pharmaceutical cGMPs for the 21st Century – A Risk-Based Approach and Process Analytical Technology* [1] and other guidance documents, for example, from the International Council for Harmonisation (ICH) [2] and International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) [3].

There are numerous pharmacopeias established in different countries or regions. This document highlights the most commonly followed pharmacopeias: The United States Pharmacopeia (USP) [4], The European Pharmacopoeia (Ph. Eur.) [5], Japanese Pharmacopoeia (JP) [6], and Pharmacopoeia of the People's Republic of China [7]. Other pharmacopeias are used for the local production along with marketing and sales of pharmaceuticals within the confines of those borders. In instances where a pharmacopeia is not established, World Health Organization (WHO) guidance may be used [8].

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

1.2   Scope of this Guide

This Guide is intended to assist with the design, construction, operation, and lifecycle management of new and existing water and steam systems. It is neither a standard nor a detailed design guide. The validation of water and steam systems, comprised of commissioning and qualification activities, is not discussed in depth in this Guide, but is covered in the *ISPE Good Practice Guide: Approaches to Commissioning and Qualification of Pharmaceutical Water and Steam Systems* [9] and the *Baseline® Guide: Commissioning and Qualification (Second Edition)* [10].

This *Baseline® Guide: Water and Steam Systems (Third Edition)* focuses on engineering issues and provides innovative and technologically accepted solutions and alternatives for water and steam systems. It is not intended to replace governing laws, codes, guidelines, standards, or regulations that apply to pharmaceutical water and steam systems. Where non-engineering issues (e.g., microbiological topics) are covered, the information is included to stress the importance of such topics and their impact on water and steam system design. The use of this document for new or existing water and steam systems is at the discretion of the designer, owner, or operator.

This Guide is intended primarily for interpretation of regulatory compliance involving the US FDA [11] and the USP [4], while recognizing the status and importance of worldwide harmonization efforts by the ICH [2] and VICH [3] guidelines. The information presented may also be applicable to other regulatory entities, such as European Medicines Agency (EMA) [12], European Directorate for the Quality of Medicines & Health Care (EDQM) [13], Japanese Industrial Standards (JIS) 14], China's National Medical Products Administration (NMPA) [15], and their representative pharmacopeias, as well as WHO [16], and Pharmaceutical Inspection Convention and Scheme (PIC/S) [17]. Reference is made to the American Society for Testing Materials (ASTM) [18], the American Society of Mechanical Engineers (ASME) [19], and the International Organization for Standardization (ISO) [20], among others.

1.3 Key Topics included in this Guide

The following key topics are addressed within this Guide:

- Specifying water quality and system planning

- Project management

- Pretreatment, purification, and final treatment

- Steam

- Storage and distribution and sanitization

- Laboratory water

- Rouge

- Instrumentation and control

- Commissioning and Qualification (C&Q)

- Microbiological considerations

1.3.1 Specifying Water Quality and System Planning

The selection or specification of the quality required for water or steam is potentially the most critical step in planning a new or renovated pharmaceutical water or steam system, from a regulatory, technical, and financial perspective (see Chapter 2). This selection is likely to have a more significant impact on performance and reliability of the system than subsequent design decisions; the risk of noncompliance and system failures should be considered. The designer should have knowledge of the applicable regulations and the technologies capable of consistently meeting those regulations.

Once process water or steam requirements are determined, system design options can be evaluated. This Guide presents alternative baseline water treatment technologies and water system design options with their advantages and disadvantages.

This Guide emphasizes evaluating system design alternatives based on:

- Feed water quality

- Pretreatment and final treatment technologies

- Storage and distribution system design alternatives

- Operation requirements

- Final product quality requirements

The goal is a system design that meets User Requirements Specifications (URS) and is compliant with regulatory requirements.

1.3.2   Project Management

Project management, as it applies to pharmaceutical water and steam systems, recognizes that these systems require adequate installation, operation, C&Q, and performance (see Chapter 3). Planning should ensure appropriate documentation, inspection, and field testing. Good project management capitalizes upon this practice suggesting that manufacturers engage stakeholders (engineers, operators, Quality Assurance (QA), installers) early in the planning, design, construction, and commissioning/qualification phases to ensure that systems are appropriately documented for regulatory qualification.

1.3.3   Pretreatment, Purification, and Final Treatment

This Guide emphasizes that water systems can be designed to meet performance criteria in many different ways while meeting the overall requirements of users (see Chapters 4, 5, and 6). A carefully planned approach to the design, with input from appropriate areas of an organization (e.g., engineering, operations, manufacturing, QA), should be implemented to provide the needed pretreatment, purification, and final treatment modules.

1.3.4   Pharmaceutical Steam

Industry standard practices for pharmaceutical steam used in various applications required to meet regulatory requirements are discussed in Chapter 7. Definitions of the steam types are included. In addition, system planning and alternative design practices are reviewed in detail to help facilitate development of the most appropriate overall system design to meet the user requirements.

1.3.5   Storage and Distribution, and Sanitization

Storage and distribution, and sanitization depict the piping and storage mechanisms specified for Purified Water (PW) or WFI (see Chapter 8). Materials of construction are imperative to maintain a pristine and viable system with little or no microbial detection. Parametric values of pressure, flow, temperature, conductivity, storage capacity etc. can be deemed Critical Process Parameters (CPP) or Critical Quality Attributes (CQA) by the user, even though these parameters are non-compendial. Sanitization chemicals and sanitization methods may be corrosive to piping material, elastomers, and other materials in the system. Careful selection is imperative to maintain lifecycle duration estimates.

1.3.6   Laboratory Water

Laboratory water can be classified in various ways that may or may not meet aspects PW and WFI (see Chapter 9). Laboratory waters are susceptible to other industry classifications that emulate USP compendial mandates. For example, laboratory water used for chromatography often has very stringent contaminant levels that are stricter than USP compendial mandates [4].

1.3.7   Rouge

The latest theories and industry practices addressing the formation of rouge in high purity water and Pure Steam systems are presented (see Chapter 10). Detailed information is provided on the types and classifications of rouge that typically occur in these systems, as well as methodologies to address the issue. Analysis and examples show the science of rouge formation to assist organizations in making informed decisions about the presence of rouge.

1.3.8   Instrumentation and Control

This Guide includes general guidance on defining and monitoring CPPs and CQAs for water and steam systems (see Chapter 11). CPPs are the parameters that directly affect the product. CQAs are physical, chemical, biological, or microbiological properties or characteristics maintained within an appropriate limit, range, or distribution to ensure the desired product quality. CQAs and CPPs may be mandated or non-compendial values and measurements, such as:

*   Conductivity

*   Total Organic Carbon (TOC)

*   Microbial level

*   Endotoxin

*   Pressure

*   Flows under unique conditions

*   Temperature

*   Reverse Osmosis (RO) recovery

*   Ozone concentration

1.3.9   Commissioning and Qualification

This Guide describes updated applications of C&Q using science and risk-based Quality Risk Management (QRM) to determine risk controls (Critical Aspects (CAs)) and associated Critical Design Elements (CDEs). These become CQAs and CPPs, which are associated with the quality attributes and requirements of the respective product impacting the utility system (see Chapter 12).

1.3.10   Microbiological Considerations

Controlling microbial proliferation requires thorough consideration throughout the conception, design, construction, qualification, operation, maintenance, and monitoring of the water system (see Chapter 13). Water may be sufficiently rich in nutrients to support the growth of some types of microorganisms, as a result of remnants of very low levels of inorganic and organic contaminants. The microbial growth in water purification and distribution systems needs to be controlled, if not completely prevented. The finished water must be suitable for use in pharmaceutical, biopharmaceutical, and medical device applications and for use by associated patients and consumers.

1.4   Guide Structure

Figure 1.1 shows the structure of this Guide. The chapters have been organized to assist the decision-making process by initially determining the type of water required and then determining the system design needed from pretreatment to final treatment. Guidance through options for storage and distribution, selecting the proper instrumentation and control, microbiological control methods, and recommendations for C&Q are provided. Additionally, the Guide contains detailed information on related topics, such as laboratory water, rouge, and Pure Steam.

Figure 1.1: Structure of the ISPE Baseline® Guide: Water and Steam Systems
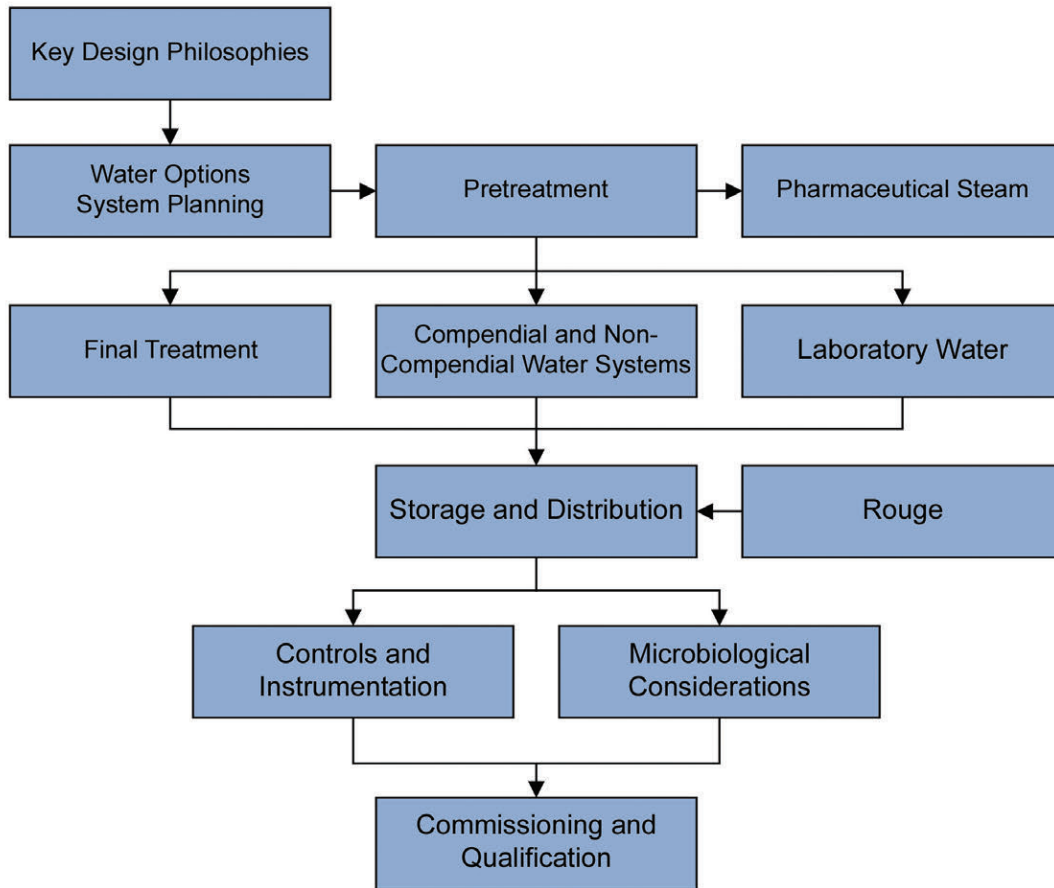
2   Key Design Philosophies

2.1   Introduction

Pharmaceutical water is the most widely used utility and ingredient in drug manufacturing and the main component in equipment/system cleaning; therefore, systems for the production, storage, and distribution of pharmaceutical water and steam constitute essential elements in most manufacturing facilities. The control of potential sources of contamination (chemical and microbiological), while delivering the required quantity of water, is the primary goal of pharmaceutical water and steam system design. This Guide identifies technologies that can assist in achieving this goal and industry methods (current at the time of publication) available to engineers for design of systems that minimize the risk.

The quality of pharmaceutical water and steam is critical both from a regulatory point of view and from a financial perspective. The pharmaceutical water and steam specifications have a significant impact on the lifecycle cost of the system. It must be demonstrated that pharmaceutical waters (non-compendial and compendial) and steam can be produced and distributed consistently to meet the stated specifications.

Establishing the level of microbial control needed in a pharmaceutical water and steam system used in the manufacture of a biopharmaceutical product requires an understanding of both the use of the product and the manufacturing process.

Pharmaceutical water and steam users should define the appropriate water purity based upon sound process understanding, system equipment capability, and user requirements. They should determine the:

*   Specific purification capability for each processing step

*   Modes for monitoring or measuring CQAs and CPPs per purification step or module

*   Limitations of the unit operation

The major compendia, USP, Ph. Eur. and JP [4, 5, 6], describe two bulk compendial waters – Purified Water (PW) and Water for Injection (WFI), which are discussed in this Guide. Additional bulk waters, such as USP Water for Hemodialysis and Ph. Eur. Highly Purified Water (HPW), are also reviewed. Annex 1, the GMP guide for Sterile Medicinal Products [21], is not addressed in this ISPE Guide.

Note: The Ph. Eur. designation of HPW was eliminated in April 2019 [5], but may still apply to water systems using this water classification that were commissioned 2002-2018.

Note: Compendial usage and compliance to Ph. Eur. is mandatory for products produced and/or sold in the governing region [5]; however, local or regional regulatory officials may require adherence to additional regulatory guidances.

This Guide primarily covers PW, WFI, Pure Steam, and pretreatment, plus additional non-compendial waters, including laboratory water. It is common practice to name non-compendial waters (exclusive of drinking water) used in pharmaceutical manufacturing by the final treatment step (i.e., Reverse Osmosis (RO) water, Deionized (DI) water, etc.). See Chapter 3.

Guidance on establishing specifications for monographed water is provided in the major compendia, the requirements of which are listed in Chapter 9, Table 9.3.

2.2 Pharmacopeial Water and Steam

The major compendia specify standards of quality, purity, generation, packaging, and labeling for a number of waters, including two bulk waters, Water for Injection and Purified Water, and Pure Steam used in the preparation of compendial dosage forms [4, 5, 6]. This Guide is concerned with the production, storage, and distribution of compendial bulk waters and steam, and does not address the other packaged waters monographed by these compendia.

2.2.1 Purified Water and Water for Injection

Official requirements for PW and WFI are provided the USP, Ph. Eur., and JP [4, 5, 6]. These monographs provide the minimum requirements for production methods, source water quality, and quality attributes. The major compendia have been largely harmonized. The water user should review the monographs for specific attribute requirements to ensure compliance for each case.

2.2.2 Pure Steam

Official requirements for Pure Steam are set forth in the USP [4]. This monograph provides the minimum requirements for production methods, source water quality, and quality attributes. The Pure Steam user should review the monographs for specific attribute requirements to ensure compliance for each case.

2.2.3 Compendial Testing Requirements

2.2.3.1 Conductivity and Total Organic Carbon (TOC)

The compendia provide chapters describing the test method and instrumentation requirements for testing conductivity and TOC. Conductivity measures non-specific conductive ions in the water. TOC is the measurement of oxidizable carbon molecules present in water.

Instruments are available for measuring conductivity in-line and TOC online from slip stream, and off-line from grab samples manually removed from the water system. Automatic off-line sample introduction systems are available for processing large numbers of grab samples. For further information, see Chapter 11.

2.2.3.2 Microbial and Endotoxin Testing

Microbial contaminants and endotoxins are traditionally sampled at Points of Use (POU) in a water system. Endotoxin testing for Pure Steam is measured in the condensate. Additional sampling, for profiling or informational usage, may be periodically performed at the outlet of the generation system, and before and after any unit operation design for total viable bacteria or endotoxin reduction (e.g., RO, UF), if warranted. Chapter 13 contains additional information.

2.2.4 Validated (Verified) Backup Instrumentation

Failure of a monitoring instrument should not be precluded when making decisions concerning type, location, and the extent of validation (verification). Online installations may be supplemented with a calibrated laboratory or an additional calibrated online instrument as backup. Validation (verification) should include the operation in off-line mode as a supplement or an alternative to online instrumentation. Off-line laboratory testing also can include a backup instrument that is maintained and calibrated in case of primary unit failure. Backup also may be provided by a qualified third-party laboratory.

2.3 Specification of Pharmaceutical Water Quality – Establishing Acceptance Criteria

It is the responsibility of the water user to confirm that the quality of water supplied in the pharmaceutical process is consistent with the quality required for the final product. It may not be sufficient to specify a water quality that meets the specification of the grades of bulk water outlined in the compendia. These grades, described in the PW, WFI, and Pure Steam monographs are minimum standards. A more stringent specification may be called for depending on the intended use of the product and on the process used to manufacture that product.

Uses of pharmaceutical water typically include:

- An ingredient in dosage form manufacturing

- An ingredient in an Active Pharmaceutical Ingredient (API) process. The term API is sometimes used interchangeably with Bulk Pharmaceutical Chemical (BPC). Note: All API are BPC, but not all BPC are API.

- A wash and/or rinse during Clean in Place (CIP), clean out of place, or manual cleaning

- A solvent or diluent for research, production, or laboratory processes

- A bulk pharmaceutical product for Large Volume Parenterals (LVPs) or Small Volume Parenterals (SVPs)

Water intended for use as a dosage form ingredient must minimally meet compendial water standards and must be produced consistently to meet or exceed monograph requirements. Evidence of control is required for all CPPs that may affect the final drug characterization (ICH Q8 [22]). For parenteral products, WFI must be used [23]. Waters with endotoxin control are expected for some ophthalmic and inhalation products. For further information, see Chapter 3.

For some applications where there are no requirements for compendial waters, the user may establish quality specifications equivalent to PW or WFI, depending on the specific application, or equivalent to these waters with additional or fewer requirements.

Note: The use of compendial monographs when not required should be closely evaluated for cost and maintenance impact.

Specifications for water used as an ingredient (exclusive of sterile bulks) in the manufacture of APIs or as the solvent in the wash or rinse cycles should be determined by the user. In some cases, drinking water may be acceptable, or certain chemical, microbial or endotoxin quality specifications may be established, or one of the compendial waters may be used. The specification should be based on the potential for alteration of the final drug product.

With the appropriate justification, non-compendial waters (including drinking waters) may be utilized throughout pharmaceutical operations, including production equipment washing/cleaning and rinsing, laboratory usage, and as an ingredient in the manufacture or formulation of bulk API. However, water meeting or exceeding compendial requirements must be used in the preparation of compendial dosage forms.

For both compendial and non-compendial waters, the user should establish an appropriate microbial quality specification. The significance of microorganisms in non-sterile pharmaceutical products should be evaluated in terms of the nature and use of the product and the potential harm to the patient. Manufacturers are expected to establish appropriate microbial alert and action levels for microbial counts associated with the types of pharmaceutical waters utilized. These levels should be based on process requirements and the historical records of the system in question.

Acceptance criteria for pharmaceutical waters and steam are determined by the manufacturing process, end product, and applicable regulatory and compendial requirements. Pretreatment and final treatment subsystems, storage and distribution systems, and operator and maintenance procedures are then designed based on, among other criteria, the quality of the feed water to meet the acceptance criteria.

2.4   Critical Quality Attributes and Critical Process Parameters

CQAs and CPPs are defined in ICH Q8 [22] and ASTM E2500 [24] and should be referenced where applicable to a water system. For further information, see Chapter 12.

2.5   GMP Compliance Issues

Satisfying regulatory concerns is primarily a matter of establishing proper specifications while using effective and appropriate methods to verify and record that those specifications are satisfied. Issues such as quality of installation, sampling and testing procedures, operating and maintenance procedures, training, record keeping, etc., may be considered as significant as the particular technologies selected to purify and distribute the water and steam.

Each pharmaceutical water and steam system should be viewed in its entirety, as design and operational factors affecting any unit operation within the system can affect the whole system from initiation to the POU. It is useful to identify the quality parameters of both the water entering the system and the water or steam produced. Water quality should be enhanced with each successive step. It does not necessarily follow that measures enhancing one quality attribute (such as conductivity, particulate level, or color) will always enhance another (such as microbial population).

2.6   Design Range versus Operating Range

This Guide provides detail on recognizing the distinction between design range, proven acceptable range, and normal operating range, and the impact this distinction has upon qualification and facility system operation (see Chapter 11). Details on the use of action and alert levels also are provided.

Alert levels are based on normal operating experience, statistical values or deviations, and are used to initiate corrective measures, such as sanitizations, but may not initiate a formal corrective action plan.

Action levels are based on operating experience considering possible yearly fluctuations or worst-case and upset conditions.

Design Range: the specified range or accuracy of a controlled variable used by the designer as a basis to determine the performance requirements for an engineered system.

Proven Acceptable Range: ICH Q8(R2) [22] *"A characterised range of a process parameter for which operation within this range, while keeping other parameters constant, will result in producing a material meeting relevant quality criteria."* The range of parametric values within which acceptable water product can be produced and validated per the URS. Proven acceptable range is sometimes referred to as "allowable operating range" in pre-ICH Q8 released documentation.

Normal Operating Range: a range that may be selected as the desired acceptable values for a parameter during normal operations. This range should be within the allowable operating range.

While a water or steam system should meet all stated design conditions, the acceptability of the system for operation from a GMP standpoint depends on operating within the proven acceptable range.

The concept of alert and action levels may be applied along with the normal operating and proven acceptable ranges (see Figure 2.1). Proactive measures can be taken when a water system is trending out of control to prevent specification limits from being exceeded. Alert levels are typically based on normal operating experience and/or statistical relevance, and can be used to initiate investigations or corrective measures before reaching an action level. Action levels are defined as the level at which some corrective action must be taken to prevent the water from reaching a specification limit. USP General Information Chapter <1231> Water for Pharmaceutical Purposes [4], identifies action and alert limits only, as specification limits are user defined. Exceeding the specification limit is an Out of Specification (OOS) condition that can dictate production stoppage, investigation, and multi-departmental actions.

Figure 2.1: Values of Critical Parameters for Product Water
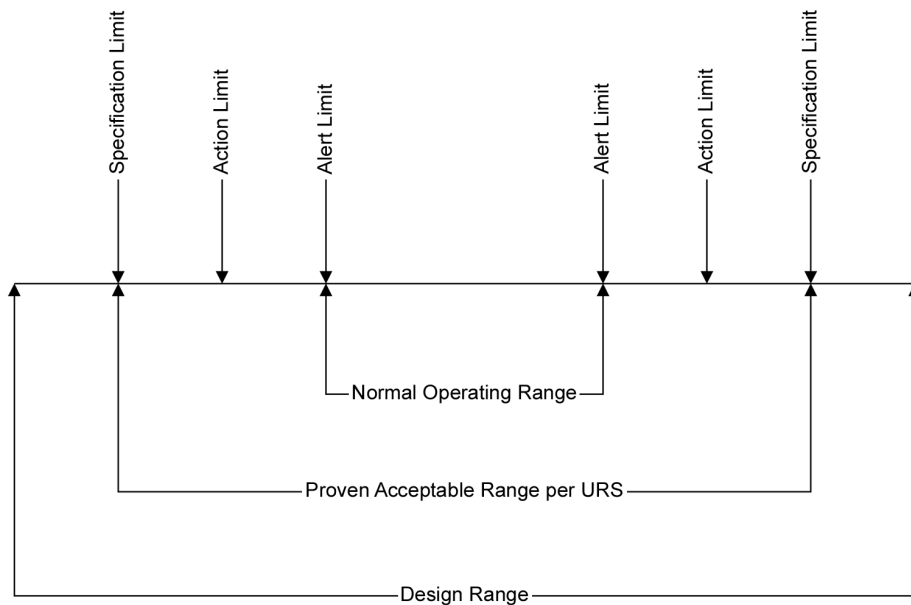
Note: These are general representations provided for example.

2.7   Process Analytical Technology

Process Analytical Technology (PAT) was introduced by the FDA with the release of the 21st Century Guidance Initiatives of 2004 [25]. PAT indicates the health of the system by measuring the in process CPPs and CQAs to show compliance to the URS and mandated requirements. The data obtained allows for the assessment of continual process improvement by understanding the complete process and developing adjustments to enhance the process, throughput, and product quality. Instituted during C&Q testing, PAT is used extensively for operations, product release, and continuous adherence to compendial, URS directives, and mandates. PAT can be used for the entire water system, any selected module, or any set of selected modules.

3   Water Options and System Planning

3.1   Introduction

This chapter outlines basic water system design criteria, and along with subsequent chapters, aims to provide a better understanding of pharmaceutical waters, how they are used, how much is needed, and their quality requirements. The primary goal of this chapter is to provide the user with a methodology for:

- Determining the incoming or source water characteristics

- Understanding, evaluating, and selecting among water quality options

- Evaluating system makeup, capacity, and instantaneous demand requirements

- Evaluating various system configurations able to meet selected quality requirements

- Understanding system planning and programming steps

Information regarding unit operations, system design, maintenance, and relative costs is addressed in subsequent chapters.

This chapter also outlines the system planning effort for pharmaceutical water systems, beginning with the selection of water quality based upon product requirements, processing operations, end use, and ongoing sampling and monitoring requirements. A decision tree is included to assist in the selection of compendial and non-compendial waters for use in production, cleaning, and support. Subsequent information guides the user through use-point and system analysis resulting in an overall water system distribution strategy. Evaluation points are provided to assess various system configurations.

3.2   Incoming or Source Water Characteristics

Any water system planning effort must begin with a determination of the incoming or source water quality characteristics. There may be substantial seasonal variations in water quality from any water supply, regardless of whether the source is public or private. Public or municipal water sources usually meet established requirements for potability (e.g., drinking water guidelines) and supporting data are generally available from municipalities. However, this is not always the case, and there may be wide variations of incoming water quality between locations as well as in different countries.

Private water sources or other water sources may be considered as a source of incoming water, but the water quality of these sources may not meet the applicable requirements for potability (e.g., drinking water guidelines). In the United States, the National Primary Drinking Water Regulations (NPDWR) determines the drinking water quality. In this case, the pharmaceutical company must treat the water to render it potable or acknowledge that the raw water meets the NPDWR, since potable water is the assumed starting water quality for the production of any grade of pharmaceutical water. Further, adding substances to adjust pH, remove chlorine, etc. may be considered based on incoming water source characteristics. Any substances added to the water may be safely added provided that their sufficient removal can be reliably documented within the limits of their detectability. See Chapter 4 for a more complete discussion on added substances and their removal.

There are also water quality differences between surface water supplies and well water supplies that may drive the selection of suitable technologies for the generation of pharmaceutical grades of water. Depending on the degree of variability in the water supply, it may be beneficial to analyze feed water characteristics for at least 12 months to develop a suitable water quality profile before evaluating water purification technologies and options.

3.3   Water Quality Options

3.3.1   *Determining Water Quality Requirements*

Quality requirements and methods of production for water used in pharmaceutical manufacturing and product development are driven by several factors including:

•   Patient impact

•   Product characteristics

•   Manufacturing processes

•   Route of administration (injection, ingestion, etc.) of the product

•   Regulations in the pharmacopeia of the country where a product is manufactured or sold

Quality by Design principles and risk analysis tools stress patient impact assessments resulting from water quality decisions at the inception of the planning process in order to arrive at the most suitable water quality option(s). To aid in the water quality selection process, compendial monographs define minimum requirements for general types of pharmaceutical water used in most applications. In addition, there are guidelines in some areas (Europe) that define the minimum required quality of water for product types [23]. However, there is also the opportunity for a manufacturer to establish water quality requirements, different from those defined in the monographs, based on specific product characteristics and processing operations. Ultimately, the product manufacturer is responsible for assuring that water used to manufacture the product is appropriate, and can be proven to reliably produce a safe product.

Although water quality attributes may be product specific, it may be impractical to produce multiple grades of water with different quality attributes particular to each product. Based on cost and other factors and limitations, pharmaceutical manufacturers may elect to generate and distribute only a few, or perhaps only one quality of water; therefore, products and operations requiring similar water qualities may be commonly grouped.

The water quality attributes defined by monographs are generally viewed as adequate for production of safe product; however, more or less stringent water quality specifications may be appropriate for some products and processes as determined by the pharmaceutical manufacturer. For example, more stringent requirements may apply to some processing operations involving significant concentration steps or products with high water content and that may be applied in large volume doses. Likewise, processes involving reliable purification and/or sterilization steps that remove impurities may, in some cases, not require water qualities as strict as those defined in the monographs. Other process characteristics can affect water quality requirements as well.

In manufacturing operations where the generation of only one quality of water is practical, the water system should be designed to meet the most stringent requirements of the most demanding product or process. When more than one quality of water is available, products and processes are often categorized and fed by the most appropriate system. The number and types of water generated is most often a function of the volume of water consumed, the variation in quality required, and the cost differential. Larger consumers may find it economical to generate and distribute multiple grades of water, while smaller users may often generate only one quality of water.

Waters used in the development, manufacture, or preparation of drugs and drug substances can be classified broadly into two categories: compendial and non-compendial. Compendial waters are defined by monographs in recognized pharmacopeias. The three pharmacopeias discussed most frequently in this Guide are:

•   United States Pharmacopeia (USP) [4]

•   European Pharmacopoeia (Ph. Eur.) [5]

• Japanese Pharmacopoeia (JP) [6]

As pharmaceutical production continues to become more global, pharmacopeias from China [7], India [26], South America [27], and the WHO International Pharmacopoeia [28] may influence water quality attributes and equipment design decisions. Ultimately, with over 140 countries establishing pharmacopeial requirements throughout the world, the locale or region where the drug product or substance is manufactured, sold or used may dictate the influence of specific pharmacopeias. As the requirements for specific water qualities are not completely harmonized, it is prudent to consult with the appropriate Quality Unit to ensure all applicable regulations are met.

Compendial waters meet the requirements for specific types of water in the applicable monographs. Examples of bulk grades of compendial waters include:

• Purified Water (PW) – defined by USP, Ph. Eur., JP, and other monographs [4, 5, 6]

• Water for Injection (WFI) – defined by USP, Ph. Eur., JP and other monographs [4, 5, 6]

• Highly Purified Water (HPW) – previously defined by Ph. Eur. monograph but deleted as of April 2019 [5]

• Water for Hemodialysis (WFH) – defined by USP and Ph. Eur. monographs [4, 5]

The specifications outlined in the monographs are the minimum requirements for compendial waters. Other specifications may be added or combined based on process requirements. For instance, an endotoxin specification could be added to PW if needed for the process or product application.

Non-compendial waters meet the requirements of potable water at a minimum and are often additionally treated to meet process requirements. They may contain added substances for microbial control and do not have to meet all compendial requirements. Non-compendial waters are sometimes described by the final or critical purification process used, for example, RO water. In other cases, non-compendial waters are described by a specific quality attribute of the water, such as low endotoxin water.

It is important to note that non-compendial waters are not necessarily of lesser quality than compendial waters. Non-compendial waters may, in fact, be of much higher quality than compendial waters if required by the application. Common non-compendial waters include:

• Potable water – water that meets US Environmental Protection Agency (EPA) National Primary Drinking Water Regulations (NPDWR) [29] or comparable regulations of the European Union [30], Japan [31], or the WHO [32]. This is the minimum quality of water used in pharmaceutical processing and represents the starting point for preparation of any compendial waters.

• Softened water – potable water that has been additionally treated and includes a water softening process to remove hardness generally associated with calcium and magnesium contaminants, as either the final or most important unit operation.

• RO water – potable water that has been additionally treated and includes reverse osmosis as either the final or most important unit operation.

• UF water – potable water that has been additionally treated and includes ultrafiltration as either the final or most important unit operation.

• DI water (or EDI water) – potable water that has been additionally treated and includes a deionization process such as IX or EDI as either the final or most important unit operation; may be classified as EDI water if the deionization process is specifically electrodeionization.

- RODI water – potable water that has been treated with a combination of RO and DI (or EDI) to meet specific application requirements.

- Distilled water – potable water that has been additionally treated and includes distillation as either the final or most important unit operation.

- Laboratory water – potable water that has been additionally treated and meets the requirements for water used in laboratory applications. For further information, see Chapter 9.

Non-compendial water is not necessarily less critical, less costly to produce, or easier to qualify compared to compendial water. It can enable the manufacturer to set product-specific quality and/or test criteria that are appropriate for the product and processes. In addition, non-compendial water systems may or may not be validated (see Chapter 12).

Generally speaking, removing more impurities and contaminants from a water source is more expensive than removing fewer impurities and contaminants; however, the specifics of each facility under consideration may be different. For example, a plant with existing excess capacity of WFI might elect to use WFI rather than a suitable lower grade of water. In the example case, documentation should identify the quality required for the product and the reason WFI was used in its place. If there is a significant difference between the two water qualities in question, an assessment also should be conducted to ensure that the water is not too pure for any application, which typically is not the case when comparing Purified and WFI grades of water.

Figure 3.1 shows a decision tree that can be followed by manufacturer organizations to determine appropriate requirements for water used throughout their pharmaceutical manufacturing processes. The completed diagram should be accompanied by documentation supporting the options chosen with review and approval by the Quality Unit. Decisions should be based on product and process-specific requirements, as water supplied to any process must consistently meet or exceed the requirements defined by the manufacturer for the safe and reliable manufacture of that product.

Figure 3.1 includes the most common water types and selections; however, it is impractical to provide a single decision tree capable of covering the full breadth of diverse choices possible.

Figure 3.1: Pharmaceutical Water Quality Decision Tree
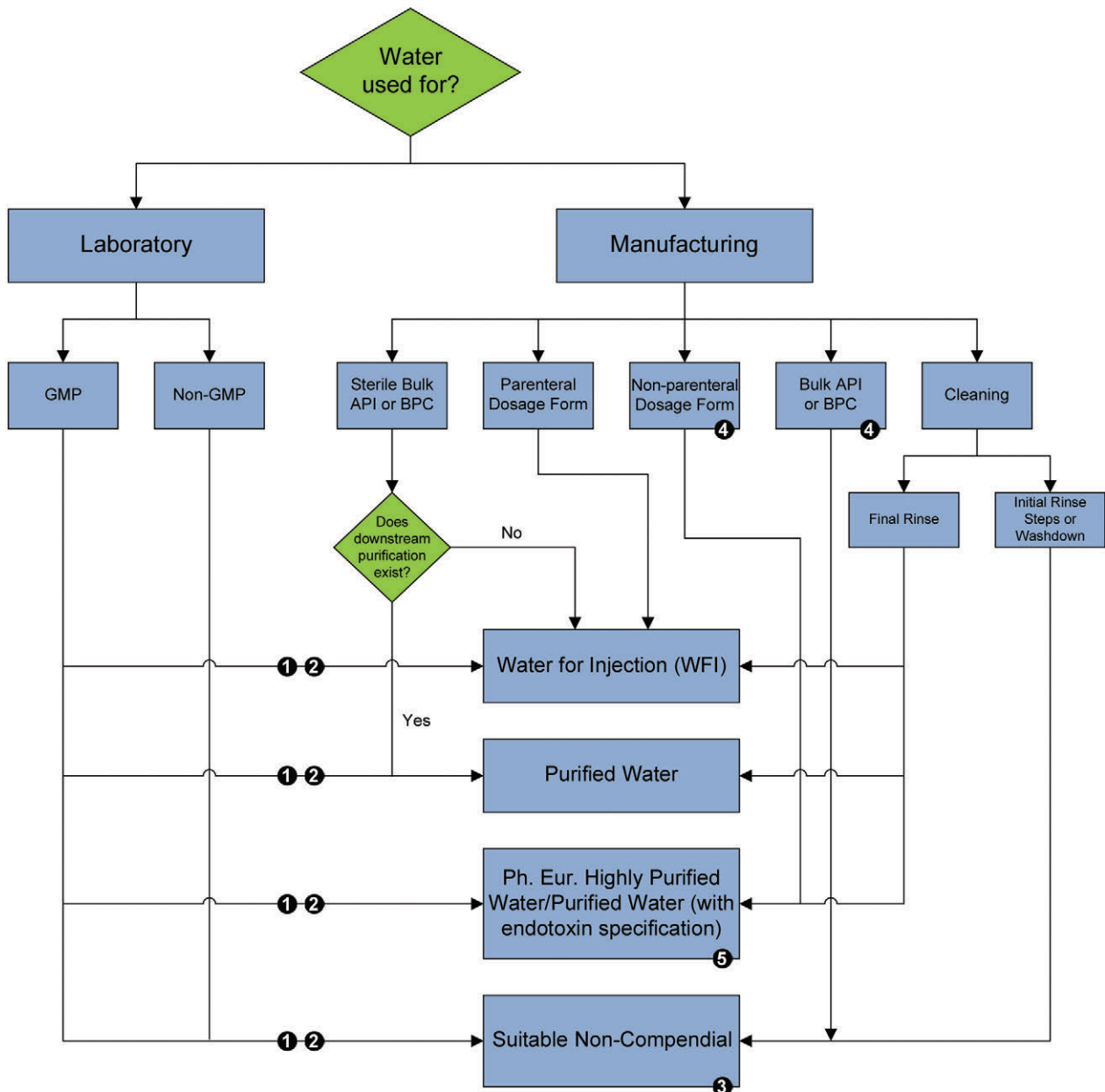
Notes:

1. By definition, some analytical methods require compendial waters. Water quality attributes should meet the needs of the analytical methods.

2. Laboratories performing both GMP and non-GMP operations should follow the GMP path. See Chapter 9 for a discussion of laboratory grade water.

3. Non-compendial water may be of higher quality than compendial water. Endotoxin and microbial quality requirements may be instituted based on the process and quality needs of the product. Minimally, non-compendial water must meet applicable potable water requirements for microbiological quality.

4. Water quality specifications that include endotoxin limits (e.g., WFI, USP, PW with an endotoxin specification, etc.) should be employed for waters used in the manufacturing of non-parenteral products where endotoxin control is required. This requirement is a function of the specific process and the nature of the downstream purification steps. Purified Water could be an intermediate grade of water between suitable non-compendial and Purified Water with an endotoxin specification and is included as an option.

5. Highly Purified Water was deleted from the Ph. Eur. April 2019 [5]

Table 3.1 provides baseline requirements for most product-contact water applications. Water quality criteria for pharmaceutical manufacturing and product development are driven by the product characteristics, manufacturing process, and the intended use of the product. Specific product and process characteristics may dictate that more or less stringent criteria than shown are appropriate.

Table 3.1 gives engineers some general guidance on the selection of pharmaceutical water quality. Product development, engineering, manufacturing, quality, and regulatory stakeholders should be consulted to give further input into the selection of the appropriate quality attributes of pharmaceutical water.

Once water quality requirements have been determined, Table 3.1 identifies some of the more common unit operations that may be utilized. The arrangement of components varies widely throughout the industry as well as from different locations of the same manufacturer. While distillation is a universally accepted method of producing WFI grade water, many pharmacopeias do not define the method used to produce a specific grade of water.

The primary criterion in evaluating process options is whether the selection will assist in consistently producing water with the necessary quality attributes. Table 3.1 is intended to provide a general recognition that systems can be created using a variety of components when suitably arranged. This is not to say that every system should have each of the components listed or that components can only be used as indicated.

Table 3.1: Typical Unit Operations Utilized Based on Water Quality Requirements

	Turbidity and Particulate Reduction	Hardness and Metal Reduction	Chlorine Removal and Organic Reduction			Organic, Inorganic, Bacteria Reduction		Organic, Inorganic, Bacteria, and Bacterial Endotoxin Reduction		Ionic Reduction		Bacteria or Endotoxin Reduction
	Primary/Course Filtration	Softening	Activated Carbon	UV De-Chlorination Unit	Sulfite Injection	Single-Pass Reverse Osmosis (RO)	Two-Pass RO	Multi-effect Distillation	Vapor Compression Distillation	Continuous Electro-deionization (CEDI)	Ion Exchange	UV Unit, Microfiltration or Ultrafiltration (UF)
Potable Water												
Softened Water	X	X										
RO Water	X	X	1	8	X	X	3					
Deionized (DI) Water	X		1	8	X	X	3			X	5	7
Distilled Water	X	X	1	8	X	6	6	4	4			
RODI Water	X	X	1	8	X	X	3			X	X	X
Laboratory Water	X	X	X	8		X	3			X	5	7
Purified Water (PW)	X	X	1	8	X	X	3	2	2	X	5	7

Table 3.1: Typical Unit Operations Utilized Based on Water Quality Requirements (continued)

	Turbidity and Particulate Reduction	Hardness and Metal Reduction	Chlorine Removal and Organic Reduction			Organic, Inorganic, Bacteria Reduction		Organic, Inorganic, Bacteria, and Bacterial Endotoxin Reduction		Ionic Reduction		Bacteria or Endotoxin Reduction
	Primary/Course Filtration	Softening	Activated Carbon	UV De-Chlorination Unit	Sulfite Injection	Single-Pass Reverse Osmosis (RO)	Two-Pass RO	Multi-effect Distillation	Vapor Compression Distillation	Continuous Electro-deionization (CEDI)	Ion Exchange	UV Unit, Microfiltration or Ultrafiltration (UF)
Water for Injection (WFI)	X	X	1	8	X	6	6,9	4	4	9	9	9

Notes:

X = Commonly employed or applied process

1. Activated carbon is commonly used in lieu of sulfite injection on surface feed water supplies or feed waters high in organic content.
2. Distillation may be used to produce PW.
3. An RO second pass may be used on feed waters high in Total Dissolved Solids (TDS) or for specific contaminant reduction.
4. Single or multi-effect is commonly used for lower capacity systems while vapor compression is common for higher capacity systems. For further information, see Chapter 5.
5. Service exchange (non-regenerable) DI is most commonly used for low flow or intermittent demand systems.
6. RO is used for vapor compression pretreatment for specific contaminant reduction, such as silica or endotoxin. RO (single or two pass) is more commonly employed for multiple-effect distillation feed.
7. UV units are used throughout water treatment systems for the reduction of bacteria, chlorine, and organic material. Filters are often employed for reduction of suspended solids, colloidal material, and bacteria. For further information, see Chapters 4 and 5.
8. A typical UV dose for photodecomposition of free chlorine is about 20 to 100 times higher than the standard disinfection UV dose. Consideration of this process is based on the ppm level of chlorine concentration in the feed water. For further information, see Chapter 4.
9. Several alternative combinations utilizing RO followed by DI, CEDI, RO, UF, microfiltration, and/or other steps may be used for production of WFI. For further information, see Chapter 6.

3.3.2 Total Cost of Ownership

Estimating the cost of pharmaceutical water production is not complicated, although it may not always be easy to properly identify all of the associated costs. Costs are actually quite predictable; however, they vary significantly depending on the scale of operation, system design, actual usage, utility costs, maintenance philosophy, and complexity. Items that can have a significant impact on overall costs include:

- Initial investment for capital equipment

- Equipment and piping system installation

- Utilities

- Labor for operation

- Sampling, monitoring, and testing

- Preventive maintenance, calibration, and service

- Consumables

- Reliability

- Waste disposal

The total operating cost to produce pharmaceutical waters is obtained by adding the cost of feed and waste water to the operating costs of the entire system (including pretreatment and final treatment processes, consumables), along with any ancillary items identified. The system operating cost includes common expenses such as utilities, etc., but also likely includes costs somewhat unique to water systems, such as periodic de-rouging and passivation of SS systems, or sanitization/sterilization of distribution piping systems.

Other significant costs should be anticipated for the initial system C&Q, ongoing sampling and monitoring including microbiological testing, calibration as well as waste treatment and sewer and disposal costs. In addition, regulated industries need to evaluate the risks (cost) of noncompliance and water system failures. Storage and distribution systems should be considered when estimating system operating, maintenance, and calibration costs.

To correctly compare various technologies, or to determine the total cost of generating pharmaceutical water, the overall lifecycle cost, including capital and operating costs over the expected lifetime of the system, should be investigated. This exercise is a critical process to determine the actual costs that a pharmaceutical water system will incur. A system with a large service component may be the least expensive to purchase, but requires a far greater operating expense. If one can reasonably predict the lifetime of a system, one may be able to justify a greater capital investment if a lower operating or overall lifecycle cost is realized. Conversely, when the water requirement is temporary or of unknown duration, a system requiring a smaller capital investment may represent an attractive alternative.

In addition, system scalability and the potential for future growth should be considered in system design as well as in the lifecycle cost analysis. The designer should be aware of the impact on the overall design if future production quantities need to be increased or decreased. Space may be allocated in mechanical areas for additional capacity to support future growth. Certain equipment designs may or may not be easily scaled up or down. On the other hand, distribution systems may not be able to handle capacity changes and are both costly and inefficient to replace in an operating facility.

The generation technology of choice and its associated capital cost are utilized to determine the total pharmaceutical water system Net Present Value (NPV). The technology choice is based on the applicable regulatory requirements for the method of manufacture, capacity requirements, feed water variations, TDS and hardness levels, organic and colloidal content, as well as anticipated water system utility costs (chemicals, power, steam, and source water). Consideration also should be given to maintenance requirements and available resources to maintain continuous operation.

Although water treatment systems for generating either compendial or non-compendial pharmaceutical process waters significantly vary in system operational costs, the NPV for each of these process waters are quite similar. The only exception is DI process water generated by a non-regenerable exchange system, typically regenerated off-site. The NPV analysis is usually based on the water system capital cost and a system operating cost for an estimated period (e.g., 5–10 years). The period chosen has to be long enough to allow the operating cost to be a significant factor, but short enough for reasonable analysis of operating cost returns versus increased capital expenditures. While the typical lifespan of a pharmaceutical water system is about 10–20 years, technology selection may be determined using a shorter Return on Investment (ROI) period, which is typically 5–10 years but may be as short as 2 years.

Due to varying feed and product water conditions, site-specific utility costs and availability, and end user driven requirements, an economic evaluation should be performed for every proposed system. One cannot assume that the process design based on the optimum lifecycle costs will be equivalent for different capacities and applications. This exercise is critical to the basis of design development and may result in significant savings over the expected life of a water system. While it may be common to base decisions on capital cost and ROI, neglecting operational and maintenance costs can lead to incorrect conclusions and result in a higher cost of products.

One other important, and slightly more difficult factor to quantify, is equipment reliability. While it is challenging to attach a financial value to reliability, the cost of ownership of a system clearly increases when including the cost of unexpected downtime during the selection process.

Ensuring the most suitable water quality is selected and the total cost of ownership of the system is evaluated can typically result in overall costs nearing optimization; however, additional opportunities for cost savings may be found in reusing system waste water for other applications (e.g., lawn irrigation, humidification, boiler feed or makeup, cooling tower makeup). Materials of construction (including finishes), instrumentation and controls, and redundancy/ reserve capacity are also extremely influential to the capital cost associated with a technology choice. Subsequent chapters in this Guide also address cost savings issues associated with the basis of design, unit operation selection, and overall system configuration.

3.4   System Planning

Water and steam are often the most widely used raw materials or utilities in a pharmaceutical facility. They also may be a considerable production expense. Improper sizing or selection of a system or its components could dramatically impact facility operations by limiting production if undersized, or compromising quality and reproducibility and/or increasing capital cost if oversized. It is important to recognize that system design or sizing is not the starting point in design. Defining water quality requirements, acceptance criteria, and usage should be the first step and if properly determined, they will optimize capital, while minimizing construction and operational costs. Simulation tools may be employed to assist in determining optimal system configurations and designs. Figure 3.2 provides a graphic representation of the system boundaries, limitations, and restrictions the designer needs to address when planning a pharmaceutical water system.

During initial planning, the limits of each boundary should be established. The arrows encircling each boundary represent inputs that establish more specific operating strategies and ranges. When documenting these requirements, the designer should, whenever possible, indicate ranges of acceptability rather than a specific value or position. Ranges allow more flexibility in final planning and when making detailed design decisions.

Certain restrictions can necessitate a specific strategy; however, as long as the decision leads to a result that is within the limits of the established system boundaries, it will most likely be acceptable. An example is a facility that requires a new use point to deliver non-compendial water with microbial control. Within the facility, there is an existing oversized WFI system in an adjacent area that the designer decides to utilize for the new use point since the quality required will be exceeded by WFI. In this example case, documentation should identify the quality required for the product and the reason WFI was used instead.

Of primary importance is the systematic approach to planning a pharmaceutical water or steam system. Planning should begin with the determination of water quality. Then, POU delivery criteria are evaluated, possibly with multiple POU arrangements, followed by an initial system planning exercise. Often, these sequential steps are repeated as information in the design process iterates, and further criteria about the overall system boundaries are identified. Ultimately, the POU requirements as well as future projections, when totaled up, will determine the sizing of the distribution piping system. It is important to keep in mind that once the distribution piping system has been sized, installed, and qualified, it is inefficient and extremely expensive to increase its size as demand increases in an operating, qualified facility.

Figure 3.2: Pharmaceutical Water System Planning
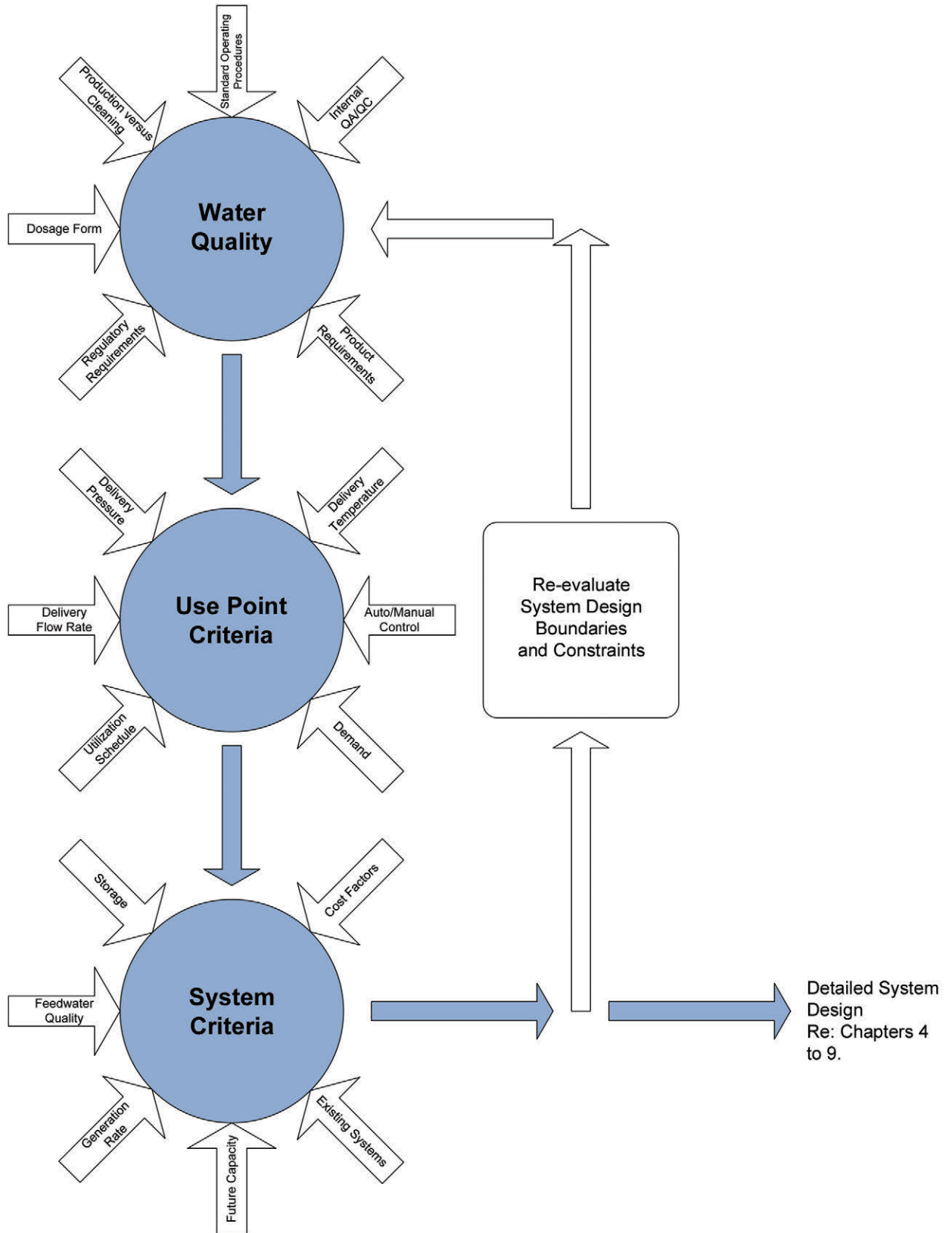
3.4.1   Establish Water Quality

The first step in the evaluation of water systems is the selection of water quality required for the specific product and process operation. Selection is based primarily on the dosage and form, the microbiological and chemical purity criteria for the product(s) for which the water is used (production and cleaning), and applicable regulatory requirements. The selection must consider underlying factors that will impact Quality Control (QC); installing and operating cost; maintenance and practicality.

System design constraints may provide the motivation to challenge water quality or other criteria, particularly when it can be demonstrated that some changes do not affect product quality or manufacturing controls.

3.4.2   Characterize Use Points

Once the initial selection of water quality has been established, the operational criteria should be characterized for each use point. When evaluating POU requirements, it is often prudent to create a spreadsheet or design database that summarizes all pertinent data, allows adequate space for notes, and is updated to serve as a reference throughout the design process.

Each POU should be identified with a unique tag and annotated with the proper values for pressure, flow, and temperature range of water delivered for use. Establishing a range, where possible, rather than a fixed value increases opportunities for system optimization by allowing a more flexible approach to final design. Classification of each use point should include the following:

- Unique identifier (tag)

- Purpose or user (e.g., cleaning, batch vessel)

- Maximum instantaneous flow rate

- Periodic consumption requirements (e.g., daily, weekly) and duration

- Pressure requirement

- Temperature requirement

- Utilization schedule

- Method of delivery (automatic or manual)

- Type of connector (fixed or hose)

- Notes or other special requirements (if applicable)

This data can be organized in many ways, but a suitable spreadsheet can simplify the planning process and indicate decision pathways for future detailed design activities. Table 3.2 provides an example spreadsheet for use in system planning.

In general terms, peak and diversified flow rate is primarily used for sizing distribution lines, whereas the total daily consumption (considering diversity for peak days) divided by the operating hours for the process gives the minimum rate for the generation plant. Both can be useful in determining storage requirements. A diversity factor is one way to normalize anticipated usage, assuming that not all water demands happen every day or at the same time. Diversified usage can be applied if activities will happen either at the same time or if they can be staggered so that a smaller pump, equipment, and piping network might be used.

Table 3.2 shows an example of a CIP system and stopper washer that are both likely to be used on the same day, but not at the same time; therefore, only the higher flow rate is relevant to loop sizing as shown in the Flow Rate column. Demand flow rates are eventually used for user connection sizing.

Table 3.2: Example of Point of Use Criteria for System Planning

ID (Tag)	Temp. °C (°F)	Pressure psig (barg)	Type	Equipment Name (purpose)	Impact on Loop Sizing Calculations			Impact on Daily Water Consumption Calculations			Comments
					Demand	Diversity	Design	Demand	Diversity	Design	
					gpm (lpm)	Factor	gpm (lpm)	gpd (lpd)	Factor	gpd (lpd)	
WFI-1	83–85 (181–185)	60–65 (4–4.5)	Manual	CIP Wash Tank	10.6 (40)	1	10.6 (40)	317 (1200)	1	317 (1200)	Assume a recirculating cycle in 4 steps for total of 23 min.
WFI-2	20–23 (68–74)	35–40 (2.4–2.75)	Auto	Stopper Washer	5.3 (20)	0	0	122 (460)	1	122 (460)	Assume one cycle per day. 100 liters/rinse, 3 rinse/cycle at 2 lpm for 60 min.

After locations and qualities have been determined, the various properties can be easily charted using spreadsheet software. Basic process flow diagrams also provide a good pictorial view of the water qualities, locations, and the POU properties.

The key to establishing the usage profile and generating a water usage chart is to break down the water consumption to specific time intervals (e.g., hourly periods) for each user and sum all the requirements over that time interval. (See Figure 3.3.) For a specific generation rate and storage tank volume, the tank volume can be determined based on the consumption specific for each time interval. The capacity of the tank and the generation rate can be optimized considering these and other design requirements such as space and economics.

Figure 3.3: Example of Hourly Water Consumption Chart
Courtesy of Clear Water Consulting, Inc.
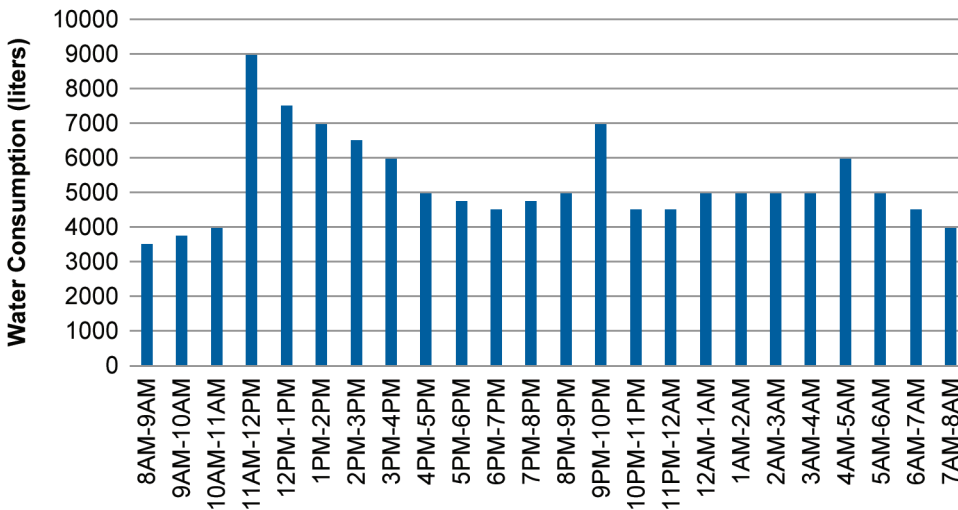
3.4.3   Establish System Criteria

Based on the established water quality and POU demand criteria, the system criteria can be established with the following having a significant influence:

•   Generation rate

•   Storage capacity

•   Peak and average demand

•   Additional or reserve capacity as a safety factor

•   System demand limit based on maximum loop draw-off

•   Maintenance requirements and downtime

•   Sanitization/sterilization method and frequency

•   Effect on existing system(s) (if applicable)

This type of analysis is beneficial for determining overall system peak demand(s), average demand, and the relationships between peak demand time periods and their flow rates in existing facilities. For new facilities, projections may be constructed by reviewing projected manufacturing schedules for water consumption requirements and performing mass balance calculations. Figure 3.4 shows a hypothetical storage tank sizing calculation using the 24 hour demand profile from Figure 3.3.

There is no guideline for minimum or optimum water level prior to the start of refilling the storage tank. Constant storage tank level may not be a requirement, particularly if cycling of the generation system on and off may be undesirable depending on the technology and water flush requirements with system start-up. Generating the types of charts shown in Figures 3.3 and 3.4 provide the tools for creating various scenarios to simulate a number of different operating scenarios:

•   Recovery times from a failure

•   Future expansion

•   Reduced capabilities

•   Preventive maintenance

•   Other factors

Additionally, using Variable Frequency Drives (VFDs) in combination with sophisticated controls on many systems permit the output (fill rate) to be carefully controlled in order to maintain the storage tank at an optimum level while keeping the equipment running at all times.

System planning and analysis also reveals other requirements that influence design, and often lead the designer to re-evaluate the primary boundaries discussed earlier. These issues include:

•   The system must be available at all times.

•   Shutdowns must be limited in number and duration.

- Plant and personnel are not equipped to handle chemicals properly. No permits are in place.

- Production is batched versus continuous.

- Is a single product manufactured or multiple product groups produced?

- Product campaigns dictate unique or restrictive operating requirements.

- Limited time is available for sanitization.

- What is the feasibility of having redundancy in selected parts of a system?

These constraints should be addressed adequately and may dictate redundancy be provided to allow adequate time for water generation (tank fill), sanitization, maintenance, service, etc.

Figure 3.4: Example of Storage Tank Capacity Determination
Courtesy of Clear Water Consulting, Inc.
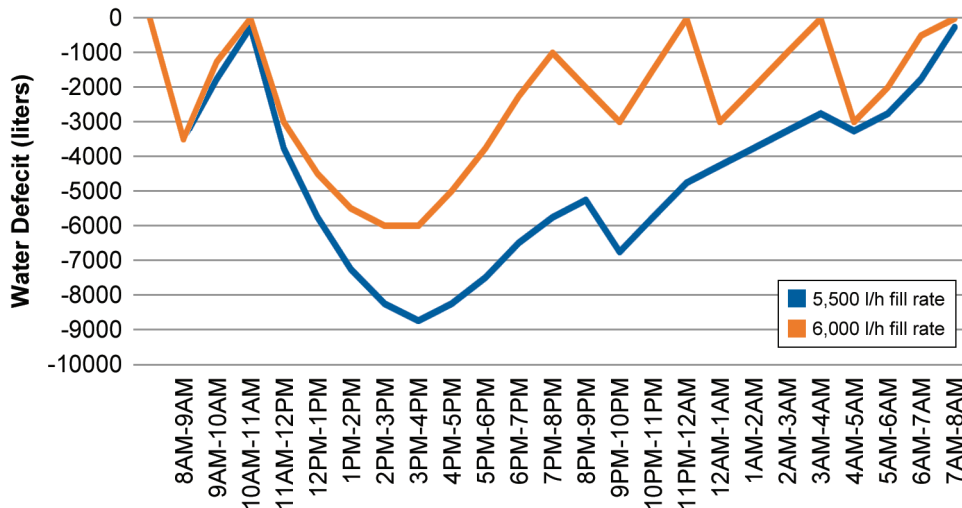
Note: This chart considers a generation system with two differing but fixed capacities. Utilizing the hourly water consumption data from Figure 3.3, Figure 3.4 calculates the overall hourly water deficit while comparing two different generation rates (5,500 l/h (blue line) and 6,000 l/h (orange line)). The maximum anticipated water deficit allows for calculation of the minimum size storage tank needed. The X-axis indicates the time of day and the Y-axis indicates the calculated hourly water deficit used to determine the size of the storage tank.

Assuming a reserve of 5,000 l as the minimum desired water level in storage, the 5,500 l/h generation system will require a 14,000 l (9,000 l maximum water deficit plus 5,000 l in reserve) storage tank, whereas the 6,000 l/h generation system will only require an 11,000 l storage tank (6,000 l maximum deficit plus 5,000 l in reserve). A higher water reserve may be used in this calculation to build in an additional safety factor.

3.4.4   *Revisit Water Quality*

With all use points characterized, the quality of water delivered to each point may be revisited. A thorough review may reveal a wide range of acceptable quality and delivery conditions generated from the implementation of Quality by Design principles. Since it is often not practical to operate multiple water systems to provide the exact water conditions desired for each end product, compromises may be required. These compromises include providing water of a higher quality than required to simplify or reduce cost; however, water should continue to be delivered at conditions within the boundary limits, unless these requirements are changed.

3.5   System Design

Once all ancillary functions are defined and risk-based Quality by Design principles have been followed to their appropriate conclusions, detailed design of the system can begin. The process requirements determine the POU in the distribution system. User locations determine how to distribute the water (e.g., central storage, multiple loops/sub-loops, etc.). One or several of the use points may require different properties that necessitate a change in the distribution philosophy from a simpler design. In this case, alternatives to the water system criteria are considered, such as increasing the number of loops, changing the loop configuration (e.g., changing from a cold loop to a hot loop with POU coolers where necessary), or creating sub-loops. The plant operating schedule also should be considered since an inability to perform regular tasks such as sanitization may render the system inoperable.

The boundaries, limitations, and restrictions identified in the initial planning stages need to be integrated into the design approach. Additional considerations include the physical area required. The space needed could be simply an allocation within an equipment area or, depending on system complexity, may require additional support space, space at a remote site for satellite equipment, or even multiple locations throughout a single building or campus setting.

Plans should be in place to manage both scheduled and unscheduled maintenance. When practical or necessary, equipment redundancy allows for work to be performed with only a partial loss of capacity. Backup equipment for critical functions should be evaluated during the design process, which is usually driven by production or related requirements.

Specific details of activities required to complete a design are provided in the following chapters and include various alternatives for unit operations and system concepts. Rationale is provided for the recommendations included; however, the design team must recognize that the requirements unique to their products and facilities will ultimately dictate the final outcome.

4   Pretreatment Options

4.1   Introduction

Pretreatment involves a series of unit operations to condition the feed water so that it will be of adequate quality to optimize the performance of the final treatment step.

This chapter discusses the process design for pretreatment including feed water quality and pretreatment effluent quality, followed by a review of the selection of treatment options for the groups of impurities:

- Turbidity and particulates

    - Silt

    - Dust

    - Pollen

    - Pipe scale

    - Iron and colloidal silica

    - Undissolved minerals

    - Organic compounds

- Inorganics

    - Calcium and magnesium salts

    - Aluminum

    - Dissolved silica and heavy metals (e.g., iron/manganese)

- Organics

    - Naturally occurring by-products of vegetative decay, i.e., humic and fulvic acids

    - Man-made organics such as pesticides, herbicides, and automotive pollution (oils)

- Microbial

    - Bacterial contamination and its by-products

    - Pyrogen and its endotoxins subsets

- Microbial-control agents

- Dissolved gases (carbon dioxide and ammonia)

4.2   Process Design of Pretreatment

Process design of the pretreatment is the specification of a series of unit operations or process steps required to treat the feed water in order to optimize treatment functionality and expected microbiological levels. Detailed mechanical design of the equipment for individual unit operations or process steps is beyond the scope of this Guide. The pretreatment system should be designed and operated to keep the water quality feed to the production stages as stable as possible. This includes hardness levels, biological load, temperature, flow rate, etc. It should allow for predictable maintenance intervals.

If a feed water source does not meet local drinking water requirements, separate conditioning techniques upstream of the water treatment system are required to assure these requirements are met.

*   Quality Considerations:

    -   Required quality of water needed to be produced by the final treatment process

    -   Temperature constraints for the water used in the pretreatment

    -   Microbial-control strategy

    -   Final treatment step

    -   Characteristics of the feed water to pretreatment considering seasonal fluctuations and external environmental influences

    -   Impurities to be removed by pretreatment

*   Microbial-Control Considerations:

    In addition to defining the options for removal of non-viable impurities, the approach taken for microbial control is an integral part of the pretreatment process design.

*   Feed Water Considerations:

    -   The feed water to the pretreatment must comply with potable water standards regulations by a competent local or national agency and/or meet WHO drinking water regulations [32]. Water sourced from an unregulated supply should be quality tested and monitored on a routine basis to ensure compliance a relevant potable water standard.

        Source water with an inability to meet a drinking water standard should be used only after a risk assessment and additional control measures have been enacted to ensure compliance before introducing water into the pretreatment system. These waters typically contain chlorine or chloramines as a microbial-control agent. In Europe, ozone is a more common microbial-control agent. The residual disinfectant concentration should be evaluated and may be sufficient to protect the initial steps of the pretreatment. If not, a system addition of a microbial-control agent should be considered.

    -   Documentation that feed water meets the necessary quality may be based on municipal data alone, if proven to be reliable and representative, or supplemented/replaced by other suitable testing. The frequency of in-process testing may be affected by the reliability of municipal data, importance of monitored variables, and an organization's philosophy. For the purposes of system design, municipal water analysis is typically not comprehensive enough, as constituents like pyrogens and silica are typically not tested.

The regulatory requirement that compendial waters should contain no added substances (USP <1231>) restricts any addition of chemicals to the final compendial water [4]. The addition of chemical agents is not prohibited during pretreatment or for sanitization, provided they are removed from the final product water; therefore, various substances are often added and adequately removed during treatment to optimize the overall system performance [4]. Examples include:

• Chlorine, chloramine, chlorine dioxide, or ozone

• Sodium chloride

• Acid and bases (caustic)

• Sulfite/sodium metabisulfite

• Sequestrants/antiscalants

Where added substances result in increased microbial growth or higher levels of endotoxin, they should be evaluated. It may be necessary to verify the absence of any added substances in the final product water, in particular those that are not of widespread use in drinking water supplies.

Business considerations for pretreatment include:

• Downtime available for maintenance/redundancy philosophy

• Physical characteristics such as pressures, flow rates, capacities

• Skill level and availability of the labor force and technical support

• Environmental/waste flows

• Available space

• Available support utilities

• Sustainability

• Costs

An important consideration is the relationship between initial capital cost and operating costs as they relate to pretreatment, and its impact on the performance and operating cost of the final treatment process. The following are generally true:

• Operation of final treatment will be adversely affected if operation of the pretreatment system is inconsistent, unreliable, or inappropriate.

• Inadequate pretreatment function will likely be reflected in long-term maintenance costs and operating reliability.

• Investment in correctly designed and appropriate pretreatment often returns many times its value in final treatment maintenance costs savings.

• Hot water sanitization is normally very effective for control of bioburden in comparison to chemical sanitization but typically has higher capital costs. Additional considerations include, but are not be limited to:

    - Labor costs

- Safety

- Environmental constraints

- Discharge volumes

- Repeatability

- Utility costs

• Pharmaceutical water systems are expected to produce water that meets or exceeds exacting regulatory or product-specific requirements. Systems should be designed to control impurity variability in the feed water, as well as seasonal impurity profile changes. A robust pretreatment design minimizes the impact of these variations on downstream unit operations and final treatment.

There is no single correct answer to the process design for pretreatment; rather there are a series of choices and options, each with advantages and disadvantages to be considered when determining the appropriate system for an application.

4.3   Feed Water and Pretreatment Testing

Compendial water systems typically use feed water complying with drinking water standards that ensure a level of consistent quality. However, within this broad definition, it is important to understand variations that may affect performance, including:

• Source of the feed water (reservoirs, ground, desalinations, etc.)

• Treatment methods upstream of the facility

• Variability of feed water supply

Feed water chemical composition and microbial variability may be associated with seasonal weather changes and anomalous events such as droughts, floods, source water changes, agricultural runoff, and other natural and man-made events. While published municipal data may be sufficient to demonstrate drinking water status, supplemental testing should be established to ensure system performance. A sampling program should be implemented commensurate with the supply water risk to the treatment process. Specific testing for contaminants known or suspected to be present in the feed water should be performed on a routine basis, particularly if they appear at variable levels, times, or if slight changes can impact system operation.

Typical supplemental testing includes but is not limited to:

• Total and free chlorine

• Total Organic Carbon (TOC)

• Microorganisms

• Endotoxin

• Turbidity

• Total suspended solids

- Conductivity and/or Total Dissolved Solids (TDS)

- Total hardness

- pH

- Silt Density Index (SDI)

- Alkalinity

Testing of feed water should be accompanied by additional testing downstream of a unit operation associated with the removal or control of the contaminants. More information can be found in *ISPE Good Practice Guide: Sampling for Pharmaceutical Water, Steam, and Process Gases* [33].

4.4   Pretreatment Unit Operations

4.4.1   Unit Operation Descriptions

Ultrafiltration (UF)

A membrane-based process for the removal of particles/suspended solids, microorganisms, colloidal matter, and high molecular weight TOC upstream of final treatment. Usually operated with a reject stream and cleaned with a backwash and/or chemical agents. Typically, these UF are around 5,000–100,000 Dalton molecular weight cut-off (0.001–0.2 µm) in size.

Multimedia and Media Filters

Column filtration containing one or multiple layers of filtration media to remove particulates/suspended solids, colloidal silica, and iron/manganese from a flowing stream of water. Multimedia typically consist of layers of anthracite, sand, and garnet. Media filters are typically backwashed to remove filtered contamination.

Flushed Screen/Disc Filters

Filters with a static screen mesh. The filters are typically cleaned with a water flush of the cake that builds up on the screen.

Cartridge/Membrane Filtration

Replaceable filters set within a filter housing. The filters are typically removed and replaced after clogging.

Chlorine Injection

The physical injection/dosage of hypochlorite/chlorine gas to generate free chlorine levels in water as a sanitizing agent at high levels or as a residual disinfectant at low levels.

Ozone

The physical injection/dosage of ozone gas into water. Ozone is a highly reactive oxidizer that can be used to reduce impurities such as microorganisms (sanitizing agent) and organic carbons.

Chlorine Dioxide

The generation and injection of chlorine dioxide into a water system as a sanitizing agent.

Ion Exchange Softener

A cation exchange process that replaces hardness ions (calcium, magnesium, ammonium, barium and strontium) with sodium ions in a flowing stream of water though a resin bed. Hard ions are removed from the resin by a brine regeneration.

Antiscalant

Chemical scale inhibitors, dispersants, or sequestering agents that minimize the potential for scale precipitation on the reject surface of an RO membrane.

Activated Carbon

Column filtration containing activated carbon media for the removal of free chlorine, chloramines, and TOC by chemical adsorption. Chloramine removal typically requires catalytic carbon.

Sodium Bisulfite/Sodium Metabisulfite

Injection of sulfite solutions into a water stream to inactivate chlorine and/or chloramines in a reduction reaction.

Sodium Hydroxide

Injection of sodium hydroxide as a caustic solution to raise pH of RO feed water for CO_2 removal.

Ultraviolet (UV) Irradiation

Irradiation of water with UV light at wavelengths of 180 - 350 nm; used for disinfection, TOC reduction, and/or dechlorination.

Electric Scale Control

Electric scale inhibitor that minimizes the potential for scale precipitation on the reject surface of an RO membrane.

Anion, Cation, and Mixed-Bed Deionizers

Ion exchange process that replaces ions from water flowing through a column containing anion ion exchange resin and/or cation ion exchange resin, for removal of both cations and anions. Resins are regenerated on-site or off-site. Depending upon the contaminant(s) present, the design of the system, and the application of the technology, deionizers may be used as a pretreatment or final treatment step.

Reverse Osmosis

A purification process that passes pressurized water across a semipermeable membrane. This process removes a broad spectrum of contaminants and depending upon the contaminant(s) present, the design of the system, and the application of the technology, RO may be used as a pretreatment or final treatment step.

4.4.2 Typical Pretreatment Unit Operation Selection

Table 4.1 is for quick reference. Refer to the discussion below for addition design considerations.

Table 4.1: Pretreatment Unit Operation Selection

Common Impurities	Chlorine Injection	Media Filter	Ultrafiltration	Cartridge/Membrane Filtration	Chlorine Dioxide	Ozone	Activated Carbon Filtration	Antiscalant	Ion Exchange Softeners	Ion Exchange	Electric Scale Control	Ultraviolet Light	Sodium Hydroxide Injection	Reverse Osmosis (RO)	SBS (Sodium Bisulfite)
Turbidity		X[1]	X	X		X									
Particulates/Suspended Solids		X	X	X											
Hardness								X	X	X	X			X	
Iron		X[2]								X	X				
Dissolved Silica								X			X			X	
Colloidal Silica		X	X	X											
Carbon Dioxide													X		
Trihalomethanes (THMs)			X			X	X							X	
Total Organic Carbon (TOC)			X			X	X					X		X	
Microorganisms	X		X		X	X					X	X		X	
Pyrogens			X			X								X	
Free Chlorine							X					X			X
Chloramines							X					X			X
Ammonia									X[3]	X[3]				X[4]	

Notes:
X = Commonly employed
1. With a highly turbid water supply, media filters may be supplemented with coagulation, flocculation, and sedimentation to achieve drinking water standards.
2. For iron removal, typically a green sand media is employed.
3. Refer to discussion in Section 4.10.1 for further detail.
4. Used with acid injection to convert ammonia to ammonium ion to be removed by RO (See Chapter 5).

4.4.3   Problems in Final Treatment Caused by Improper Performance of Pretreatment

Impurities that must be removed by pretreatment to enable reliable operation of the final treatment depend on the final treatment design and its tolerance for those impurities. If pretreatment is inadequate, the resulting problems, categorized in Table 4.2, can be significant.

Table 4.2: Magnitude of Problems in Final Treatment Caused by Impurities

Final Treatment (Chapter 5)	Impurity					
	Fouling: Particulates	Fouling: Bacteria	Fouling: Organic	Scaling: Hardness/ Minerals	Corrosion: Chlorides	Degradation: Chlorine
Reverse Osmosis	Moderate	Large	Large	Moderate	None	Large
Continuous Electro-deionization	Moderate	Moderate	Moderate	Large	None	Large
Single Effect Distillation	Moderate	Minimal	None	Moderate	Moderate	Large
Multi-Effect Distillation	Large	Minimal	None	Large	Moderate	Large
Vapor Compression Distillation	Moderate	Minimal	None	Large	Small	Large
Ultrafiltration	Moderate	Moderate	Moderate	Moderate	Small	Small

As noted, unit operations selected for use as pretreatment are typically based on the needs of the treatment that follows.

4.5   Control of Fouling: Removal of Turbidity and Particulates

Particulates typically are insoluble suspended materials present in the water. Total suspended solids should be measured in milligrams per liter (mg/l). Sources of particulates include dust, pollen, colloidal silica, insoluble minerals, and corrosion products.

Turbidity is a cloudy appearance caused by the presence of suspended and colloidal materials due to soil runoff in water supplies, and may contain inorganic, organic, or microbiological material. Turbidity measurements are an optical property based on the amount of light reflected by the suspended particles measured in Nephelometric Turbidity Units (NTU). Turbidity cannot be directly related to particulate counts since it is affected more by particle size, shape, and color rather than concentration. Light colored particles reflect more light than dark colored particles and small particles may reflect more light than larger particles of equivalent concentration.

The SDI is an additional means to measure colloidal and particulate fouling capacity of water. The test measures the rate at which a 0.45 µm filter is plugged when subjected to a constant water pressure.

Removal of particulates and turbidity is required to prevent fouling/plugging of final pretreatment processes, especially those using a membrane (e.g., RO).

Factors affecting the removal of turbidity and particulates include:

*   Particle size and shape relative to the filtration media

*   Coagulation or the tendency of particles to adhere to each other or the media, which may be enhanced by the addition of a flocculating agent or alum

*   Surface effects, including surface tension, hydrogen bonding, and electrostatics

4.5.1   Clarification

Addition of alum, lime, ferric chloride, or other flocculating agents, as well as pH adjustment aids in sedimentation and clarification to remove particles larger than 25 µm. Flow rates, generally, are large and cost per unit volume is low. This process is typically not utilized for the production of pharmaceutical waters as it would be redundant to treatment typically performed by a municipality; however, it may be employed if the feed water source is an unregulated source (e.g., private well). Clarification, typically, is not 100% efficient, and may require additional filtration to prevent particulates from causing blockage in subsequent pretreatment operations.

4.5.2   Media Filtration

Media filtration is an effective and common method of removing particulates from the water, with some minor effect on reducing turbidity. Designs typically flow water down through a single size or multiple size granular media bed in a column. The bed of media may be of a single material or multiple layered materials. Particulates are removed from the water and collected in the media bed during operation.

Particulates accumulated during operation are removed by a back flush (backwash) operation, typically based either on pressure drop or time. This back flush in the upward (reverse) direction also decompresses the filter bed and is followed by a down-flow rinse to resettle the media and remove fines. Waste water from the back flush is generally not considered chemical waste and is typically 3–10 times the operating flow rate depending upon the media.

Sand is the most common media used based on cost and availability in a wide range of sizes and purities.

Depth filtration is accomplished using multi-sized media resulting in less frequent backwash compared to single media beds. In multi-sized media filtration, the larger media is typically at the top with the flow directed downward through progressively finer layers of media. The overall porosity of the bed, based largely on packing, permits removal of particles in the range of 10–40 µm, relative to the media selected.

In addition to sand, filtration media used in a multi-sized media may include anthracite, carbon, or manganese. Anthracite may be used when leaching of the silica from sand is a problem due to high temperatures or alkalinity. Multi-sized media filters using anthracite may allow higher flow rates and require less backwashing (regeneration) because of the sharply angular particles, unlike silica particles that have a more rounded shape.

A depth filter using carbon might be selected if the water has a high loading of organics or if there is a particular reason to combine removal of particulates, organics, and chlorine. A layer of an activated granular carbon, such as coconut, lignite, or anthracite, may be added.

A depth filter using media coated with potassium permanganate or manganese zeolite may be selected for water having high concentrations of iron or manganese. Generally, an oxidant, such as potassium permanganate or chlorine and permanganate, is added prior to the filter to convert metals to higher oxidation states that are insoluble, allowing for precipitation and filtration to occur, resulting in concentrations as low as 0.3 mg/l of iron and 0.05 mg/l of manganese.

Media filters with a single media and particle size may be used but generally do not provide depth filtration. The media may be just sand. Additionally, zeolite-based filter material is available that permits removal of particles in the range of 5 µm at a higher flow capacity than typical multi-sized media filters.

Microbial growth is a key operating consideration in media filters because of the large surface area and relatively low velocity. Particularly where carbon is utilized, and depending on the type of carbon used, the carbon media itself maybe a source of nutrients; therefore, appropriate consideration should be given to sanitizing routinely either chemically or with heat. The filter bed may be designed with constant recirculation to minimize stagnation and growth.

Advantages: large capacity per unit cost; low cost of operation and maintenance if properly applied; well suited to chlorinated water supplies; excellent for feed water pretreatment

Disadvantages: particle reduction limited to 10 μm (approximately); can become a source of microbiological contamination if improperly maintained, designed, or operated

4.5.3 Barrier Filtration

This type of filtration relies on a barrier through which the water must flow. The barrier retains particulates allowing for their elimination by either replacing the cartridge barrier or via a purge stream. Barrier filtration includes:

- Cartridge or membrane filtration

- Ultrafiltration (UF)

4.5.3.1 Microfiltration

Microfiltration is frequently used to polish the water after IX or carbon filtration and before RO. When used for polishing, the barrier typically is rated nominally for 1–10 μm for the simple removal of particulate carryover from the previous operation or to protect against upset. Alternatively, if the objective is to remove insoluble forms of silica and iron to achieve an SDI of less than 5 for suitable feed to an RO, a rating of < 1 μm is more appropriate, and available at the lower end of microfiltration. An absolute rated cartridge filter also may be suitable.

Advantages: lower capital cost; particle removal (size) based on cartridge selection

Disadvantages: ongoing cost of operation and maintenance; potential for microbial growth if not suitably maintained and cleaned beyond built-in cleaning programs

4.5.3.2 Pretreatment Ultrafiltration

UF (typically 5,000–100,000 Dalton molecular weight cut-off or 0.001–0.2 μm) can be used for removal of particulates as long as an automated backwash is integrated into the system. Typically, this is achieved by utilizing multiple banks of UF membranes. While in operation, single banks are taken off-line alternately and back washed with previously filtered water. This removes the boundary layer that may have built up on the membranes. Normally, this bank is rinsed with feed water to drain before being put back into service. A common UF system backwashes each bank, or train, of UF modules once every hour for 3 minutes (2 minute backwashes, 1 minute rinse). This helps prevent excess buildup of the boundary layer.

Chemically-enhanced CIP operations can be performed on a more infrequent basis to further minimize fouling potential.

Advantages: reduced fouling potential compared with microfiltration; increased particulate removal compared to media filtration

Disadvantages: higher capital cost; ongoing cost of operation and maintenance

4.6 Control of Scaling: Removal of Hardness and Metals

Hardness (calcium and magnesium ions) in a water supply can result in scale formation, which is a deposit of minerals left over after the water has been removed or evaporated. This can be found in boilers, cooling towers, RO membranes, clean steam generators, and distillation systems. When water is separated from its impurities in the final treatment process, those compounds with low solubility are concentrated to the point where they precipitate. This precipitation or scaling is the result of exceeding the solubility of the divalent and trivalent cations, usually as a sparingly soluble salt, such as carbonate or sulfate. Methods of control include:

- **Ion exchange:** primarily removal of calcium and magnesium, as well as divalent and trivalent cations, such as iron, aluminum, and silica (e.g., water softening IX, which removes divalent and trivalent ions and replaces them with sodium, is a very common process used)

- **Chemical injection:** can range from simple (e.g., acidification to convert carbonate to carbon dioxide (which may be removed by degasification)), to complex (e.g., using proprietary sequestrants (antiscalants)). Note that acidification should be done with great care to prevent catastrophic corrosion due to over injection of acids.

- **Electric Scale Control:** a process that passes an electrical current through water to disassociate some of the water molecules and inhibit scale formation on the RO membrane

Hardness is measured either online or off-line by collecting a sample. The results typically are reported in ppm.

4.6.1 Water Softening by Ion Exchange

Water softening via IX is applicable for all flow rates and hardness levels, and is well understood. It involves only the handling of salt, and produces a non-hazardous waste stream; however, the high TDS in the brine regeneration waste stream may limit disposal options.

In addition to possible problems with effluent disposal, softeners filter out water-borne contaminants and deposit them on the resin. Organic resins provide an environment for microbial growth, due to the temperature and nutrient-rich environment, which often needs to be controlled. A sanitant, with a residual effect, is commonly added to the water. Oxidizers such as free chlorine are sometimes administered for microbial control. If a mature biofilm has developed in the system, usually the only method of sanitization is removal of the media, manual scrubbing of the vessels and circulation of chemical sanitizing agents. Water softening is easily controlled manually or automatically.

The function of an IX water softener is removal of scale-forming calcium and magnesium ions from hard water. In many cases, other multivalent ions, such as soluble iron (ferrous) are removed with softeners. Ferrous iron removed in the IX process will foul the resin and are not released during the regeneration process, resulting in reduced capacity and/or a need to chemically treat or replace the resin. Softeners should not be used to remove ferrous iron.

A typical IX water softener consists of a softener vessel(s) containing synthetic resin beads, brine makers/storage tanks, and associated pumps. The beads are treated to selectively attract cations (Ca++, Mg++) and exchange these ions with sodium (Na+) based upon their relative activity compared to the resin. This process of IX continues until available exchange sites are filled, at which point the resin is exhausted and should be regenerated.

Regeneration can be scheduled on a volume basis or softener output hardness. Additionally, it can be on a time basis if actively being used to introduce disinfection agents.

Regeneration is achieved by introducing an aqueous sodium chloride (brine) solution to the resin bed, exchanging the hardness ions for sodium ions. The resin's affinity for the hardness ions is overcome by using a concentrated solution of brine, typically 10%. The amount of sodium chloride (brine) needed for regeneration depends on the regeneration mode (co-current or counter-current), and the resin bed size. The spent brine solution plus the associated water back flushes and rinses are waste streams and might typically approximate the nominal throughput for one hour for each regeneration cycle.

Advantages: well-known and recognized technology; low cost and effective; works well in a chlorinated environment with chlorine having a minor effect on resin life and efficiency; regeneration should not be relied upon for microbial control.

Disadvantages: risk of microbiological growth due to the large material surface area in the resin bed, even if exposed to chlorine, particularly at elevated temperature and nutrient levels; salt handling for brine regeneration and disposal of spent brine solution; resins may be incompatible with ozone and certain sanitization agents; in some areas, brine discharge to sewer systems may be restricted or banned.

A key decision in the process design is location of the softener within the pretreatment system. The primary options are either before or after removal of the microbial-control agent (often chlorine) in the feed water or that may have been added for control of microbial growth.

Softener located prior to removal of microbial-control agent: the principal advantage is protection of the softener from microbial growth by the microbial-control agent present in the feed water. If the microbial-control agent is chlorine, it will have only a minor effect on resin life and efficiency at the chlorine levels typically encountered in chlorinated municipal feed waters (< 1 ppm).

Softener located after removal of microbial-control agent: the advantage is minor increased resin life and capacity (due to absence of chlorine, if used as a microbial-control agent); however, this must be balanced by the need to protect the softener from microbial growth.

4.6.2 Demineralization/Deionization for Specific Contaminant Removal

If present in high concentrations, certain impurities such as iron, silica, and aluminum present unusual removal problems.

4.6.2.1 Iron

Iron is a common water contaminant. It is one of the more difficult contaminants to remove because it may change valence states; that is, change from the water-soluble ferrous state to the insoluble ferric state.

In solution, ferrous iron behaves like calcium and magnesium; however, when oxygen or an oxidizing agent is introduced, ferrous iron becomes ferric and precipitates, leading to a rusty (red brown) appearance in water.

Certain bacteria can further complicate iron problems. Bacteria, such as *Crenothrix, Sphaerotilus,* and *Gallionella,* use iron as an energy source, eventually forming a rusty, gelatinous sludge that can clog piping and equipment, particularly barrier processes such as RO.

Typical unit operations for ferric iron removal are multimedia filter or UF with upstream oxidation to convert ferrous iron to ferric iron. At very low iron levels, replaceable cartridge filters with a final rating < 1 μm might be a low-cost alternative.

Iron removal filters (with greensand media) can be used. In the presence of enough oxygen, the media causes the iron to form solid iron particles that are trapped in the media and removed during the backwash.

4.6.2.2 Silica

Like iron, silica may be present in more than one form and is a major problem in some parts of the world. It may be a soluble ionized species or an insoluble material, sometimes as a colloidal mixture with organics and other metals. The concentration of ionized silica can be reduced by antiscalant injection, strong base IX, or RO. ROs with the purpose of silica removal are operated at elevated pH to increase the saturation point of silica. Insoluble silica forms can be removed by RO, UF, or a replaceable barrier filtration with a rating in the range of 0.5 μm.

4.6.2.3 Aluminum

Like iron and silica, aluminum can exist in multiple valences and its chemistry is complex. It also can be a component of colloidal complexes. Its solubility, particularly as hydrated oxide compounds, is a function of pH. Aluminum may be present in the water either naturally or as a result of an alum treatment used by a municipality for coagulation.

Aluminum that is present as a colloidal component can be removed by fine barrier filtration. Softening or deionization removes aluminum in an ionized form. Aluminum can be removed by RO if the pH is > 6 or < 8. If aluminum is a potential concern, softening or deionization followed by pH adjustment and then RO may be required for removal.

4.6.3 Antiscalant

Injection of a sequestering compound/antiscalant (usually a proprietary organic compound) to RO feed water acts to bind and complex the offending ions or compounds to form a complex or compound that is more soluble and does not precipitate in the final treatment process. The ion and sequestrant have a large molecular weight and are removed in the final treatment by the purge stream. Sequestrants are commonly proprietary compounds that require testing to confirm applicability, dosage level for a particular feed water, and analysis to verify removal in the final treatment process. It is recommended to use antiscalant chemicals whose composition is allowed to be used as an added substance in drinking water applications.

4.6.4 Electric Scale Control

Scale can be controlled within an RO pretreatment system by applying a current to water in a reactor chamber. Applying a current across a flowing stream of water disassociates the water into OH- and H+, and shifts the pH locally at the electrodes. At the surface of the cathode, a high pH is generated, triggering a precipitation of pH-dependent scale-forming ions. This process immediately reduces a portion of scale in the flowing water as well as slowing the kinetics for downstream scale formation.

When employed with a continuously recirculating system, scale formation on RO membranes can be inhibited in addition to removal of scale-forming ions before precipitation occurs. This process requires routine cleaning/removal of precipitate from the cathode surfaces. This may be done manually or automatically coupled with a system flush. Depending on the level of chloride present in the feed water, free chlorine will be generated in the reactor chambers and will need to be removed in downstream equipment.

The sizing and applied current of the system depend upon:

- Makeup of scalants present in feed water

- RO product flow rates

- Feed water hardness concentrations

Advantages: no chemicals required; bacterial reduction by generated chlorine; low power usage; negligible waste water generated; system can be heat sanitized when made from SS; produces hydroxides and acids, most of which are rejected by the downstream ROs.

Disadvantages: kinetics chemistry of technology is less understood than alternative IX or antiscalant options; capital cost can be higher than alternatives; must be integrated with recirculating RO systems; ineffective as stand-alone system at hardness levels > 400 ppm; precipitates need to be physically removed from the system.

4.7   Control of Dissolved Gases – Contact Membrane Degasification

Dissolved gas removal may be required to obtain final conductivity quality. Typically, this consists of either carbon dioxide (CO_2) or ammonia. Refer to Sections 4.10.2 Chloramine(s) Removal and 4.11 Changes in Anion Composition/ Concentration for related discussions. Additionally, refer to Chapter 5 for the removal of CO_2 in stills and clean steam generators.

Degasification is the removal of CO_2, which raises the conductivity of the final treated water. The use of caustic injection to raise pH is a common step upstream of ROs. The process design favors or inhibits the formation of CO_2 (see Section 4.10.1). Alternatively, CO_2 can be removed down to a concentration of about 5–10 ppm with a contact membrane degasifier.

A contact membrane degasifier is usually located after the first or second RO pass. The semipermeable membrane will have a strip gas or a vacuum on the outside of the membrane fibers to draw the dissolved gas from the water and out to the surrounding atmosphere. Ambient air used as strip gas should be sterile-filtered to avoid contamination. Care should be taken as to the air quality feed to the membrane because oil and other contaminants in the air can blind the membrane and render it useless.

The contact degasser negates the need for pH adjustment before the RO. The best position for the degasser membrane is between the last pass of RO and the CEDI as this will keep the total flow rate through the degasser to a minimum, reduce the CO_2 levels to a minimum before the feed to the CEDI, and reduce fouling of the membrane.

Degasification columns or towers are discouraged as they have serious associated problems. Airborne bacteria, environmental pollution, dust, pollen, and airborne insects may be brought into contact with the process water.

Advantages: replaces sodium hydroxide dosing with associated instrumentation and control issues; will operate without maintenance; standard hot water sanitizable units available.

Disadvantages: high initial investment costs, especially for hot water sanitizable models; needs considerable amounts of clean filtered air.

4.8   Organic Material and Removal

Removal of organic material may be required in order to obtain the desired final water quality or to minimize the potential of organic fouling of downstream components. Common methods for removal of organics are:

- Ozone

- Barrier filtration (microfiltration, UF, or RO)

- UV light

- Activated carbon

4.8.1   Introduction

Organic and microbiological contaminants need to be addressed in water treatment systems. The concerns are twofold: contaminants entering the system and contaminants created/growing in the system. Organics usually enter with the feed water and may leach from some non-metallic materials of construction. Microbiological contaminants may enter with the feed water or grow in the system.

The first issue to consider is the water source since it affects organic loading. If the water is drawn from a well, organic loading is usually low. Surface water (lake, river, or reservoir) likely contains relatively high levels of organics and the composition and quantity may show seasonal variation.

Water from a municipal system is usually chlorinated, sometimes with ammonia added to form chloramines. Microbiological content of the feed water will be low and will generally be inhibited until the chlorine/chloramine is removed.

The second issue to address is biological growth occurring within the water pretreatment system. Most pretreatment systems are designed to keep an oxidant in the water for as long as possible to minimize the potential for growth. Free chlorine is commonly added to the water to control microbial levels if the residual levels are low. Special design and maintenance requirements need to be addressed in all equipment that operates without a microbial-control agent, chlorine, or chloramine present. These include materials of construction and piping layout (setup and fittings for sampling, and periodic sanitization and instrumentation for monitoring) compatible with the sanitization method selected.

4.8.2   Organic Contaminants

The organic contaminants found in many water sources include:

Pyrogenic Contamination: pyrogens are substances that can produce a fever in mammals. Pyrogens are often endotoxins, organic compounds (e.g., lipopolysaccharide) that are shed by bacterial cells during growth or are the residue of dead cells. They are chemically and physically stable and are not necessarily destroyed by conditions that kill bacteria. Their molecular weight may vary, generally 20,000–320,000 Dalton. Pyrogen levels are quantified in Endotoxin Units (EU) per milliliter. Pyrogens are of great concern to the pharmaceutical industry, since high concentrations may cause responses in humans ranging from fever to shock, or death. Endotoxins are a subset of pyrogens.

Total Organic Carbon (TOC): this is a measure of organic materials contaminating the water and is specified in ppm or ppb. TOC is a direct measure of the organic material that is oxidizable. It is a very fine measurement used in sophisticated water treatment systems where any organic contamination can adversely affect product quality. TOC is not a good measure of microbial contamination and gives no indication about the composition of the organic contaminants.

Dissolved Organic Compounds: these occur both as the product of the decomposition of natural materials and as synthetic compounds, such as oils or pesticides. Naturally occurring organics include tannin, humic, and fulvic acids. They detract from the aesthetics of water (i.e., color), but unless they come in contact with certain halogens, they have no known health consequences in normal concentrations. Under conditions of free halogen compounds (principally chlorine and bromine), they form chlorinated hydrocarbons and THMs, which are suspected carcinogens.

Organic compounds are not necessarily biodegradable; for example, the biodegradability of humic and fulvic acids is very limited. On the other hand, low-molecular weight organic substances such as organic acids, THMs, or urea are very biodegradable. The capability of standard water treatment steps such as RO, CEDI or distillation to reduce the content of volatile low-molecular weight organic substances is limited.

4.8.3   Removal of Organics

Technologies available to remove organic materials have different benefits and drawbacks. The use of chlorine and chloramines to remove bacterial contamination is the most common. Treatment devices used to remove one or more of other types of organic material include:

•   Organic Reduction by Ozone

Ozone for disinfection may be generated either electrolytically or by the corona method. Refer to the *ISPE Good Practice Guide: Ozone Sanitization of Pharmaceutical Water Systems* [34].

Ozone is an extremely powerful oxidant that kills microbes and prevents microbial growth, as well as reduces the concentration of organics. Ozone is not used frequently in pretreatment systems due to the preference for chlorine and materials of construction that are readily degraded by ozone. For further information, see Chapter 8.

- Organic Reduction by Activated Carbon

Activated carbon is considered one of the most common methods of reducing organics. It provides multiple functions including removal of organics and removal or reduction in the amount of chlorine and chloramines (if these are present and the carbon filter is appropriately designed).

Activated carbon reduces organic material concentration by adsorption onto the carbon particles in the bed. Removal efficiency depends on bed depth, cross-flow velocity, and adsorptive capacity of the carbon. Designs of carbon columns based on organic removal are generally based on bed depths of 4 feet (1.2 m) and hydraulic rates of 0.5–1.5 gpm/ft^3 (67.5–202.5 lpm/m^3) of empty bed volume, depending on the sanitant to be removed and the organic concentration in the feed water. Carbon bed volume is a balance between total adsorptive capacity and the frequency of replacement of the carbon bed. Reduction of feed water organic concentrations typically ranges from 30–60%. Additional downstream process steps, for example, RO, may be required to meet compendial limits for TOC or oxidizable substances.

Periodically the carbon should be replaced when its capacity to adsorb diminishes, which is typically at a higher frequency when used for organic reduction in comparison to dechlorination. For further information, see Section 4.9.

Advantages: reduces organic concentration; removes color; removes chlorine effectively; technically not complex; relatively low cost.

Disadvantages: high potential for increase in bioburden and biofilm development; medium to high capital cost for thermally sanitized units; shedding of fines requires downstream filtration; periodic replacement of the spent carbon is needed.

- Organic Reduction by Microfiltration

Microfiltration includes the use of depth cartridge filters, pleated filters, and cross-flow filtration membrane elements. These filters can remove particles ranging 10–0.1 µm, thus capturing bacteria, cysts, and large molecular weight organics. Depth and pleated filters allow water to flow through a wall of fibers perpendicular to the water direction. The particles are trapped on the outside wall of these filters or within the filter walls (for depth filters) because of the pore size of the filter. When the filter pores are filled, the filter should be replaced.

- Organic Reduction by Ultrafiltration

UF can be used to remove organics, bacteria, and pyrogens from a water source. Cross-flow UF forces the water to flow parallel to the filter media, and particles too large to pass through the membrane elements are expelled from the system in a concentrated stream to drain (typically 5–10% of the feed flow). This allows the filters to be self-cleaning and eliminates the need to replace these membrane elements frequently. The UF membrane elements need to have any suspended solids removed from the feed stream prior to the UF system. For reliable operation UF modules typically have a cut-off of around 100,000 Dalton as pretreatment, which also means that only high molecular weight substances are removed.

Advantages: effective filtering barrier; no by-products; works with chlorine.

Disadvantages: medium to high capital cost; 10% constant concentrate stream; can be source of microbial growth; organic reduction limited to high molecular weight substances.

- Organic Reduction by RO

  RO, if included in a pretreatment system to remove anions or cations, will also remove organics and microbiological impurities. Like UF, a purge stream removes impurities that are too large to pass through the RO membrane.

Advantages and **disadvantages** are similar to UF. For further information, see Chapter 5.

- Organic Reduction by Ultraviolet Light

  Low-pressure $UV_{185\,nm}$ lamps can be used for organic reduction. In addition, medium pressure UV units are commercially available with a wider wavelength spread. Successful organic reduction is a function of the UV dosage, average irradiance, and contact time in a UV chamber. Consideration of this process is based on the concentration of organics in the feed water and the purity of the water (interfering compounds). In addition, the reduction depends on the composition of the organics in the feed water stream, as some organic molecules may be more difficult to oxidize than others. The UV dose needed for a particular water stream may depend on:

  - The type of residual chlorines present: free chlorine versus chloramines

  - The background of natural organic concentration in feed water source

  - Turbidity, color, and suspended solids

  - The ratio of target effluent chlorine concentration to influent chlorine concentration

Advantages: no harmful chemicals are added to the water stream; low maintenance; can be hot water sanitized or ozonated.

Disadvantages: systems can be large in size and take up floor space based on inlet flow rates; the effectiveness of the process depends on many variables of the feed water quality; the initial capital cost can be higher than other methods.

4.9   System Design for Control of Microbial Growth

Bacterial contamination is usually expressed as total viable microbial counts per ml or as Colony Forming Units (CFU) per unit volume. CFUs are determined by counting the growth resulting from incubating samples. Each colony is assumed to form from one bacterium.

If the concentration and application of microbial-control agents are insufficient, additional microbial-control functions may be needed, which is more likely if the supply water comes from an unregulated source such as a private well. Control measures include periodic heat or chemical sanitization of the initial equipment in the pretreatment system. Increased monitoring of feed water and pretreatment may be warranted. In most cases, the microbial-control agent must be removed prior to final treatment. A means of either continuous or periodic sanitization should be implemented for subsequent activities following removal of the microbial-control agent.

Common methods used in pretreatment to control microbial growth and prevent the formation of biofilm include:

- Microbial-control agents, such as chlorine or chloramines

- Periodic sanitization (heat or chemical)

- UV light

- Avoiding water stagnation, including implementing water recirculation during periods of low water use

- Temperature control to avoid microbial growth

- Periodic system flushing

A common strategy in the design of the pretreatment system is to leave the microbial-control agent provided by the municipality in the water through as many pretreatment steps as possible, in order to protect these steps from microbial growth. Free chlorine levels may dissipate in the system as water passes through different treatment stages. Re-chlorination may be employed and microbial monitoring at the different stages is needed to ascertain the effectiveness of the microbial-control approach.

The microbial-control agent (chlorine or chloramine) must be removed at a specified point in the process since, typically, it is not compatible with the final treatment processes. At this point, the preferred option is periodic sanitization, either with heat or a chemical disinfectant, or alternatively but less ideally, a carbon bed may be replaced. This needs to be included in the design of the pretreatment system, along with the provisions for validating and monitoring its effectiveness via sampling and testing. In general, the design of the system should maintain control of microbial growth and/or reduce the microbial load sequentially stage by stage. This can be achieved by careful design of sanitization agent addition, UV lamps, continuous operation etc. For further information, see Chapter 13.

Additionally, it is recommended to implement hygienic sampling valves and avoid ball valves. Hygienic design may be selectively considered to reduce microbial growth, particularly after removal of residual disinfectants.

4.9.1 Continuous Chlorine Disinfection

In addition, feed water to a site may not be equivalent to that distributed from a municipal treatment facility due to the potential for contamination or loss of the microbial-control agent in the distribution system. Further, if a feed water tank is utilized, the system must be designed to ensure that the quality of the feed water is maintained within drinking water specifications in the feed water tank and all the way through the system.

Microbial-control agent monitoring should begin at or before water enters the system, most often at the start of a pretreatment system. A free chlorine level of 0.2–0.5 ppm is generally considered adequate to control microbial growth and usually has negligible effects on pretreatment equipment and its performance. Chlorine levels are affected by pH, and as a result, pH monitoring may be required if chlorine levels are erratic or difficult to maintain. Controlling chlorine excursions is critical due to the potential effect on final treatment processes (see Table 4.2).

Free chlorine levels will vary in the system as a consequence of passage through different treatment stages. Microbial monitoring at the different stages is needed to ascertain the effectiveness of the microbial-control approach.

Municipalities frequently use chlorine, often introduced as sodium hypochlorite, to disinfect water before and during distribution. Chlorine is fed into the system to kill bacteria at typical dosage levels of 0.2–2.0 ppm of free chlorine. In Europe and elsewhere, residual disinfectant levels may be much lower or altogether absent. In the US, the free chlorine level at outlying distribution points is often targeted at about 0.2–0.5 ppm. If the water supply is heavily contaminated with organics however, the chlorine may react and form Trihalomethanes (THMs). In other cases, chlorine can dissipate and no residual level is maintained at outlying points in a municipal distribution system.

Chlorine concentration should be monitored in the feed water and in the different treatment stages of the pretreatment system prior to its removal. Re-chlorination in a water treatment system should consider adequate contact time to be effective. This may require the use of feed water break tanks for certain systems. Some feed waters can only be treated by continuous dosage of chlorine dioxide that is effective at 0.2–0.4 ppm for the removal of biofilm and reduction of general microbial levels.

Molecular chlorine can have adverse effects on the components in a water purification system. It causes oxidative deterioration of the membranes, particularly polyamides, often used in UF and RO. It also brings about degradation, embrittlement, and loss of capacity in deionization resins (oxidation rate varies with resin type), although the amount is low to moderate at chlorine concentrations usually found in drinking water. Additionally, it corrodes SS, particularly at elevated temperatures, and may carry over into the product in a distillation system; therefore, in most systems making PW, chlorine is removed during pretreatment.

Advantages: low capital cost; common treatment; complements municipal water treatment; maintains a residual; easy to test and maintain levels.

Disadvantages: can create THMs and other biodegradable organic substances; does not control all microbial growth; residual chlorine may cause degradation to many final treatment systems.

4.9.2   *Periodic Sanitization*

Sanitization methods, employed on a scheduled or as needed basis, include:

- Heat

- Ozone

- Chemical sanitization

- Regeneration or replacement of media

- Flushing

- Drainage

With heat, USP indicator organisms [4] are killed above 65°C (149°F) and the majority of pathogenic organisms do not proliferate. Temperatures > 80°C (176°F) result in complete kill of all non-resistant bacteria. Sanitization times range from 1–2 h at the specified temperature. Total cycle time, including heat-up and cool down, may be 4–8 h. Heat is commonly used in carbon beds, filters, RO membranes, and storage and distribution systems. For further information, see Chapter 13.

Chemical sanitization agents (when chlorine cannot be used) include hydrogen peroxide, iodine, ammonium compounds, and organic or inorganic peroxygen compounds. Sanitization times range from 0.5–4 h, with additional time for set up to feed the sanitization agent into the system and to flush it from the system. Total cycle time may be 8 h.

Controlling temperature to minimize microbial growth allows an increase in the period between sanitizations. Temperatures < 15°C (59°F) slow microbial growth, but may be more expensive to operate than systems running at ambient temperature. Avoiding stagnation and dead legs minimizes microbial growth. Recycle loops around various unit operations can be used during shutdown periods, that is, recycle around a depth filter and softener while sanitizing the carbon bed or while cleaning and sanitizing RO systems. Water systems with recycling loops may build up heat and cooling should be considered.

Sanitization methods (frequency and length of sanitization) are system and sanitizing-agent dependent, and should be verified.

Typically, a plate and frame or shell and tube heat exchanger is used in pretreatment systems. Preferably a double tubesheet shell and a tube heat exchanger are used. If a non-hygienic heat exchanger is selected, the heating/cooling media pressure should be below the pressure of the process water. The pressure difference should be maintained and monitored for pretreated water and raw steam to ensure cooling/heating media are not introduced to pretreatment water in the event of an internal leak.

4.9.3 Continuous UV Light Disinfection

Treatment with UV light at various wavelengths is a popular form of microbial control and disinfecting, based on the ease of use. Water is exposed, at a controlled rate, with radiation emitted by UV light tubes of low or medium pressure. The UV light deactivates DNA in microorganisms, oxidizes organic material and microbes, and prevents replication of bacteria, depending on the wavelength.

In pretreatment systems, UV is normally used when chlorine/chloramine and heat are not available or feasible. The feed water to a UV system needs to be free of suspended solids, which can shadow bacteria, preventing adequate UV contact. UV is typically used in controlling feed water to an RO unit or DI system that cannot tolerate chlorine or heat, and in controlling non-chlorinated water recirculation during system idle time. The UV system does not leave a residue in the treated water and, therefore, is effective only if there is direct UV light contact with microorganisms. UV lights should be continually monitored to confirm that the design intensity is within the specified range to ensure adequate microbial control.

Note: UV lights may not adequately perform when used as the primary means of microbial or organic contaminant control, but perform well as a part of a total microbial-control plan.

4.10 Removal of Microbial-Control Agents

During pretreatment, microbial-control agents, primarily chlorine and chloramine(s), should be removed because of their detrimental effect on final treatment equipment and performance. Chlorine causes deterioration of most RO membranes and is corrosive in distillation. Chloramines can pass through pretreatment and decompose in the distillation process with an adverse effect on water quality.

4.10.1 Chlorine Removal

For chlorine removal, activated carbon is a simple process for the adsorption of chlorine. The carbon will reduce some of the chlorine to chloride ion, which is removed in the final treatment ion-removal process. Sulfite reduction is simple with sulfite oxidized to sulfate, and chlorine reduced to chloride ion.

Chloramine removal can be complex. Chloramine adsorption on carbon occurs at a much slower rate than chlorine, requiring longer contact times and lower hydraulic flow rates. The potential for dissociation of the adsorbed chloramines into ammonium ion and ammonia is problematic. Ammonium ions are removed by RO. Ammonium ions decompose to ammonia in a distillation process. Ammonia passes through RO and distillation processes during final treatment.

Sulfite reduction for chloramines results in ammonium and chloride ions. These can be removed by RO. The ammonium ion partially decomposes to ammonia in the higher temperature distillation process, resulting in carryover and effects on the water quality.

Removal of ammonia (from chloramine) and dissolved CO_2 gas can require appropriate pH control to maintain these species as ions for removal in an RO. The equilibrium of carbonate, bicarbonate, and CO_2 is pH dependent, with alkaline conditions required to maintain the ionic species. The equilibrium between ammonium ion and ammonia is pH and temperature dependent, with acidic conditions required to maintain the ionic species. At no single pH point are these species all carbonate and ammonium ions; thus, two pH adjustment steps followed by the appropriate removal technologies are required to remove both chloramines and CO_2.

Ammonia (from chloramine) can also be removed downstream of a correctly sized activated carbon filter using IX, often called a polishing softener. For this to operate correctly, ions with higher affinities for IX need to be absent from the feed to the polishing softener.

4.10.1.1 Chlorine Removal by Activated Carbon

Activated carbon removes chlorine by adsorbing it onto the carbon particles in a carbon bed. There is also some reduction of chlorine to chloride. Removal efficiency depends on bed depth, face velocity, and adsorptive capacity of the carbon. Design is based on the rate of adsorption, with adsorption rates typically being more rapid for chlorine than organics if performed in the same operation. Designs based on chlorine removal will occur with bed depths of as little as 2–4 ft (0.61–1.20 m) and hydraulic rates of 2–4 gpm/ft^3 (270–540 lpm/m^3) of empty bed volume. Carbon bed volume is a balance between total adsorptive capacity and the frequency of replacement of the carbon bed.

The use of carbon to remove chlorine provides the perfect conditions for microbiological growth – low flow rates in a warm media with lots of nutrient present; therefore, a program to periodically sanitize the carbon bed is preferred, or alternatively, replacement of the carbon bed. Heat (either Pure Steam, process steam, chemical free steam, or hot water at ≥ 65°C; 149°F) is effective with sanitization frequency varying from daily to a couple of times a week or less. With a proper sanitization program, microbial growth in carbon beds can be controlled. Bacterial levels should be established using baseline data to demonstrate control of bacteria growth and subsequent removal. Sanitization frequency varies based on this target. Following the sanitization, the carbon bed is usually rinsed to remove fines before being returned to service. Frequent backwashing, where used in a system, of the carbon beds may assist in microbial control within these units.

Advantages: reduces organic concentration; removes color; removes chlorine effectively; technically not complex for non-heat sanitized units; relatively low cost.

Disadvantages: high potential for increase in bioburden; medium to high capital cost for thermally sanitized units; shedding of fines requires downstream filtration; periodic replacement of the spent carbon needed; carbon may need to be removed/bypassed while performing chemical sanitization of pretreatment.

4.10.1.2 Chlorine Removal by Sulfite Addition

The addition of a reducing agent reduces chlorine to chloride. Sulfite (sometimes in the form of sodium bisulfite) is generally the reducing agent of choice. The chemistry is:

$$SO_{3-} + Cl_2 + H_2O \rightarrow 2Cl^- + 2H^+ + SO_4=$$
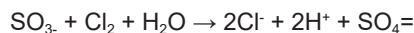
Sulfite dosing is commonly controlled by an Oxidation Reduction Potential (ORP) or chlorine sensor.

The addition of sulfite may require an accompanying pH adjustment step. The chloride and sulfate formed may be removed by a subsequent deionization step or RO.

Advantages: effective removal of chlorine; lower capital cost than carbon filters that can be heat sanitized; no regeneration or replacement required; low operating cost.

Disadvantages: technically more complex; chemical handling including sodium bisulfite and acid/base for pH adjustment; potential for microbial growth in sulfite feed tank requires frequent (< 5 days) preparation of sulfite solution; higher capital cost for feed systems and monitors; higher cost than disposable carbon; there is an additional concern regarding buildup of sulfite in recirculation loops.

4.10.1.3 Chlorine Removal by UV Irradiation

UV light can be used in the reduction of chlorine. In this process, where 100% photodecomposition of free chlorine is achieved, UV light photolysis decomposes free chlorine to form approximately 80% chloride ions and 20% chlorate ions. The typical UV dose for photodecomposition of free chlorine is at least 20 times higher than the standard disinfection UV dose. Generally, medium pressure UV lamps are incorporated, as the radiation wavelengths needed for the destruction of hypochlorous acid HOCl and hypochlorite ion OCl$^-$ are 240 nm and 290 nm respectively.

Successful chlorine removal is a function of the UV dosage and contact time. Consideration of this process is based on the ppm level of chlorine concentration in the feed water. The UV Transmittance (UVT) in a typical municipal feed water source is about 85–97%. The UV dose required for the dechlorination of a particular water stream also depends on:

- The type of residual chlorine present: free chlorine versus chloramines

- The background of natural organic concentration in the feed water source

- Turbidity, color, and suspended solids

- The ratio of target effluent chlorine concentration to influent chlorine concentration

Advantages: no harmful chemicals are added to the water stream, low maintenance, and can be hot water sanitized or ozonated, no microbial growth in the UV chamber.

Disadvantages: systems can be large in size and take up floor space based on inlet flow rates; the initial capital cost can be higher than the other methods; higher risks for breakthrough of chlorine due to feed water quality fluctuations and/or improper sizing; increased instrumentation, such as ORP or chlorine analyzers, to mitigate risks compared to carbon filtration.

4.10.2 Chloramine(s) Removal

Chloramines are formed by the reaction of chlorine and ammonia. Municipalities add ammonia to form a longer acting disinfectant than chlorine and to reduce the formation of THMs during the chlorination of municipal water. Chloramines consist of three compounds: monochloramine (NH_2Cl), dichloramine ($NHCl_2$), and trichloramine (NCl_3). Dichloramine is a particularly strong biocide.

Chloramines present problems since their removal typically is not achieved in a single step. Three methods for chloramine removal are listed below.

4.10.2.1 Chloramine(s) Removal by Activated Carbon

Where chloramines are present in the water, the chloride ion is removed by activated carbon using catalytic carbon, and releases ammonia/ammonium into the water. The reaction is much slower than for chlorine alone or organics, and the ammonia/ammonium must be removed by a downstream process. The chloramine reaction requires bed contact times of 3–6 times longer than those required for chlorine alone.

The removal of chloramines by activated carbon results in the dissociation of chloramines to ammonium ion and ammonia. The ratio ammonium ion:ammonia is dependent on pH and temperature. The ammonium ion can be removed by cation exchange (water softening). If chloramines are present in the feed water, it may be desirable to locate the activated carbon bed for removal of the microbial-control agent prior to the water softening operation in the pretreatment system design.

The advantages and disadvantages of using activated carbon for the removal of chloramines are similar to those for chlorine. The potential dissociation of chloramines to form ammonia is a disadvantage and can cause problems in final treatment.

4.10.2.2 Chloramine(s) Removal by Reduction

Reduction with sodium metabisulfite will convert chloramines to ammonium ion and chloride ion. These are removed by an IX operation or the ion-removal process in final treatment. If chloramine is present, it may be desirable to locate the microbial agent removal prior to the water softening operation in the pretreatment design.

The advantages and disadvantages of sulfite reduction are similar to those for chlorine.

4.10.2.3 Chloramine(s) Removal by UV Irradiation

Like chlorine, chloramines can be removed by UV irradiation. The similar properties and reactions of chlorine apply to the reaction and removal of chloramines. UV photolysis reduces chloramines to chlorides and nitrates, which are easily removed by RO.

A major design consideration for UV dechloramination is the sizing of the UV unit regarding the number of UV lamps required. The typical UV dose for photodecomposition of chloramines can be 2–3 times higher than the standard dechlorination UV dose. Feed water parameters, such as turbidity, dissolved solids, and color, should be considered for proper sizing. Assistance from UV suppliers or pilot testing of UV irradiation units for both chlorine and chloramines according to a supplied water analysis should be considered.

Advantages: simplicity; no added substance; low maintenance, no moving parts; reliability; no microbial growth in UV chamber

Disadvantages: high capital investment; large systems for treatment of chloramines; must run continuously; higher risks for breakthrough of chlorine due to feed water quality fluctuations and/or improper sizing; increased instrumentation needed to mitigate risks compared to carbon filtration

4.11 Changes in Anion Composition/Concentration

Pretreatment systems typically remove non-ionic impurities and cations; thus, any change in anionic composition or concentration is usually secondary. Distillation processes in final treatment may be affected by chlorides, which can be removed by RO prior to the final treatment step.

The pretreatment processes that affect anionic composition are:

- Deionization

- Degasification

- Carbon bed filtration for the removal of chlorine and chloramines

- Reduction to remove chlorine and chloramines

- Barrier filtration (UF and RO)

IX resins are designed to remove either cations or anions. An IX resin that is designed to remove anions (anionic resin) typically will exchange the anions:

- Chloride

- Sulfate

- Nitrate

- Carbonate

- Bicarbonate (if the pH is appropriate for the hydroxyl ion)

The IX may be in a single bed, mixed beds, or twin beds, and will affect anionic composition if an anionic resin is present. For further information, see Chapter 5.

Carbon bed filtration adsorbs chlorine and chloramines from feed water. A quantity of the chlorine is reduced to chloride and is removed in a subsequent ion-removal process, usually in final treatment.

The removal of chlorine and chloramines by reduction, often with bisulfite, changes the ionic composition and concentration as the bisulfite is oxidized to sulfate and the chlorine or chloramines are reduced to chloride and ammonium.

RO may be used to remove chloride ions prior to some distillation processes.

4.11.1 pH and Carbon Dioxide

pH and CO_2 gas have an inverse relationship that needs to be considered when designing pretreatment systems for RO systems or where there is a need to minimize CO_2 gas prior to final treatment.

pH, the negative log of the hydrogen ion concentration, is a measure of the concentration of hydrogen ions (H^+) in a water-based solution. The more hydrogen ions present, the lower the pH and the more acidic the solution.

The concentration of hydrogen ions (pH) is especially important because it affects the chemistry of the water. For instance, the pH of the water, along with other parameters, signifies whether the water will corrode piping or if certain contaminants (carbonates) are likely to precipitate and cause scaling.

In water or aqueous solutions, a certain ratio of water molecules, H_2O, separates (or dissociates) into the ions H^+ and OH^-.

$$H_2O \leftrightarrow H^+ + OH^-$$
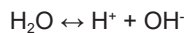
Because of the properties of water, when the concentrations of hydrogen ions (H^+) and hydroxyl ions (OH^-) present in any water-based solution are multiplied together, the value is always the same. This number is the equilibrium ion product, Kw, which has been determined to have the value shown below:

$$Kw = [H^+] \times [OH^-] = 1.01 \times 10^{-14} \text{ at } 25°C \ (77°F)$$

Where: $[H^+]$ = Concentration of H^+ (moles/l)
$[OH^-]$ = Concentration of OH^- (moles/l)

Free carbon dioxide is the term used to designate CO_2 gas dissolved in water. The designation free carbon dioxide differentiates a solution of CO_2 gas from combined CO_2 present in the form of bicarbonate and carbonate ions. (A solution of CO_2 gas will pass through a downstream RO membrane, whereas bicarbonate and carbonate ions can be removed by downstream RO systems.)

In the case of high purity water, low levels of free carbon dioxide from the atmosphere can cause the pH to drop from 7.0 to 5.5 and the conductivity to increase from 0.1 µS/cm to > 1 µS/cm. Low levels of CO_2 can prevent a water purification system such as a two-pass RO from producing water with a conductivity of ≤ 1 µS/cm, and/or water that may have difficulty passing online conductivity requirements.

Free carbon dioxide in water is produced by the decay of organic matter, dissolution of CO_2 from underground sources, and in solution from the atmosphere. Since the CO_2 content of the atmosphere is quite low (less than 0.04%), this is not a major source of CO_2 in the water and surface waters normally are relatively low in free carbon dioxide; however, well waters usually contain an appreciable quantity of free carbon dioxide.

The pH of the water causes the equilibrium between free carbon dioxide (gas) and bicarbonate alkalinity (dissolved ion) to shift, more or less, to CO_2. As the pH is lowered, the equilibrium is shifted toward CO_2, which is a neutral species dissolved in the water with the ionic charge being maintained with anions from the added acid and the net formation of water. As the pH is increased, the equilibrium is shifted toward bicarbonate and then carbonate with the ionic charge being maintained with cations from the added base and the net formation of water. The determination of the level of CO_2 present in the water as it proceeds through the treatment process is important to understand because it can affect the final water quality and cause premature exhaustion of IX systems.

The complicated interplay between pH and CO_2 can be avoided by use of a contact degasser that removes dissolved gases by a semipermeable membrane with a vacuum pull on the outer chamber.

4.12   Materials of Construction and Construction Practices

Piping to the pretreatment system may be copper, galvanized steel, SS, or a suitable thermoplastic. Piping in the pretreatment system, where high temperatures are not encountered, is usually plastic (PVC, Chlorinated Polyvinyl Chloride (CPVC), PP, or other material) based upon cost and corrosion resistance. Leaching from some plastics such as PVC and CPVC may make these materials undesirable. Vessels may be fiberglass reinforced PP or PVC, lined carbon steel, or SS.

The piping and equipment in a portion of the pretreatment system may encounter high temperature (periodic heat sanitization) or high pressure (RO plus degasification). In these portions, piping typically is SS or a plastic that can be heat sanitized, such as PVDF. Equipment designed for high pressure may be lined carbon steel, SS, or a high-strength plastic. Mill (interior) finish is satisfactory for plastic or SS; electropolishing for SS is unnecessary.

The capital cost of hygienic construction practices, such as orbital welding and hygienic fittings, may not be warranted in the pretreatment system; however, it may be implemented in key areas such as downstream of the residual disinfectant removal step. Lean construction practices and use of plastic pipe that is solvent cemented, heat fused or SS pipe or tube that is welded or flanged with mill finish is common. Plastic pipe with organic solvents can elute TOC, which may be undesirable. Diaphragm valves, butterfly valves, and limited use of ball valves predominate for flow diversion with globe and needle valves for flow control.

Selecting the minimum cost piping components that will not degrade water quality should be weighed against possible microbial contamination. The pretreatment sanitization strategy should be simple and robust. For unit operations or regions of the world where there is little to no residual disinfectant, it is recommended to use SS piping and implement hot water sanitization. SS piping has the additional advantage of being resistant to ozone.

Sample points, of a hygienic design where appropriate, should be provided upstream and downstream of each piece of equipment for monitoring and troubleshooting. Points for field measurement of pressure and temperature are also useful for troubleshooting.

Internal column lining or coating should be considered for multimedia filters, activated carbon filters, and softeners that are constructed of carbon steel. Filter media expands upward within the vessel during backwash operations and tends to abrade the column surfaces.

4.13   Water Conservation

Many of the unit operations used for pretreatment systems employ media filled columns. These are common for media filtration, activated carbon, and water softening processes. These processes require periodic backwash or regeneration maintenance steps that use high instantaneous flow rates. The frequency of these maintenance steps is a function of the incoming water quality. For certain feed waters, the frequency, and subsequently the water consumption, can be excessive. Traditional water softening requires a brine regeneration step and rinse step in addition to a backwash.

Water consumption may be minimized by optimizing the regeneration or backwash frequency of these units. This may include conducting these maintenance steps based on system performance and operation, rather than a preset time interval. Unnecessary or excessive backwash episodes can be particularly wasteful for media filters. The volume of water discarded for some systems can be as much as twice the normal feed water flow rate. Installing non-calibrated flow meters to ensure backwash rates are within the proper range is recommended for commissioning purposes. In instances where backwashing is a primary factor in microbial control, a balance needs to be determined between water conservation and microbial control.

Additional novel or innovative technologies are available to minimize water consumption and recycling. These include backwash steps modified with air scouring techniques, high-efficiency softening systems, alternate hardness removal techniques, or organic reduction techniques other than traditional packed bed activated carbon adsorption.

5 Final Treatment Options for Production of Compendial Purified Water, Compendial Water for Injection, and Non-Compendial Waters

5.1 Introduction

This chapter discusses the final treatment technologies typically implemented in the generation process of compendial (e.g., USP, Ph. Eur., JP [4, 5, 6]) Water for Injection (WFI), Purified Water (PW), and non-compendial waters. Final treatment options reduce pretreated water conductivity, Total Organic Carbon (TOC), microbial contaminants, endotoxin, nitrates, and other contaminants as necessary to meet the required finished water quality. Some final treatment processes such as Reverse Osmosis (RO) and distillation reduce multiple contaminant groups in a single process, while others, such as microfiltration, may reduce the amount of a single contaminant group. Some unit processes such as ultraviolet (UV) light may be considered both pretreatment and final treatment depending upon location in the system configuration and purpose. A process such as UV can be used as pretreatment to protect final treatment processes downstream and also as polishing final treatment for specific trace-contaminant removal.

Systems used to produce compendial and non-compendial waters are described in Chapter 6. Some systems implement pretreatment and a single final treatment process such as distillation, while others employ pretreatment and multiple final treatment processes as their optimum system design.

The final treatment processes commonly used in compendial and non-compendial pharmaceutical water systems include:

- RO

- Ion exchange (IX)

- Distillation

- Continuous electrodeionization (CEDI)

- Membrane degasification

- Ultrafiltration (UF)

- Microfiltration

- UV light

Equipment construction is discussed for each unit process section to promote the proper selection of materials, surface finishes, and other design factors. The total system capital cost is often influenced more by equipment design details than by unit process selection. Many aspects of equipment can be over-designed and hence, become unnecessarily costly. As an example, polished surface finishes and hygienic connections may be ideal for distribution and considered for portions of generation, but unnecessarily expensive for many pretreatment processes and final treatment skids with regard to application and risk assessment.

Appropriate consideration should be given to an individual component's function, location, required microbial performance, sanitization, and other factors to optimize design. In most cases, it is not necessary to construct every makeup system component with the same level of surface finish and detail as the distribution system for effective operation. Many generation systems operate successfully without polished surfaces. Care should be taken so that all components of the system are still capable of producing the high-quality outputs required.

A design review should be performed to determine the best system equipment design for consistent operation to meet specifications and optimize lifecycle cost. The requirement to replace system components (e.g., filters, RO membranes) at a frequency such that the appropriate water quality and system output are maintained should be considered and determined during system operation.

This chapter does not differentiate between compendial and non-compendial water system equipment. Non-compendial water is often manufactured and validated in a manner consistent with compendial water. Non-compendial water for pharmaceutical manufacturing is simply water defined by factors other than the requirements of various pharmacopeial groups. The water quality parameters may be less stringent or more stringent than compendial waters. Non-compendial waters may include several compendial water quality attributes, as well as additional characteristics. The lowest quality non-compendial water for pharmaceutical use is generally water meeting drinking water standards, such as US EPA NPDWR [29], WHO [32] or equivalent. Non-compendial waters can exceed the quality standards of PW or WFI where the product or process requires extremely pure water.

5.2   Ion Exchange

5.2.1   Description

IX is a process utilizing organic polymer-based resins for the removal of ionized contaminants. Water passes through porous IX resin beads and ionized contaminants (cations and anions from the salts in the feed water and charged organic compounds) are exchanged for hydrogen and hydroxyl ions.

Cation and anion-exchange resins are manufactured from organic polymers that can be made to function with a fixed positive or negative chemical charge. The fixed charge site has a mobile counter ion attached to be in electrical equilibrium. Cation resins have negative fixed charge and remove cations (positively charged) from water. Anion resins have fixed positive charges and remove anions (negatively charged) from water.

As water passes through the IX resins, the exchange of ions in the water stream for the hydrogen and hydroxide ions (H^+ and OH^-), held by the resin, occurs readily and is driven by chemical equivalent weight. Higher equivalent weight ions, such as sodium, calcium, magnesium, chloride, sulfate, bicarbonate, etc., readily displace the hydrogen and hydroxyl ions from the exchange sites. The product stream has significantly lower conductivity as the conductive elements have been almost entirely removed. Typical IX systems are easily capable of producing water meeting USP Stage 1 PW conductivity requirements [4].

The IX resin reaches an exhausted state when most of the IX sites have exchanged H^+ and OH^- for ionized water contaminants. The resins must be regenerated when ionic leakage in the effluent produces unacceptably high conductivity. The IX sites prefer to remain in the exhausted state with a higher chemically charged ion than H^+ or OH^-. Thus, the regeneration process is driven by excess chemical concentrations of a regenerant acid or base solution.

IX systems are available in tank or cartridge configurations using virgin resin or resins regenerated on-site or off-site. On-site regeneration requires regeneration-chemical handling and neutralization but provides maximum internal process control. Off-site regeneration is an outsourced operation that removes the need for chemical handling and neutralization, but reduces process control and necessitates vendor management.

IX systems come in two basic physical configurations commonly referred to as two-bed (or separate bed) demineralizers or mixed-bed demineralizers. A two-bed IX system includes separate cation and anion resin tanks. Such systems often function as the workhorse of a strictly deionization (DI) water system in terms of salt removal. Two-bed demineralizers utilize a simple regeneration process, but typically produce a higher conductivity effluent than a mixed-bed demineralizer. Some two-bed demineralizer systems use a cation polisher downstream in lieu of a mixed-bed polisher.

Mixed-bed demineralizers consist of a single tank with a mixture of cation and anion removal resin. The resins are thoroughly mixed in the service cycle and must be separated into two distinct layers for regeneration. The regeneration cycle is more complex and hence possibly less consistent, but extremely low conductivity water can be produced.

5.2.1.1   Mechanical Requirements

A typical IX system is comprised of:

- One or more tanks

- IX resin

- Piping and valve system

- Water/chemical distributors internal to the tanks

- Regeneration system (typically off-site)

- Conductivity or resistivity meter and cell

Other common instrumentation includes a flow meter and pressure gauges. IX systems are available in both on-site and off-site regenerable (rechargeable) versions. In both forms, tanks may be constructed from:

- Fiberglass Reinforced Plastic (FRP)

- Stainless steel (SS)

- Carbon steel with an inert interior lining such as vulcanized rubber

- Polyvinylidene Fluoride (PVDF)

- Polypropylene (PP)

- Polyethylene (PE)

- Polyvinyl Chloride (PVC)

In selecting the material, care should be taken to select one that will not leach high amounts of unwanted ions. Off-site regenerated or rechargeable systems are usually transported to a facility equipped to either regenerate or replace the resin. For this reason, these units are typically supplied with fiberglass or light gauge SS vessels. Larger, off-site regenerated systems are recharged with new or regenerated resins on-site, and the exhausted resin is returned to an off-site regeneration facility. New resin provides greater capacity and some possible QC advantages, but at a higher cost. Regenerated resin produces a lower operating cost, but may raise QC issues, such as resin segregation, regeneration quality, and consistency.

Audits should be conducted to prove that off-site regenerated resins meet all quality requirements necessary for proper system operation. IX resins must be properly segregated from resins that may contain inappropriate contaminants, or dedicated to specific pharmaceutical manufacturing sites if practical.

5.2.1.2 Tanks

The most common tank material is FRP, which is favored for low capital cost and excellent corrosion resistance. Lined steel or SS tanks may be implemented where larger sizes or greater interior access is required. Steel tanks are welded and typically manufactured and designed in accordance with the ASME BPVC Code for operating pressures 100–150 psig (7–10.5 kg/cm^2 gauge). ASME Code stamping, or equivalent, is not necessarily required for this type of equipment; however, local regulations and end user safety concerns should govern this decision [19].

5.2.1.3 Distributors

Each IX tank includes distributors at all pipe to tank interfaces. Distributors are required to ensure that resin does not escape from the tank while water is flowing through the system and to provide adequate distribution of flow through the vessel. Distributors typically are supplied in SS, PVC, CPVC, PP, or PVDF. Structural integrity of a distributor system is a key element in any design since a ruptured distributor can cause a significant loss of resin and may take a considerable amount of time to repair.

5.2.1.4 Piping and Valves

The selection of a piping and valve system depends upon several factors including budget, product water quality (in terms of chemical analysis), and preferred methods of sanitization. Many IX systems are provided with PP, PVC, or CPVC piping and valves. The advantages of these materials include low cost, ease of assembly, and high corrosion resistance. PVDF also has been utilized in DI systems to some extent. PVDF is more expensive than either PVC, CPVC, or PP; however, PVDF is superior in terms of the lower level of organic leachables from either the piping or joining compound materials into the process water. Furthermore, PVDF is available in a piping design that more closely resembles the orbital welding in hygienic stainless piping systems.

SS systems may offer greater structural integrity than plastic piping systems and may require less support and smaller expansion loops than thermoplastic piping in hot water or steam sanitization applications. SS is more vulnerable to corrosion than thermoplastic piping. Thermoplastic piping in PVDF can be hot water sanitized with proper attention to piping support and thermal expansion. Selection generally is based on:

- Total cost of ownership considering installed cost

- Ongoing maintenance requirements

- Sanitization method

- Corrosion resistance

- Service lifecycle requirements

5.2.2 Application

The major purpose of IX equipment in water systems is to satisfy the conductivity requirements of the water quality specification. DI systems may be used in isolation or in conjunction with RO to produce PW, WFI, or various types of non-compendial waters.

IX systems can effectively reduce organics in many applications with proper resin selection and maintenance; however, compendial TOC requirements may not be met without additional membrane processes in certain applications where high feed water TOC levels exist.

Many small volume systems for compendial and non-compendial waters, and for production and laboratory water, use off-site regenerated IX units as the primary treatment. When using off-site regeneration, segregation of the resin may be desired. For further information, see Chapters 6 and 9. The systems may include UV light units or microbially retentive filters to meet microbial limits.

Capital cost and chemical handling are minimized, but operating costs can vary significantly. Maintenance requirements typically are low and outside services normally are used to replace the resin tanks and other consumable items. These systems can produce extremely low conductivity water.

Larger volume systems may use on-site regenerated demineralizers to minimize operating costs, but these are uncommon in newer installations. These systems can be low in capital cost, but can require significant regenerant chemical usage. Membrane-based systems have replaced a significant percentage of these systems as many organizations minimize chemical handling and discharge.

5.2.3 Pretreatment Requirements

IX systems require pretreatment to remove sufficient undissolved solids from the water stream to avoid resin fouling or degradation. Although dechlorination also is recommended to avoid resin degradation by oxidation, the low levels of chlorine normally found in potable water supplies usually demonstrate only long-term effects on most IX resins. See Chapter 4 for additional information.

5.2.4 Cost Savings Factors

Most of the cost saving opportunities for an IX system revolves around the correct choices in materials of construction, pretreatment options, instrumentation, and sizing of the DI system. Acceptable piping materials of construction can vary from PVC to 316L SS. A correctly designed system minimizes equipment size, considering microbial control and maintenance. Choosing to monitor only the critical parameters such as conductivity (resistivity), flow, pressure, etc., can reduce the instrumentation needed.

Cost saving choices should be made with respect to capital purchase and ongoing operating costs, with options including DI off-site regenerable bottles, on-site regenerable DI vessels (with automatic or manual controls), or another water treatment unit operation.

5.2.5 Microbiological Concerns, Cleaning, and Sanitization

Although IX resin beds, due to the hydrogen ion and hydroxide IX sites, have pH values at the extreme ends of the range, microbiological activity remains a concern. The regeneration of both the cation and anion-exchange resin beds effectively sanitizes the system; however, as the system processes water, the resin becomes exhausted and the pH approaches neutral. Organic matter may be deposited on or absorbed by the resins, particularly an anion resin, and bacterial growth can occur in IX beds. For this reason, regeneration frequency is more important in IX systems that are not designed with auxiliary microbiological control components, such as UV lights. Polishing IX systems typically are positioned in a system with bacterial control elements, such as sub-micron filters and UV sterilizers, and may operate for several weeks without requiring regeneration.

IX resins can be sanitized chemically with a variety of agents. The degree of resin attrition is a function of resin type and the chemical agent. The most implemented chemical sanitizer is peracetic acid, as minimal attrition occurs. Sodium hypochlorite, hydrogen peroxide, and iodine have also been used for sanitization. Minimal IX damage will occur if chemical strength and exposure time are appropriate. Some resins are capable of hot water sanitizations at temperatures 65°C–85°C (149°F–185°F). IX resins suitable for limited thermal sanitizations include strong acid cation resin, and standard polystyrene cross-linked with divinylbenzene Type 1 strong base resin. Hot water sanitization is extremely effective.

5.2.6   Advantages and Disadvantages

Major advantages are the degree of flexibility in flow rate of IX systems, lack of sophisticated maintenance requirements, consistent production of Stage 1 conductivity, and the ability to use the chemical regeneration of IX resins as a means of periodic microbial control.

The major disadvantages include the need for outside services, the necessity for microbial reduction processes downstream, storing and handling acid and caustic chemicals, neutralization of waste chemicals (for on-site regenerated systems), and the reduced ability of IX resins to remove dissolved organics relative to membrane-based systems.

Advantages:

- Simple design and maintenance

- Flexible in water flow production

- Low capital cost for single train DI systems

- Simple operation with few adjustments

- Removes ionized substances for lowest effluent conductivity possible

Disadvantages:

- High cost of operations on high Total Dissolved Solids (TDS) in feed water without RO pretreatment

- Requires chemical handling for on-site regenerable DI (safety and environmental issues)

- Full on-site DI system can take a significant amount of floor space due to primary vessels, chemical storage, and neutralization system

- Off-site DI systems necessitates outside service and significant costs for regeneration services

- Off-site regeneration involves consequent loss of control over the use, handling, and care of DI vessels

- Not considered a microbial barrier in most applications

5.3   Reverse Osmosis

5.3.1   Description, Materials, and Configurations

RO is a pressure driven process utilizing a semipermeable membrane capable of removing dissolved organic and inorganic contaminants from water. A semipermeable RO membrane is permeable to substances such as water, semipermeable to other substances such as salts, acids, bases, minerals, and dissolved organics, and impermeable to colloidal materials, bacteria, and endotoxins. Most RO membranes have a projected Molecular Weight Cut-off (MWCO) of 100–200 Daltons and are effective at removing most materials larger than the rated MWCO. Because of the hydrogen bonding properties of water and other factors, dissolved salts and minerals of a significantly lower size than RO membrane pore sizes may be effectively removed with 90–99% efficiency. All RO systems generate some waste water, which discharges concentrated impurities to drain or reuse if implemented.

Because of its performance characteristics and extremely small pore size, RO is one of the most commonly used technologies in water purification. It is capable of removing almost all seasonal variations that occur in surface water supplies and is the backbone of many pharmaceutical water systems.

RO membranes are produced commercially in hollow fiber and spiral wound configurations, with the latter used almost exclusively for pharmaceutical water production. Membranes are commonly available in two materials – Cellulose Acetate and Thin Film Composite (polyamide or other similar composite), with TFC membranes the predominant material in use today. Composed of polymeric materials, the output capabilities of all RO membranes are influenced by temperature, with higher throughput at higher temperatures (at constant pressure).

Cellulose acetate is the oldest commercially produced RO membrane material, but its use has been almost entirely replaced by TFC membranes. Cellulose acetate membranes are chlorine tolerant and resistant to fouling, but have several limitations that have precluded their widespread use in the pharmaceutical industry such as:

- Susceptibility to hydrolysis at common operating pH levels

- Allow passage of more carbon dioxide through the membrane

- Can be consumed by bacteria present on the membrane

- Energy intensive to operate

TFC RO membranes offer numerous advantages over Cellulose acetate membranes because TFC membranes:

- May be safely operated at pH 3–11

- Are not vulnerable to bacterial attack

- Operate productively at lower water temperatures and pressures

- Have lower energy requirements

- May be cleaned with a wide variety of membrane cleaners

- Have a longer life expectancy

- Offer the highest rejection of contaminants of all membrane types

- May be sanitized using chemicals or heat

The primary disadvantage of TFC RO membranes is their very low tolerance to free chlorine and chloramine in the feed water. TFC membranes degrade in the presence of chlorine and chloramine at the levels found in many municipal water supplies. Many TFC membrane elements have some stated chlorine/chloramine ppm-h exposure tolerance; however, care must be taken to avoid excessive chlorine exposure to ensure lengthy membrane life. The dechlorination of the feed water allows the opportunity for some bacterial growth to occur, which may necessitate additional sanitization efforts.

Most industrial spiral wound RO membranes incorporate a brine seal at the leading end of the RO element. This seal is designed to expand between the membrane and the pressure vessel containing the RO membrane, directing the water flow through the element and preventing the flow of water between the membrane and the pressure vessel. The presence of a brine seal creates an area of stagnant water between the outside of the RO membrane and the inside of the RO pressure vessel. Because all chlorine and chloramine have been removed prior to the RO elements, bacteria will grow in this stagnant area. For this reason, most pharmaceutical applications use spiral wound RO membranes without a brine seal on the leading end. Commonly referred to as loose wrap or full fit membranes, they are configured to allow a modest amount of flow between the RO membrane and the pressure vessel while diverting most of the flow to the membrane. Modified brine seals allowing some bypass flow may also be utilized to prevent stagnant water and minimize microbial growth in a similar fashion.

5.3.2 Applications

RO units can be successfully implemented in compendial and non-compendial pharmaceutical water systems in several ways. RO may be used without post treatment to produce non-compendial water or may be used to supply a distillation unit, rinse water, or other applications where some quality parameters are less stringent than compendial waters. RO units also can produce compendial waters meeting quality parameters when properly implemented on appropriate feed waters. Additionally, RO systems have been installed as part of an overall water purification system in both non-compendial and compendial applications that meet or exceed the CQAs for PW and WFI.

Most electrically regenerated deionizers require the presence of RO for effective operation, and may be used upstream of deionizers to reduce operating costs.

Double-pass RO units (also called two pass or product staged) have two RO units installed in series with product water from the first unit used as feed water to the second. They may be capable of producing water that meets the regulatory requirements for TOC and conductivity, but variations in feed water characteristics such as pH and carbon dioxide levels may preclude the consistent production of water meeting the compendial requirements for conductivity without some additional treatment.

RO systems can be designed using a wide variety of membrane configurations based on the desired rate of production as well as the amount of waste water generated. They are designed in arrays such that turbulence is reasonably maintained to minimize both precipitation and fouling of the RO membranes to prolong membrane life. Reject water from one set of membranes sent to another set of membranes as part of the RO system is called reject staging, and is a commonly used design tool to increase productivity while minimizing the amount of water sent to drain. Recycling the reject water may be employed to maintain higher turbulence while minimizing the volume of water sent to drain as waste.

5.3.3 Pretreatment Requirements

RO membranes must be protected from scale formation, fouling, and degradation or oxidation. For a complete discussion of appropriate pretreatment for RO systems, refer to Chapter 4.

5.3.4 Design and Performance Characteristics

A single process pass of RO elements typically reduces the level of raw water salts, minerals and organics, bacteria, and endotoxin by approximately 90%–99.5%. RO is generally ineffective at removing many dissolved organics < 100–200 MWCO, and is minimally effective at removing dissolved gases from a water supply. Single-stage RO product water does not normally meet the conductivity requirements of most compendial PWs without further purification steps. Some double-pass RO systems may produce water meeting the Stage 1 conductivity requirements [4], but typically require further treatment to meet or exceed those requirements consistently. It is not uncommon for a single-pass or double-pass RO system to contain TOC-reducing UV treatment, IX, and microfiltration or UF steps to reliably produce water meeting or exceeding the CQAs for compendial PW and WFI.

System design should be based upon:

- Required product water quality

- Incoming water source characteristics such as seasonal variability, mineral scale potential and fouling potential

- Pretreatment requirements

- Operating performance characteristics

- Sanitization options (heat or chemical)

- Capital and operating costs

- Feed Water pH

- Ammonia content of feed water

RO units should incorporate sufficient membrane area to ensure reliable operation. Membrane manufacturers offer recommendations for membrane area or flux rate (gpd/ft² of membrane) required as a function of the feed water quality and operating temperature and pressure. One of the most important factors for the optimization of membrane area is understanding the fouling and scaling potential. The Silt Density Index (SDI) of a water supply offers an indication of the feed water tendency to foul membranes as a result of filterable contaminants. Lower SDI values tend to reduce fouling and therefore reduce membrane cleaning frequency. Many membrane manufacturers and system suppliers recommend a feed water SDI reading of three or less for reliable membrane operation. SDI values above 3 may require an increase in the number of elements to reduce permeate flow per area unit on the reject side of the membrane to reduce membrane fouling.

In general, the higher the membrane area for a fixed product water flow rate, the lower the rate of membrane fouling. This may not be the case in every instance, as differences in the percent recovery also impact performance. A high percentage recovery for an equivalent flow and membrane area tends to foul more. An increase in membrane area usually increases the equipment capital cost because of the additional membranes and pressure vessels needed. Optimization of RO systems generally involves the selection of membrane area to control capital cost without resulting in excessive membrane cleaning and replacement.

For proper operation, RO elements have minimum and maximum flow rates for all elements in an array configuration. Flow rates too low typically lead to premature element fouling or scaling, and too high can cause element damage.

RO systems are designed at specific baseline operating temperatures and pressures to predict the flux, or permeate flow rate per membrane area. Any deviations from these conditions could result in changes in the amount or quality of permeate water produced. For example, an increase in design temperature could lead to increased permeate flow exceeding the recommended flow rate for the equipment. The net trans-membrane driving pressure can be lowered to reduce the flow rate to the recommended flow rate. A reduction in trans-membrane driving pressure can cause a reduction in salt rejection.

RO operating cost optimization is based upon a comparison of pumping costs and feed water temperature required to produce the required product flow. Current membrane design often allows RO operation with water temperatures as low as 4.4°C (40°F). Lower feed water temperature generally improves salt rejection while reducing microbial fouling rates and operating costs.

Since RO is a tangential flow technology, reject or concentrate flow is essential to remove the contaminants rejected by the membrane. RO waste water can be reused or recovered as stated in Section 5.3.6.

Percent recovery, the percentage of feed water converted into product water, is calculated as follows:

Percent recovery = ((Product Water Flow Rate) / (Feed Water Flow Rate)) × 100

Typical recovery rates range from 10%–20% to 80%–90%, with larger systems typically able to recover more water without incorporating reject recycling. Smaller systems may utilize internal reject recycling as an effective means of improving their overall the recovery rates. The percent recovery depends on several factors including:

- Feed water quality provided to the RO unit

- System capacity/configuration

- Lifecycle cost requirements

- Expected water quality

- Waste water limitations

- Maintenance factors

An RO system operating a higher percent recovery generates less waste water to achieve its desired output rate, but tends to have higher maintenance costs due to the fouling/scaling effects of the concentrate. Depending on the feed water, higher recovery RO units typically require more frequent cleaning, maintenance, and possibly membrane replacement. Higher recovery increases the product water conductivity if the configuration is fixed.

The percentage of minerals and salts removed by an RO system is called percent rejection:

Percent rejection = ((Feed Water Conductivity – Product Water Conductivity) / (Feed Water Conductivity)) × 100

The water quality produced by an RO system is dependent upon several factors, including, but not limited to:

- Membrane type

- Operating pressure

- Feed water quality

- Feed water temperature

- Recovery

It is important to understand that from a salt and mineral removal standpoint, RO should be looked upon as a percent reduction technology. Should the feed water conductivity increase significantly, the product water quality generated by the RO will increase somewhat proportionally. For this reason, it is conceivable that the feed water quality could change sufficiently so that the product quality from the RO system may no longer meet water quality requirements.

Dissolved gases may not be reduced by RO membranes. Of particular importance are carbon dioxide and ammonia, which penetrate RO membranes and may increase the product water conductivity beyond the PW Stage 1 conductivity limit. Carbon dioxide and ammonia also contribute to the loading of IX resins present downstream of the RO unit. To alleviate these potential issues, a degasification unit operation could be added before or after the RO process.

Another option is to adjust the pH of the feed water prior to the RO to minimize dissolved gas levels. Carbon dioxide and ammonia are minimized at different pH, so it can be difficult to minimize both using this method. Raising the pH to 8.3 minimizes carbon dioxide by converting it to bicarbonate, which is more readily rejected by the RO membrane. Ammonia can be minimized by lowering the pH to about 7.0, converting ammonia to ammonium ion, which is rejected by the RO membrane. While the exact mechanism is uncertain, the presence of ammonia in the feed water reduces the percent rejection of RO membranes.

Most RO systems operate at 5°C–25°C (41°F–77°F). Most membrane elements are limited to high-pressure production operation at an upper temperature limit of 45°C (113°F) since structural damage can occur at higher temperatures. RO operation will allow some microbial growth, and therefore, most ambient operation RO units are periodically sanitized with chemicals or hot water as stated in Section 5.3.7.2. Operation on unheated feed water typically results in minimal energy consumption, best ionic rejection, and best microbial control. Operation on temperature-controlled heated water may increase energy consumption but may reduce operator adjustments in units lacking automatic flow control.

5.3.5 Controls, Instrumentation, and Automation

Proper controls and instrumentation along with some level of automation are needed to protect the RO equipment from conditions that could damage one or more components as well as to monitor and control many parameters of the RO system's operation.

Devices are typically included to protect RO high-pressure pumps against:

- Low feed water pressure

- High-pressure conditions

- High-temperature conditions

Monitoring equipment may also be included to measure:

- Feed Water conductivity, product water conductivity and percent rejection of the system

- Interstage membrane pressure in larger systems

- Product, reject, and recycle water flow rate and pressure

- Feed Water pressure and temperature

- Feed Water pH

- Feed Water ORP, chlorine/chloramine, or sulfite

Product water conductivity from the RO system is directly related to feed water conductivity. As a result, monitoring feed water and product water quality can provide a method for notifying an operator of an issue before the product water quality from the RO system increases. The feed water and permeate conductivity can be directly compared to provide online monitoring of RO percent rejection. Product water conductivity and temperature may be used for water quality compliance measurement when the RO unit is the final conductivity reduction process.

RO units also may monitor additional parameters, such as membrane interstage pressure to detect membrane fouling and to determine the need for cleaning or sanitization, which are discussed later in this section.

Product, reject, and recycle flow rates are typically monitored. This information may be used in conjunction with operating temperature and membrane pressure information to generate the normalized product flow for the system. Normalized product flow compensates for the effect of varying temperatures and pressures and allows for a determination of membrane flow under standard conditions. This is extremely helpful in determining when RO membranes require cleaning or replacement. Feed temperature is typically monitored as well as pressure for feed, concentrate, and permeate using properly calibrated instruments.

Small changes in feed pH may have a dramatic effect on final RO system conductivity if carbon dioxide and/or ammonia are present in the feed water. pH may be monitored and controlled (if required) utilizing an accurate pH meter with a proportionally driven feedback loop to regulate the rate of chemical injection. Using a simple on/off signal for chemical feed pump control is typically not recommended.

Chlorine, ORP, or sulfite level monitoring may be used to protect chlorine-sensitive TFC RO membranes against oxidation, depending on the pretreatment used prior to the RO system.

RO units from different manufacturers may incorporate varying levels of automation. Programmable logic controllers are common with many systems and Human-Machine Interfaces (HMIs) are integrated into a system's control scheme with increasing frequency in the pharmaceutical industry. Variable Frequency Drives (VFDs) may be included with RO systems to minimize hydraulic shocks on system start-up. VFDs may be combined with modulating control valves to automate heat sanitization cycles and/or to vary the output production rate of the unit based on demand or time of day to reduce energy requirements.

5.3.6   Reverse Osmosis Concentrate Reuse

RO concentrate may be sent directly to drain if it satisfies the discharge requirements for its location, but is frequently used for other purposes. RO concentrate can be purified in a recovery process such as another RO pass. The recovery RO product water is often recycled back to feed the primary RO unit. The concentrate from the recovery RO pass is sent to waste in most cases.

RO concentrate water may be used to supplement cooling tower makeup, to cool compressors, as a source of quench water, or to reduce other heat loads. RO concentrate may be additionally treated for recycling into the non-potable water supply or it may be directly added to a rainwater harvesting system.

When a double-pass RO system is utilized, concentrate from the second pass normally is returned to the feed water stream of the first pass RO.

When RO units are operated in product recirculation mode with product water recycled to the feed of the RO unit, RO concentrate can be recycled back to the RO feed side up to 100% recovery. The percent recycled in product recirculation varies with factors such as RO feed water pretreatment, feed water chemical injection, etc.

5.3.7   Cleaning and Sanitization

Cleaning and sanitization vary based on whether an RO system has been designed for chemical sanitization or heat sanitization. RO units typically require periodic sanitization to maintain compliant microbial performance and to minimize microbial fouling.

5.3.7.1   Chemical Cleaning and Sanitization

For chemically cleaned and sanitized RO systems, in single-pass RO systems or in the first pass of double-pass RO systems, RO membranes eventually foul with contaminants and require periodic cleaning. Monitoring important parameters assist operators in determining the type of fouling, which dictates the most effective method of cleaning.

RO membranes provide clues that they are fouling when any of the following conditions occur:

- Normalized product water flow is reduced over time

- RO pump pressure increases to produce the same amount of product water

- Percent rejection begins to degrade

- Pressure-drop increases between various stages within the RO system

- Differential pressure increases between feed water and permeate

Membrane fouling or scaling may be caused by several factors including:

- Fouling by silt or colloidal materials, which typically create pressure losses across the first set of membranes in a system, or where the tangential flow is at a minimum within a system.

- Scaling by precipitation happens when the concentration of some materials exceeds their solubility and then precipitates on the membranes. This typically occurs at the last membrane or set of membranes in a multi-element system.

- Biological fouling on the feed side of the RO membranes may increase product water TOC and microbial counts.

- Fouling by silt, colloidal, or organic materials may also be detected by a reduction in the percent rejection of the system.

Acidic cleaners are used to remove accumulated metals and mineral salts from the membranes. Alkaline cleaners remove silt, organic, colloidal, and some biological contaminants from the membranes. RO membranes can be cleaned in situ in the pressure vessels with an appropriate cleaning skid, or removed from the unit and cleaned off-site. Some operators choose to replace RO membrane elements with new elements rather than use cleaning chemicals.

RO membranes should be cleaned before they are chemically sanitized. In pharmaceutical applications, RO membranes can be sanitized with a chemical agent, although the vast majority of sanitizing chemicals are oxidizing agents, which may shorten membrane life.

5.3.7.2 Heat Cleaning and Sanitization

Numerous RO membranes and systems are available that may be routinely hot water sanitized at 80°C–85°C (176°F–185°F) under low-pressure conditions. Hot water sanitization may be implemented as an effective means for critical microbial control. Typically, membranes are heat sanitized on a regular basis (weekly or more frequently). The optimal sanitization frequency can be determined during system qualification and ongoing operation. The membrane element heat tolerance should be checked to understand maximum temperature and exposure time limitations. The heating process also is often effective at removing some of the organic and biological contaminants that normally require chemical cleaning. This may be a significant advantage of a heat-based system over a chemical-based system. Hot water can often remove some fouling contaminants but could increase adherence of scaling contaminants to the membrane surface.

5.3.7.3 Double-Pass RO Cleaning and Sanitization

In a double-pass RO system, the membranes in the second pass typically never foul with silt, colloidal materials, or minerals, but may become coated with bacteria, depending on the water quality. These second pass membranes generally only require periodic sanitization to maintain effective performance.

As an end note, it is important to remember that even under ideal conditions, RO membranes have a finite lifetime of 2–7 years. Aggressive chemical cleaning and sanitization or heat sanitization on a regular basis may slowly reduce the performance of RO membranes, and operators should monitor CPPs to determine when RO membranes require replacement.

5.4   Distillation

A suitable quality pharmaceutical still should purify water chemically and microbiologically through phase changes, while ensuring entrainment cannot compromise quality. Through this process, water is evaporated, producing steam. The steam disengages from the water leaving behind dissolved solids, non-volatiles, and other impurities. Impurities may be carried with water mist/droplets, which are entrained in the steam; therefore, separation devices should be used to remove fine mist and entrained impurities, including endotoxins. Purified steam is condensed into WFI. Distillation systems typically provide a minimum of 3 $\log_{10}$ (99.9%) reduction in endotoxin concentration.

Design options to be considered include:

•   Single Effect (SE)

•   Multiple Effect (ME)

•   Vapor Compression (VC)

It should be recognized that ME distillation uses multiple effects (columns) to reduce energy costs; however, as in the case of SE and VC distillation, an ME still distills the water just once, with each effect producing a fraction of the overall distillate volume.

In an ME system, purified steam produced by each effect is used to heat water and generate more steam in the subsequent effect, condensing to produce a portion of the distillate. It is only the first effect that requires heat from an external source, due to the staged evaporation and condensation process. It is only the purified steam produced by the final effect that is condensed, using an external cooling medium.

VC stills produce similar quality water using a different technique. Energy imparted to the generated steam by a mechanical compressor results in compressed steam with increased pressure and temperature. The higher energy steam is then discharged back into the evaporator/condenser vessel, condensing to produce distillate and generate more Pure Steam.

General areas of concern for stills include carryover of impurities, evaporator flooding, stagnant water, non-condensable gases, pump and compressor seal design. These concerns may be addressed using mist eliminators, high water level indicators, hygienic pumps and compressors, proper drainage, deaerators, adequate blowdown control, and conductivity sensing to divert unacceptable water to drain.

These unit operations have the ability to remove chemical and biological contaminants; however, each application should be reviewed with the equipment manufacturer under consideration, as proper operation is dependent on feed water pretreatment, flux, recovery, membrane/media material selection, temperature, and other critical factors.

5.4.1   Heat Exchanger Design

Heat exchangers may be used in the design of frequently used distillation units, to provide added energy using utility steam to preheat the water or provide continuous motive steam for operation. These heat exchangers recover energy that would be otherwise wasted and improve the efficiency of the still. Additionally, heat exchangers typically are used to condense the highly purified steam into liquid.

It is important to provide assurance that fluids of a lower quality are not allowed to enter product streams, because of the critical nature of WFI. This is particularly important in shell and tube heat exchangers where utility steam and coolant are used. In these areas, heat exchangers should be equipped with a double tubesheet arrangement. The double tubesheet provides an air gap to ensure that in the event of a leak at the location where the tube is joined to the tubesheet (see Figure 5.1), the leak will be to the atmosphere rather than into the process stream; however, it should be noted that this design feature will not overcome issues related to tube failure.

Where it can be demonstrated that the higher purity fluid also is at a higher pressure, a single tubesheet heat exchanger may be used, such as in ME stills for the second through the last effects. In these evaporators, the Pure Steam is at the higher pressure based on the design of ME stills.

Design of hygienic heat exchangers should consider the need for periodic cleaning, passivation, and inspection, and allow for thermal expansion.

Figure 5.1: Heat Exchanger Tubesheet Design
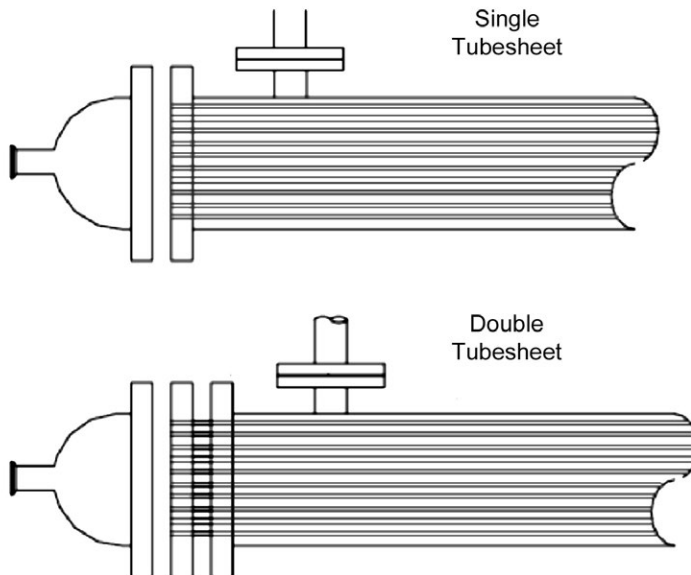
5.4.2 Distillation Technology Pretreatment Requirements

Distillation technologies require adequate pretreatment to prevent or minimize corrosion and scale formation in the equipment. The scope of the pretreatment varies based on the source of the feed water, as well as the distillation technology utilized. VC stills generally are more tolerant of dissolved mineral content in the feed water because of the lower operating temperatures. Conversely, ME stills, because of higher operating temperatures, require more stringent control of dissolved minerals. A membrane-based still feed water system typically produces lower endotoxin levels in the still feed water, potentially leading to lower endotoxin levels in the distillate of any still.

Silica scale is of concern for all stills and should be evaluated as part of the feed water analysis. Soluble and colloidal silica should be analyzed. In many cases, ensuring that the blowdown rate is sufficient to maintain the silica level below saturation prevents silica scale formation. VC stills operating at low temperatures tolerate higher levels of silica in the feed water. Silica scaling issues should be discussed with potential equipment suppliers during evaluation. It is important to note that silica is typically not recorded in water analysis conducted by municipalities.

Stills have very low resistance to corrosion from residual municipal chlorine and chloramine disinfectants; therefore, chlorine and chloramines should be removed to non-detectable levels for maximum still life. Ammonia and ammonium by-products from chloramine reduction need to be addressed in the system design.

5.4.3 Basis for Economic Comparison

Estimates of the utilities consumed per volume of WFI produced are discussed. The three primary factors affecting the operating cost of any still design are:

* Steam

* Electricity

* Coolant consumption

Using these estimates and the local cost of each utility, costs can be projected based on anticipated production volume. Note that when comparing different distillation technologies, it is important to consider the cost of the pretreatment and the distillate production profile. Depending on site location and feed water analysis, pretreatment requirements may be vastly different between ME and VC, particularly if RO is not required for one technology. In these comparisons, CAPEX, feed and waste water costs, consumable costs, regeneration/sanitization costs, and maintenance costs over the lifetime of the equipment need to be considered.

5.4.4 Construction Materials

The most common material for contact with WFI and Pure Steam is 316L SS. Aluminum has been used in some VC compressors, although some compendial water specifications limit aluminum for dialysis products; thus, the use of aluminum-wetted parts needs to be evaluated [5]. Titanium is offered as an option by some still suppliers.

Gasket materials in contact with WFI or Pure Steam typically are specified to be in compliance with the Class VI plastics (sometimes referred to as non-metallics) as determined in USP <88> Biological Reactivity Tests, *in vivo,* USP <87>, ISO 10993, or 21CFR Part 177 [4, 35, 36]. This requirement should be assessed based on the use of the WFI product. Common hygienic gasket and sealing materials include blended PTFE/316L SS, PTFE, PTFE/EPDM Envelope, EPDM, and Viton. Several forms of EPDM are available and suitability should be confirmed.

Additionally, gasket materials should be suitable for the maximum temperature to which they will be exposed, and as VC and SE stills generally are exposed to lower temperatures, a broader selection of suitable materials may be indicated. A preventive maintenance program to replace elastomers should be established for reliable operation. The proper inspection and replacement interval are considered site and application-dependent.

As with any hygienic requirement, sealing mechanisms should be appropriate with hygienic clamp, butt fusion, and orbitally welded joints, which are prevalent to allow for cleaning (refer to ASME BPE standard [37]). The use of threaded, flanged, or other non-hygienic joining mechanism is not recommended where these joints may come in contact with WFI or its precursor water or steam.

5.4.5 Surface Finish

Although it is common for the SS components within a still to be polished, the type and level of polish varies significantly. Mechanical polishing and electropolishing are both used with the intention to minimize the potential for microbial growth on the surfaces and to improve cleanability. Some pharmaceutical product manufacturers specify electropolished surfaces.

The use of highly polished finishes can increase equipment costs significantly and because of the relatively high operating temperatures, microbial growth within a still will probably be inhibited, regardless of finish used. The ROI of low Ra surface finish should be considered before setting it as a requirement, as microbial control may not be enhanced. Mechanical polish of surfaces of 25–32 microinch Ra maximum (0.64–0.8 μm) is often specified. Passivation of equipment when produced is common. Rouge formation is typical in distillation systems based on the operating temperature, and routine periodic inspection is recommended to monitor the presence of rouge and evaluate the need to remove it at appropriate intervals. For further information, see Chapter 10.

5.4.6 Process and Systems Description

5.4.6.1 Single Effect (SE) Distillation

Introduction

The SE still is the simplest distillation design concept primarily consisting of an evaporator, separator mechanism, and a condenser. The evaporator boils the feed water using an external energy source; the separator removes entrained water and associated contaminants from the steam produced; the condenser changes the Pure Steam into WFI utilizing an external cooling source. SE stills may use falling or rising film technology.

Advantages:

- Simple design

- Lower capital cost

- Small footprint

- Low-pressure operation

- Can be retrofitted for Pure Steam production

- Effective for infrequent production or low volume, ≤ 150 gph (570 lph)

Disadvantages:

- High operating costs

- Prohibitive operating costs > 150 gph compared to other distillation technologies

Utilities and Pretreatment

SE stills are available in electric or steam-powered versions although electric units typically are more expensive in capital and operating cost. Steam-powered units generally operate using utility steam in the range of 15–60 psig (1–4 barg).

Cooling fluid is required for both steam and electric-powered stills. SE still designs may require high coolant flow rates or necessitate a high-temperature rise in the coolant if adequate flow is not available, because of the high WFI discharge temperature. Appropriate commercial cooling technology can be applied providing it is non-corrosive to the contact materials, will not foul the exchanger, and has suitable capacity. Care should be taken when using a coolant source with high TDS content, as treatment for scale prevention may be required. Chlorinated water generally is not advisable because of the corrosive nature of chlorine in contact with SS at elevated temperatures.

Feed water pretreatment should remove volatile compounds (such as ammonia) that may be carried through, contaminating the steam and WFI produced. In addition, pretreatment should remove chlorine and chloramines and control silica and hardness levels, typically to < 1 ppm (approximately). Chlorine and chloramines will damage the still and although excessive levels of silica and hardness generally will not affect the quality of the WFI produced, scale formation and fouling may result in more frequent cleaning.

SE stills typically are capable of a 3 log_{10} pyrogen reduction. Feed water pretreatment for WFI should comply with local drinking water regulations; therefore, microbial control normally is anticipated. The pretreatment system should be properly designed and maintained to ensure that feed water microbiology and endotoxins are controlled. In general, a pretreatment system consisting of softening, dechlorination, and deionization could be sufficient. Some waters could require membrane pretreatment for endotoxin reduction. For further information, see Chapter 4.

Economics

Commercially available SE stills are configured similarly and equipped with the same basic components; however, capital cost can increase with added instrumentation and controls, as well as by higher-grade materials and finishes.

Steam consumption is approximately 1.10 to 1.25 times the distillate produced on a mass basis depending on the feed water temperature. Lower feed water temperatures require more energy to bring feed water to its boiling point. For example, producing 100 lb (45 kg) of distillate requires 125 lb (57 kg) of utility steam when using feed water at 21°C (69.8°F).

When water is the coolant, approximately 9–10 gal (34–38 L) of cooling water is required for each gallon (3.79 L) of distillate based on a coolant temperature rise of 56°C (132.8°F). It is important to recognize that the flow and temperature rise are inversely related, such that as the temperature rise is decreased, the coolant flow rate is increased. The heat capacity of alternative coolants should be taken into account, as they may be less than that of water (e.g., propylene glycol mixtures).

SE stills are considered appropriate for small or intermittent applications where operational costs are of lower importance than other factors or when Pure Steam and WFI are required from a common source.

5.4.6.2 Multiple-Effect (ME) Distillation

Introduction

An ME still is similar in design to an SE still except that multiple evaporator and separator stages are included. ME stills use a staged evaporation and condensation process to produce WFI at a reduced energy consumption compared to an SE still. Utility steam is applied only to the first evaporator (effect), while the subsequent effects use the steam produced in the previous effect as the source of energy. Similarly, coolant is applied only at the final effect to condense Pure Steam into WFI. The effects subsequent to the first effect use feed water as the cooling source (which is evaporated) as the Pure Steam from the preceding effect is condensed (producing WFI).

Advantages:

•   Extra effects reduce the utility steam consumption

•   First effect can also be used to produce Pure Steam (See Chapter 7)

•   Electrical heating feasible for low volume production, typically < 100 gph (380 lph)

•   Pretreatment requirement works well with systems that also require USP PW production

•   Fewer moving parts than VC stills

•   High operating temperature may reduce dissolved gas levels

Disadvantages:

•   Reliant on adequate utility steam pressure; low utility pressure results in lower distillate production

•   Increasing effects will reduce utility steam consumption, but increase capital cost and footprint

•   Higher pressure operation results in high material and vessel certification costs

•   Ambient temperature distillate production results in higher cooling utility costs

•   Comprehensive pretreatment equipment required to meet strict feed water requirements

It is important to note that the ME still does not evaporate the water more than once, and does not produce water of a higher quality than an SE or VC still. The interconnecting effects of the ME still serve only to minimize utility consumption. Typical ME stills have 3–8 effects. As the additional effects are included, the energy efficiency of the still is increased and cooling water requirements are reduced; however, the capital cost and floor space required are also increased and should be evaluated to optimize the design.

Utilities and Pretreatment

ME systems typically require utility steam in the range of 80–120 psig (5–8 barg) supplied to the first effect. Electrically operated units are available; however, electrically operated stills typically are selected for applications of < 100 gph (380 lph). The capacity of an ME still is proportional to the pressure applied at the first effect. As the available utility steam pressure is reduced, the capacity of the still is diminished. Based on the higher operating pressures, ME stills are generally specified with vessels that fall under a pressure vessel code.

Cooling fluid is required for both steam and electric-powered stills. ME still designs may use feed water as a source of coolant to conserve energy by preheating the feed water (less heating needed), while simultaneously reducing the condenser load (less cooling needed). However, feed water alone may not be sufficient and supplemental cooling may be required.

ME stills may require high coolant flow rates or necessitate a high-temperature rise in the coolant if adequate flow is not available because of the high WFI discharge temperature. Appropriate commercial cooling technology can be applied providing it is non-corrosive to the contact materials, will not foul the exchanger, and has suitable capacity. Care should be taken when using a coolant source with high TDS content, as treatment for scale prevention may be required. Chlorinated water is generally not advised because of the corrosive nature of chlorine in contact with SS at elevated temperatures.

Pretreatment for ME stills is typically comprehensive as most have low limits for chloride (to minimize chloride-stress corrosion potential), and silica (to minimize silica scale potential). Many ME feed water systems include pretreatment, RO, and an IX process.

Economics

Commercially available ME stills are configured similarly and equipped with the same basic components. Increasing the number of effects increases the capital cost and can be compounded by added instrumentation and controls, as well as by higher grades materials and finishes.

The primary cost associated with ME still operation is from utilities and may vary by manufacturer, based on the number of effects included or local utility costs.

Increasing the number of effects in an ME still does not result in increased output or improved WFI quality; it reduces the amount of steam and cooling water required to produce an equal amount of distillate with fewer effects. ME units with 7–8 effects may operate without external cooling.

Table 5.1 shows information representative of applications with feed water at 21°C (69.8°F) and WFI discharge at 85°C (185°F). Note that electrical operating costs are negligible.

Table 5.1: Approximate Multiple-Effect Still Utility Consumption per 1,000 gal (3,785 l) of Water for Injection

Effects	1	3	4	5	6	7	8
Steam lb/h	9,800–10,200	3,300–3,700	2,600–3,000	2,100–2,500	1,900–2,300	1,500–1,800	1,340–1,600
kg/h	4,445–4,626	1,496 – 1,678	1,179 – 1,360	952–1,134	86–1,043	682–818	609–727
Coolant MBtu/h	7.9–8.1	2.0–2.2	1.4–1.6	1.0–1.2	0.8–1.0	0.07–0.1	0
kW	2,313–2,371	585–644	409–468	293–351	234–293	20.5–29.3	0
Note: MBtu is 1,000 BTU (British Thermal Units).							

Utility consumption estimates can be influenced by feed water temperature, product water temperature requirements, plant steam pressure, and other factors including supplier equipment configuration.

An increased number of effects will decrease the operating cost; however, there is a diminishing return as the number of effects is increased. The appropriate number of effects should be determined by financial analysis comparing the capital and annual operating costs for alternatives under consideration. The result can be influenced by site-specific utility costs, utilization, and the time frame used for the financial analysis. A reduction in distillate discharge temperature through heat recovery can reduce steam consumption and improve economics.

5.4.6.3 Vapor Compression (VC) Distillation

Introduction

VC distillation conceptually is similar in design to a heat pump or the mechanical refrigeration cycle. Major system components include:

- Evaporators

- Compressors

- Heat exchangers

- Deaerators

- Pumps

The compressor typically is a single-stage centrifugal type with relatively low developed pressure, but high flow-rate capability. VC is intrinsically a thermally efficient distillation process because it recycles a high percentage of the latent heat. Unlike an SE or ME still, VC stills have a primary chamber in which evaporation takes place on one side of the heat transfer surface, and condensation takes place on the other side of the same surface. Horizontal tube design VCs use a pump to spray feed water on a tube bank, while condensation of distillate occurs inside the tubes. Vertical tube design VCs use natural circulation via evaporation inside the tubes, with the distillate condensing on the outside of these tubes.

Feed water is evaporated on one side of the tubes, and the generated steam passes through a disengagement space and separation system, to remove entrained water droplets, before the Pure Steam is drawn through the compressor. The energy imparted by the compressor results in compressed steam with an increased temperature of 4°C–5.5°C (39.2°F–41.9°F), which is equivalent to an increased pressure of 3–5 psig (0.2–0.34 barg). The higher energy steam is discharged to the condensing side of the heat transfer surface. There, the steam condenses giving up its latent heat, which is transferred through the tube wall to the feed water. Additional water is evaporated, generating more vapor as the process is repeated. The condensate produced is WFI and the portion of the feed water not evaporated is recycled. A portion of the feed water (referred to as blowdown) has highly concentrated impurities and is usually discharged as waste or used for other applications.

Advantages:

- Low utility steam consumption due to thermally efficient recycling of latent heat

- Flexible feed water quality requirements

- Accepts higher silica levels in feed water

- Simple pretreatment only as feed to a VC in many cases, no need for RO pretreatment unless specific additional contaminant reduction required

- Variable production with increased efficiency at reduced production using VFD

- Hot and ambient distillate production possible without auxiliary cooling

- Can deliver distillate to tank level above still distillate outlet level

- High product flow rates available

Disadvantages:

- Compressor is a critical point of failure

- High electrical costs

- Can be cost prohibitive for low distillate production

- Cannot be used to produce Pure Steam

Utilities and Pretreatment

Energy is input in two forms:

- Electricity to drive the compressor and pumps

- Relatively low-pressure steam as makeup heat

The amount of WFI produced is proportional to the amount of compressor work input; it is limited by the amount of heat transfer surface and heat transfer efficiency.

The utility costs associated with VC still operation vary by manufacturer, based on the net saturated temperature across the compressor and local utility costs.

The amount of WFI produced is proportional to the amount of compressor work input and is limited by the size of the heat transfer surface.

$$Q = U \times A \times \Delta T$$

Where: Q = Amount of compressor energy added
           U = Heat Transfer Coefficient
           A = Heat Transfer Area
           ΔT = Net saturated temperature across the compressor

There is a trade-off is between increasing surface area (higher capital costs, reduced compressor energy, reduced operating costs) and increasing ΔT (lower capital costs, increased compressor energy, increased operating costs).

Table 5.2: Approximate Vapor Compression Still Utility Consumption per 1,000 gal (3,785 L) of Water for Injection Produced

Capacity Range 200 gph (757 lph) to 7200 gph (27,255 lph)	Minimum	Maximum
Electricity kWh	44	80
Steam lb/h	900	1100
kg/h	408	498
Coolant gpm	2	4
lpm	7.6	15.2

The information in Table 5.2 is representative of applications with feed water at 21°C (70°F) and WFI discharge at 85°C (185°F).

Utility consumption estimates can be affected by feed water temperature, product water temperature requirements, plant steam pressure, and other factors, including supplier equipment configuration.

A feed water analysis should be performed and the results used to select and configure a suitable VC still system. It is recognized that pretreatment requirements may be less stringent than for an ME still, because of the lower operating temperatures in a VC still.

If the feed water is chlorinated or treated with chloramines, removal of the chlorine and chloramines is necessary to minimize corrosion and rouging. Residual ammonia, if not removed, contributes to conductivity, such that the distillate may not meet the requirements for WFI.

If a carbon filter is used for chloramine removal, it should be recognized that ammonium and ammonia are by-products of the chloramine removal inside the carbon filter. If the carbon filter is installed upstream of a softener, ammonium (a cation) is removed in the softener. Ammonia is a gas and is not removed by a softener unless converted to ammonium via pH adjustment. (See Chapter 4 for additional information.) In the softening process, hardness is removed first, then ammonia, because of the cation selectivity order. In this of type system, there is built-in scale prevention since ammonium breakthrough occurs before hardness leakage and causes an increase in distillate conductivity. Conductivity, which normally is monitored, usually is alarmed as well.

Deaeration and Venting in Vapor Compression Stills

Feed waters have dissolved gases, the amount of which depends on water temperature, composition, and pH. Other gases occur due to the breakdown of some of the constituents during heating, as is the case of alkalinity. Non-condensable gases, which include carbon dioxide and oxygen, are liberated as the temperature of the water increases. These gases, if not removed, have two detrimental effects on VC units. Since the gases are non-condensable, they can blanket the heat transfer surface and inhibit heat transfer translating into reduced output. In addition, some gases may increase the potential for corrosion. VC stills often incorporate a decarbonator section where Pure Steam effectively strips out non-condensable gases from feed water.

5.5 Polishing and Removal of Specific Contaminants

5.5.1 Ultrafiltration

5.5.1.1 Description

UF is a cross-flow process similar to RO. A pressurized feed stream flows parallel to a porous membrane filtration surface (unless dead-ended operation is selected). A pressure differential forces water through the membrane. The membrane rejects particulates, organics, microbes, pyrogens, and other contaminants too large to pass through, while allowing most ionic contaminants to pass through. UF systems may run dead ended.

Membranes are available in both polymeric and ceramic materials. Polymeric membrane elements are available in spiral wound and hollow fiber configurations. Ceramic modules come in single channel and multiple channel configurations.

5.5.1.2 Application

UF is used both for pretreatment and in several ways in PW and WFI systems, and normally is used downstream of IX processes for organic, colloidal, microbial, and endotoxin reduction.

5.5.1.3 Limitations

UF cannot remove 100% of contaminants from water. No ionic rejection occurs and organic rejection varies with the type of membrane material, configuration, and porosity. Different nominal organic molecular weight rejection ratings are available. Dissolved gases are not rejected by UF.

UF normally requires a waste stream to remove the contaminants on a continuous basis. The waste stream varies, but is usually 2%–10% of the total volume filtered. When in a polishing position, UF may be used in a dead-ended configuration like single-use cartridges without a waste stream.

5.5.1.4 Performance

UF is used to remove a variety of contaminants. The appropriate UF membrane should be selected to meet the performance requirements. Organic molecules can be rejected significantly, but the rating of UF membranes varies in MWCO of 3,000–100,000 Daltons. Reduction of typical raw water organics is not as effective as RO. Pressure drops vary with membrane selection and operating temperature. UF membranes may be capable of continuous operation at temperatures up to 90°C (194°F) to provide good microbial control.

UF reduction of endotoxin (pyrogens) varies from 2 log10 to 4 $\log_{10}$ as a function of membrane selection. UF has been shown to be capable of the consistent production of water meeting the compendial WFI endotoxin limit of 0.25 EU/ml in typical system applications [e.g., 4, 5, 6]. UF produces good microbial reduction with typical ratings of 3 $\log_{10}$ to 4 $\log_{10}$ reduction as well as good particle reduction.

5.5.1.5 Advantages and Disadvantages

Advantages:

- UF can remove a number of contaminants, such as endotoxin and organics, better than microfiltration

- Cross-flow operation may provide long membrane life

- UF elements may tolerate rigorous sanitization procedures using hot water steam or ozone

- High water recovery rates

• Low energy requirements

Disadvantages:

• UF cannot remove ionic contaminants

• UF can require a waste stream, which can be a significant cost factor

• Some UF membranes may be more difficult to integrity test than microfiltration cartridges

5.5.1.6 Cost Savings Factors

Capital costs can be influenced by the optimum sizing of membrane area and membrane selection. Piping material and finish significantly impact capital cost. Some systems may incorporate a variety of plastic piping materials while others use hygienic 316L SS. The sanitation method and the frequency of sanitation usually play a major role in material selection and may influence instrument costs in the monitoring parameters of operation and sanitation.

5.5.1.7 Sanitization

UF membranes can be sanitized in several ways. Polymeric membranes generally are tolerant of a wide variety of chemical sanitizing agents, such as:

• Sodium hypochlorite

• Hydrogen peroxide

• Peracetic acid

• Sodium hydroxide

Polymeric membranes may be capable of withstanding hot water sanitization or steam sanitization.

Ceramic UF elements usually can tolerate common chemical sanitizing agents, hot water, steam, and ozone during sanitization or sterilization procedures.

5.5.1.8 Waste Water Recovery

Pharmaceutical UF units normally are fed deionized water for PW or highly purified water production or special non-compendial water applications; therefore, the waste water is still low conductivity water that can be recycled upstream to RO units or fed directly to boilers, cooling towers, or used elsewhere.

5.5.2 Microfiltration

5.5.2.1 Description

Microfiltration is a membrane process used for the removal of fine particles and microorganisms. Generally, a waste stream is not employed. Microfiltration cartridges normally are disposable and are available in a wide range of materials and pore sizes. In final filtration, the filters are usually 0.04–0.45 µm. Microfilters can be used in a wide range of applications, including aseptic filling of pharmaceutical products not tolerant of terminal sterilization.

Microfilters routinely are employed in pharmaceutical water systems for microbial retention downstream of components where some microbial growth may exist. Microfilters can be extremely effective in this area, but operating procedures should be in place to ensure filter integrity during installation, and membrane replacement to ensure proper performance. The filters should be a part of a comprehensive microbial-control plan, not as a solitary microbial-control unit operation in the system. Minimizing the number of locations of microfiltration makes maintenance easier. For further information, see Chapter 13.

5.5.2.2 Advantages and Disadvantages

Advantages:

- Simple design and maintenance

- Flexible in water flow production

- No waste stream

- Cartridges are integrity testable

- Heat and chemical sanitization of microfilters is possible

Disadvantages:

- Can be used only as part of a total microbial-control plan

- No ion or endotoxin removal

- Shorter life, due to the dead ended design, so replacement is required

5.5.2.3 Performance

Microfiltration can be as effective as UF in microbial reduction and can minimize water consumption, as no waste stream is necessary; however, microfiltration cannot reduce dissolved organic levels or remove particles as small as those removed by ultrafilters due to the difference in pore size. Heat and chemical sanitization of microfilters is possible with the appropriate selection of materials.

5.5.3 Ultraviolet Light Treatment

UV light treatment decreases the free-floating bacteria and organic contamination levels in water. UV wavelengths and the intensity level required depend on the desired function. Since the intensity of UV penetrating the contaminants drives the reduction process efficiency, films on the UV windows and quartz sleeves, particulates, and other materials that reduce the transmission of UV energy into the water decrease the energy applied to the contaminants and should be avoided.

UV light treatment adds nothing to the water (no added substances) and leaves no residual. UV units are simple to operate and are compatible with both chemical and hot water sanitization, but because these units do not remove bacteria or provide downstream continuous protection, they represent a portion of a total microbial-control solution. UV units are available in 304 and 316L SS wetted parts and with surface finishes selected based on where they are installed in a system. For example, units installed in a pretreatment location may implement 304 SS wetted parts and flanged connections, but units installed in a distribution loop would be constructed from 316L SS and furnished with hygienic connections.

The two types of UV lamps most commonly used in the pharmaceutical industry are:

• Low-pressure lamps

• Medium/high-pressure lamps

The low or medium pressure refers to the pressure in the lamps in operation and not to water pressure. Low-pressure mercury vapor lamps produce a UV output at two wavelengths: 254 nm and 185 nm. When $UV_{254\,nm}$ output is desired, an optical coating is applied to the lamp to prevent the escape of $UV_{185\,nm}$ light into the process stream. Medium/high-pressure lamps emit radiation across a wider spectrum of wavelengths. With any UV light system, shorter wavelengths translate to higher energy. UV units can increase the conductivity of the water during treatment when organic substances are oxidized into carbon dioxide and water. The impact may be absent or minimal but should be considered when placing UV units in a system.

5.5.3.1 Microorganism Contamination Level Reduction

In general, low-pressure UV light units at 254 nm wavelength output or medium pressure UV units are used for decreasing/limiting the bacterial contamination. UV light rays damage microorganisms (bacteria, virus, yeast, mold, or algae) and break through their outer membrane to modify the DNA and prevent replication. At sufficient doses, $UV_{254\,nm}$ radiation is capable of about a 2 to 6 $\log_{10}$ bacterial reduction. Typically, UV treatment units are followed by sub-micron filtration to remove the inactivated bacteria from a water system. It is important to note that while UV lights are effective for microorganism control, these units will not remove or prevent biofilm formation in a water purification system.

Microbial-control UV light units generally may be installed in several locations in generation systems downstream of activated carbon units, deionizers, or other processes where microbial levels may require control. UV units are also implemented upstream of several unit processes to reduce microbial levels into downstream equipment. Filtration upstream of UV units may help to reduce the likelihood of microorganisms being shielded from UV light by particulate from carbon units, softeners, or other media-type processes upstream.

5.5.3.2 Organic Contamination Level Reduction

Low-pressure UV units combining 185 nm and 254 nm wavelength radiation (also referred to as TOC-reducing UV lamps) or medium pressure units may be used to effectively reduce residual organic levels. Organic molecules are converted into ionized species under the effects of the higher energy UV light, with the characteristic effect of increasing the conductivity of the water proportionately to the organic levels in the system. When installed near the end of a treatment train, these units are typically followed by high purity IX resins (which will not re-introduce organics) or CEDI units to remove the ionized species created while simultaneously restoring the conductivity of the water.

Organic reduction UV units may be installed in generation systems downstream of primary organic reduction processes, such as RO, CEDI, or high-grade polishing IX resins. Installation downstream of primary organic reduction processes increases the transmission characteristics of the water and therefore minimizes the required UV energy necessary.

Organic reduction UV units may be installed to meet a TOC specification that is significantly below the compendial limit of 500 ppb (0.5 ppm) [e.g., 4, 5, 6]. Since TOC generally indicates the abundance of food available to support bacterial growth, the popularity of these units installed with downstream ion-reduction processes is increasing, particularly in PW systems. The UV energy required for TOC reduction usually is significantly higher by a factor of 3–6 than the recommended UV intensity levels for microbial control, which means that more contact time is needed for effective TOC reduction. For further information, see Chapter 13.

5.5.3.3 Ozone Destruction

In systems where ozone is introduced as part of a microbial-control scheme, $UV_{254\,nm}$ units are effective at decomposing any residual ozone present in the water. For a more complete discussion, see the *ISPE Good Practice Guide: Ozone Sanitization of Pharmaceutical Water Systems* [34].

5.5.3.4 Monitoring, Maintenance, and Replacement

In pharmaceutical applications, it may be desirable to monitor the output of UV energy as evidence that the lamps are operational and fulfilling their intended function. UV unit manufacturers have developed intensity monitors to allow the UV energy output of the units to be monitored. When new lamps are installed, the intensity monitors are calibrated following established procedures and the intensity monitor is then used to track the energy output of the UV lamps over time. UV bulbs that have been pre-burned to a certified baseline intensity are available.

The energy output of all UV lamps degrades with time and a plan for frequency of exchange should be established. The frequency of lamp replacement depends upon the application, but typical UV lamp replacement frequencies are usually around 12 months. For critical TOC reduction applications, lamps may be replaced more frequently.

Quartz or borosilicate glass sleeves are normally used to separate the UV lamp from the flowing water, and periodic cleaning and replacement of these sleeves is required, based on where the unit is installed. Units installed as part of a pretreatment process may be more susceptible to coatings and will require regular cleaning to ensure effective energy transmission into the water stream. Replacement of sleeves every few years ensures that the UV energy produced by the lamps is evenly transmitted to all the water flowing inside of the unit.

5.6 Continuous Electrodeionization

5.6.1 Description

CEDI is a technology combining IX resins, ion selective membranes, and the use of an electrical field to continuously remove ionized species and regenerate the resins.

The CEDI processes are distinguished from other EDI (such as capacitive deionization) and IX processes in that the processes are continuous rather than batch or intermittent, and that the ionic transport properties of the IX media are a primary sizing parameter, as opposed to ionic capacity.

CEDI units typically have a number of successively functioning ion depleting (purifying) and ion concentrating cells that can be fed from the same water or different water sources. Water is purified in CEDI devices through ion transfer. Ionized species are drawn from the water passing along the ion depleting cells and transferred into the concentrate water stream passing across the IX membranes. The IX membranes are permeable to ionized species, but not permeable to water.

The ion purifying cells typically have continuously regenerated IX media between a pair of IX membranes. Units may incorporate mixed (cationic and anionic) IX media between a cationic membrane and an anionic membrane to form the purifying cell. Units may incorporate layers of cation and anion IX media between IX membranes to form the purifying cell. Single purifying cells (cationic or anionic) may be created by incorporating a single IX resin between IX membranes. CEDI units can be designed with the cells either in a plate and frame or in a spiral wound configuration.

The power supply creates a direct current electric field between the cathode and anode of the CEDI device. It contributes to the ionic transport for:

• Continuously removing ionized species

• Continuously regenerating the IX resin

Continuously Removing Ionized Species

Cations in the feed water stream passing across the purifying cell are directed toward the cathode. Cations, stopped by the anion-permeable membrane, are transported through the cation exchange media and the cation-permeable membrane to the concentrating compartment.

Anions, blocked by the cation-permeable membrane, are directed toward the anode. They are transferred across anion-exchange media and the anion-permeable membrane to the concentrating compartment. The cations and anions gathered in the concentrating cells are eliminated to the waste through the water flow.

Continuously Regenerating the Ion Exchange Resin

As the ionic strength of the PW stream decreases, the high voltage gradient at the water-ion exchange media interfaces can cause water to split into its ionic constituents (H^+ and OH^-). The H^+ and OH^- ions are created continuously and regenerate the cation and anion-exchange resins, respectively, at the outlet end of the purifying cells. The continuous high IX resin regeneration level allows the consistent production of high purity water (0.055–1 μS/cm referred to 25°C) in the CEDI process.

A typical CEDI process drawing is shown in Figure 5.2.

Figure 5.2: Typical Continuous Electrodeionization Process Drawing
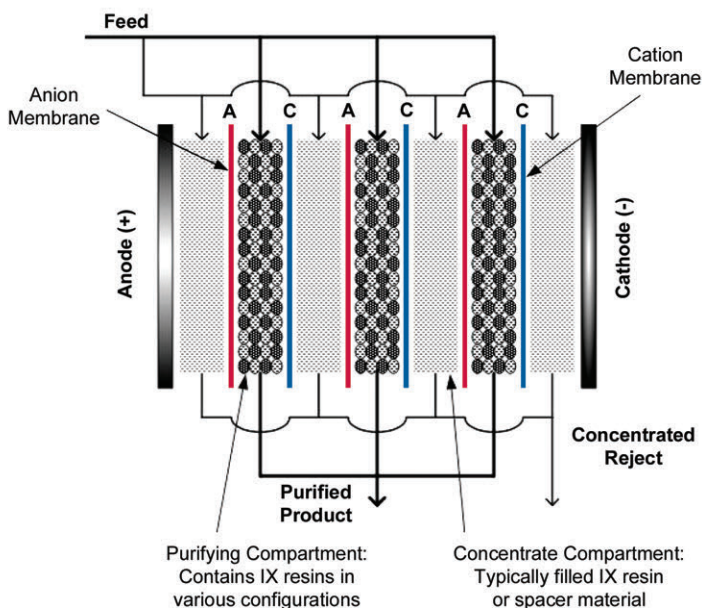
5.6.2 Application

CEDI is commonly found downstream of pretreated water from RO units in compendial PW, WFI, or non-compendial water installations. This type of combination allows the consistent production of water with low conductivity and organic levels, while optimizing the CEDI unit life span.

5.6.3 Limitations

CEDI technology aims to remove the ionized species, but is not designed to have an effect on the uncharged contaminants in the water. A concentrate stream is required to remove the contaminants from the system, and so a part of the water is constantly rejected. CEDI has temperature limitations in production operations. Most CEDI units are operated between 5°C–40°C (41°F–104°F).

5.6.4   Pretreatment Requirements

CEDI units should be protected from scale formation, fouling, and thermal or oxidative degradation. The RO/pretreatment equipment typically reduces hardness, organics, suspended solids, and oxidants to acceptable levels.

5.6.5   Performance

CEDI unit performance is a function of feed water quality and unit design. Ionized solids reduction is generally > 99% allowing production of lower than 1 µS/cm (reference value of 25°C) conductivity water from RO feed water. RO/CEDI systems may produce water with 0.1 µS/cm or lower conductivity.

5.6.6   Cost Saving Factors

Pharmaceutical applications often do not require post treatment after CEDI. Systems may incorporate UV light or sub-micron filtration either to reduce sanitization requirements or to provide microbial levels considerably below those expected for PW production.

5.6.7   Advantages and Disadvantages

Advantages:

• Typically designed to produce low conductivity water (in compliance with compendial PW and WFI)

• Elimination of chemical handling and associated costs

• Elimination of outside service needs (off-site regenerated resin, management costs, etc.)

• Removal of ionized substances, including the weakly-ionized substances (e.g., carbon dioxide, ammonia, and some ionized organics)

• Limited environmental effect technology (low energy required, low waste generated, no chemicals required for regeneration, etc.)

• Electric field in membrane/resin module provides some bacterial control

Disadvantages:

• Uniqueness of designs for each manufacturer (modules often are not interchangeable)

• UV or sub-micron filtration may be required for further bacterial reduction

• RO generally required as a pretreatment

• Rinse up after chemical sanitization may take hours to reach low conductivity and TOC

• May require chemical preservation for lengthy shutdown periods

• High-pressure drop in service

5.6.8   *Sanitization*

CEDI units typically are chemically sanitized with a number of agents including:

•   Peracetic acid

•   Sodium percarbonate

•   Sodium hydroxide

•   Hydrogen peroxide

Hot water sanitization normally is used with a number of CEDI modules. Modules may tolerate heat sanitization as well as, or better than, chemical sanitization, while others may experience longer life with chemical sanitization. Hot water sanitization provides superior microbial control relative to chemical sanitization and eliminates chemical discharge. Hot water sanitization is typically performed at much lower pressures than allowable pressure in service. Pressure control is generally required.

6 Systems for Production of Compendial Purified Water, Water for Injection, and Non-Compendial Water

6.1 Introduction

This chapter discusses the final treatment technologies and basic system configurations related to the generation process of compendial Water for Injection (WFI) (e.g., USP, Ph. Eur., and JP [4, 5, 6]), Purified Water (PW), and non-compendial waters.

Various basic system configurations are presented in the following paragraphs and diagrams as general guidelines utilizing Reverse Osmosis (RO), Ion Exchange (IX) and distillation as the major purification final treatment processes. The system configurations presented are intended to be flexible as many configurations can produce water meeting the desired specifications. Equipment and system design factors are discussed for the appropriate selection of construction materials, sanitization method, instrumentation, and controls.

Systems are typically comprised of pretreatment and final treatment processes selected to consistently meet the product water Critical Quality Attributes (CQAs) and Critical Process Parameters (CPPs) established for a particular product or process or for multiple products or processes.

The source water characteristics and product water quality requirements typically drive the equipment and process selection along with other factors including:

- Local and international regulatory requirements

- Microbial-control considerations

- Daily and instantaneous water consumption needs

- Utility availability

- Capital and operating cost considerations

- Maintenance concerns

- Reliability factors

- Robustness of design considerations

- Risk-aversion concerns

- Consistency across multiple locations

- Budget considerations

The final treatment processes are typically selected first, and then appropriate pretreatment processes are chosen to ensure the reliable operation of the final treatment units. Risk-aversion considerations vary with products, processes, and manufacturers and may make a significant impact on system design. Water and energy conservation have become an important design factor in many systems.

A design review should be performed to optimize the system for consistent operation to specifications and lifecycle cost optimization. Replacing system components (e.g., filters, RO membranes) at a frequency that maintains the appropriate water quality and system output should be considered.

System designs and costs can vary widely for similar and diverse applications based on the above considerations. Refer to Chapters 4, 5, and 13 for additional information on pretreatment and final treatment equipment.

Several system configurations are shown in Figures 6.1 to 6.5. It is important to note that with each of these diagrams, the intent is to provide general design guidelines rather than to establish or stipulate specific unit operation requirements. Since multiple system designs may be used to successfully generate a particular grade of water, the presence of a particular unit operation in any of the following diagrams should not be considered a requirement for inclusion in that process. Conversely, the absence of a particular unit operation does not preclude the use of that process.

6.2 Purified Water

PW can be produced by an extensive combination of unit operations in various configurations. PW must meet specifications for conductivity and TOC to comply with USP [4] and/or other relevant pharmacopeial monograph requirements [5, 6]. The microbial requirements are not part of the USP PW monograph, but information is provided in General Information Chapter <1231> Water for Pharmaceutical Purposes. It has been accepted in the pharmaceutical industry that 100 CFU/ml is the maximum action level. The microbial limit of 100 CFU/ml is stated in the Ph. Eur. *Aqua Purificata* monograph and many other pharmacopeial PW monographs [5, 6]. See Chapter 9 Table 9.3 for additional information on other requirements established by USP and various pharmacopeias.

The typical pretreatment and final treatment technologies used in PW systems are shown in Figures 6.1 and 6.2. Consideration is given to the final treatment unit operation most often used, including:

- IX

- RO

- Continuous Electrodeionization (CEDI)

- Distillation

- Membrane Degasification (MD)

- Ultrafiltration (UF)

- Microfiltration (MF)

- Ultraviolet light (UV)

The most common PW system designs implement an RO membrane-based process with final polishing by CEDI, IX, or a second RO stage as the final primary treatment process. Membrane-based system usage has increased due to chemical consumption reduction, quantitative contaminant rejection (ionized solids, organics, colloids, microbes, endotoxins, and suspended solids), reduced maintenance, consistent operation, and effective lifecycle cost. The primary disadvantage of RO is potential high waste water discharge if water recovery measures are not taken. Refer to Chapter 5 for additional information on RO.

RO final treatment requires pretreatment protection from scale, fouling, and oxidation. Refer to Chapter 4 for additional information on the pretreatment options available. The selection of sanitization method(s) for pretreatment and final treatment can have a significant impact on both capital cost and consistent achievement of low effluent microbial levels.

A second pass of RO (product staged RO or two-pass RO) can be the ionic polishing step downstream of primary RO. Reduction of TOC, endotoxin, and microbial levels are excellent. Conductivity levels from two-pass RO can meet USP Stage 1 requirements in some cases, but often consistent Stage 1 conductivity production varies or may require significant operator attention to manage carbon dioxide and ammonia feeding into the system. Two-pass RO typically will consistently meet Stage 2 conductivity requirements [4].

IX in the form of CEDI or off-site regenerated IX resin is implemented downstream of RO much more frequently than using another RO stage. These processes typically provide consistent attainment of Stage 1 conductivity, low TOC, and with proper sanitization low microbial and endotoxin levels [4]. Refer to Chapter 5 for additional information on CEDI and IX operation and sanitization options. RO-based systems are used to produce all types of pharmaceutical waters including PW, WFI, and non-compendial waters. Final polishing processes for the reduction of trace microbes and/or endotoxin are implemented where needed to meet final water quality requirements such as WFI and other high-quality applications. RO-based system process options are shown in Figure 6.1.

Figure 6.1: Reverse Osmosis System Technology Map
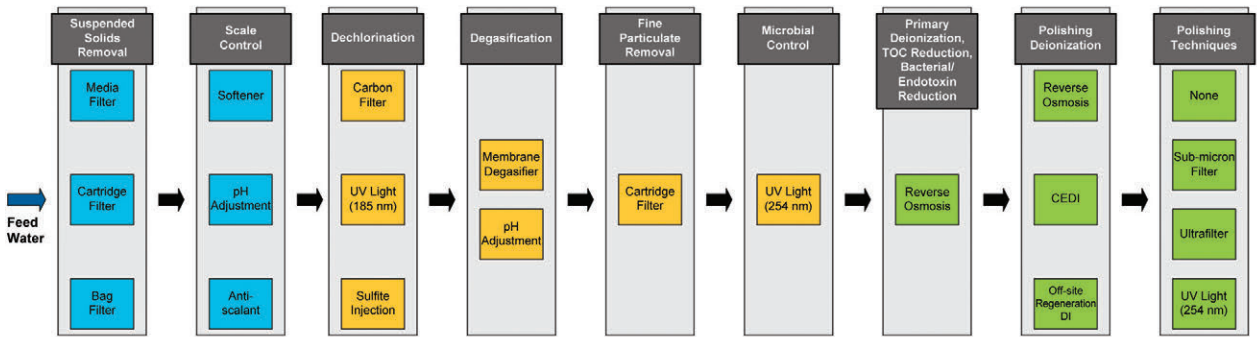
Some systems for the production of PW or non-compendial waters use IX final treatment with no RO process. The IX resin vessels may be regenerated off-site or *in situ*. Coarse filtration may not be required or may be a back-washable multimedia type or disposable. Carbon dechlorination is the most popular choice, but it may be by chemical injection or UV. An organic resin-based scavenger may be used in high TOC (> 5 ppm) source water applications to meet final TOC requirements. Various IX combinations can easily meet conductivity requirements. Polishing processes for the reduction of particulate, microbes, and rarely endotoxin are common downstream of IX as shown in Figure 6.1. IX-based system process options are shown in Figure 6.2.

Figure 6.2: Deionization System Technology Map
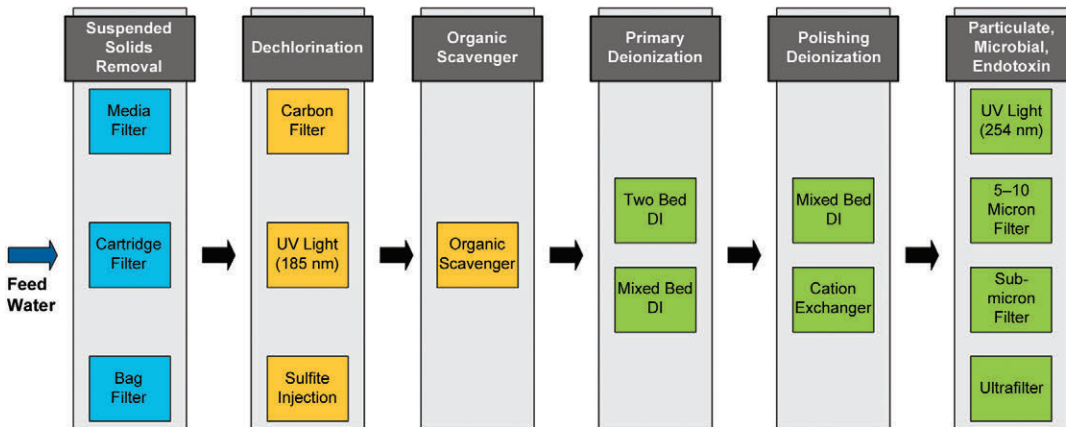
Distillation for the production of only PW is relatively uncommon. PW production from stills used to produce WFI is quite common if the economics favor production of one water quality only. PW-only production by distillation may occur when alternative systems are not in favor due to historical issues or risk-aversion drivers.

The systems described are most commonly implemented in a makeup mode to a storage tank based upon a level control signal. Some systems may not implement a storage tank and feed distribution loops directly. Systems may recirculate a quantity of water back from distribution to the makeup system when no makeup demand exists. This design helps to maintain minimum conductivity in storage and distribution and can be particularly useful in systems where ozonation or other factors may increase conductivity in storage.

6.3   Water for Injection

WFI is the purest grade of bulk water covered by pharmacopeial monographs (at the time of publication) based on strict microbiological expectations. Medicinal preparations made with WFI that are injected directly into a patient's circulatory system bypass the body's primary defensive systems. The expectation is for WFI to be used for the manufacture of parenteral, inhalation, and some ophthalmic products, as well as for the finishing steps of sterile or apyrogenic parenteral grade API). The regulations for WFI are more stringent than for other grades and to varying degrees more prescriptive, because of its criticality. This section addresses final treatment methods for the production of WFI, system advantages and disadvantages, and the variation between compendial groups.

Distillation has long been considered the benchmark and the final processing step for most qualified WFI systems. One of the most significant regulatory changes regarding WFI occurred in April 2017 when the Ph. Eur. changed the WFI monograph (0169) to allow alternative technologies to distillation (Ph. Eur. "Comments concerning revised texts published in Supplement 9.1" [5]). The monograph modification makes implementation of membrane-based alternative systems more practical as the European market is no longer excluded for parenteral products produced using non-distillation techniques. Some pharmacopeias such as Ph. Eur. and JP mention examples of the alternative technologies that may be used to produce WFI while others including USP do not [4, 5, 6].

Additional information for implementing the revised Ph. Eur. WFI monograph is found in the EMA "Questions and answers on production of waters for injections by non-distillation methods – RO and biofilms and control strategies" [38]. The document contains considerable guidance in the areas of equipment design, construction, sanitization, monitoring, sampling, and qualification. The ISPE Affiliate for Germany, Austria, and Switzerland (D/A/CH) published a comprehensive handbook for the production of WFI without distillation in 2019 [39].

To select appropriate technologies, the manufacturer of products should first consider where the products will be distributed and what regulations are applicable to those markets. Using the most stringent aspects of each pertinent regulation usually ensures the system design will meet requirements. Some pharmacopeias specify process requirements. For example, the Chinese Pharmacopoeia requires PW to be used as feed water for a distillation system intended to produce WFI water [7]. Additional information regarding specific compendial requirements can be found in Chapter 9, Table 9.3.

Technological aspects of the most commonly considered unit operations are presented in this chapter, including their function, maintenance, and associated costs.

Specific feed water pretreatment may be necessary to allow final unit operations to meet compendial requirements. These issues are discussed as they relate to WFI production. In addition, system outlet piping, including valves, instruments, and accessories, usually is the responsibility of the installer, and should be suitably designed and installed to allow for maintenance of water quality, including appropriate sanitization.

6.3.1   Water for Injection System Selection

WFI should be produced using robust technologies capable of consistent and reliable operation. Distillation is used as the benchmark. Systems should be evaluated for risk of failing WFI CQAs and CPPs, paying particular attention to microbial and endotoxin levels.

Pharmaceutical distillation units operate > 100°C (212°F) in the evaporator sections so microbial level attainment is typically not an issue. Endotoxin level attainment is typically achieved when proper still pretreatment is implemented. Stills are often rated at a 3 log_{10} reduction for endotoxin; therefore, the endotoxin feed level should not be greater than the level specified by the manufacturer to meet the required effluent endotoxin level. This is stated in the 1993 "FDA Guide to Inspections of High Purity Water Systems" [40]. This may mean inclusion of membrane pretreatment. The endotoxin quality requirement should be reliably attained between still design and operation of appropriate pretreatment.

Vapor compression (VC) stills require pretreatment protection from scale, chlorine/chloramine and excessive silica levels, if present. Softening and activated carbon are the most common pretreatment processes for hardness-based scale reduction and chlorine/chloramine removal respectively. Carbon and softening are typical for feed water containing free chlorine. Softening followed by activated carbon and a polishing softener (or pH adjustment) for ammonium reduction is normal for feed water supplies containing chloramine. Conservatively sized carbon followed by conservatively sized softening is an alternative process for chloramine disinfection sources. VC stills may implement only these pretreatment processes or may also require the use of RO or UF, and possibly an IX process, to ensure attainment of the endotoxin and conductivity requirements. Use of additional feed water treatment such as RO is based upon source water quality and risk assessment. VC system process options are shown in Figure 6.3.

Figure 6.3: Vapor Compression Distillation System Technology Map
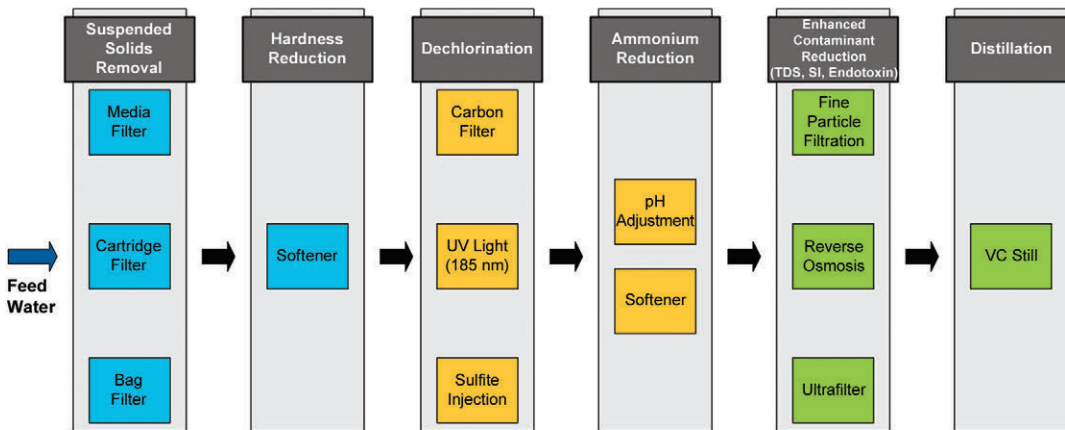
ME stills require protection from scale, dissolved solids, chlorides, and oxidation. ME stills require the feed water Total Dissolved Solids (TDS) limit to be low, and typically limit chloride and silica, so most ME stills have comprehensive feed water purification systems. Generally, systems include pretreatment, RO and IX resin or CEDI. Polishing processes such as membrane degasification, UV light and microbial-retentive filters may also be part of still feed systems. Many facilities use ME feed water purification systems to produce PW for less critical uses in the facility. ME still-based system process options are shown in Figure 6.4. Additional information regarding still types, pretreatment requirements and utility considerations is presented in depth in Chapters 4 and 5.

Figure 6.4: Multiple-Effect Still Technology Map
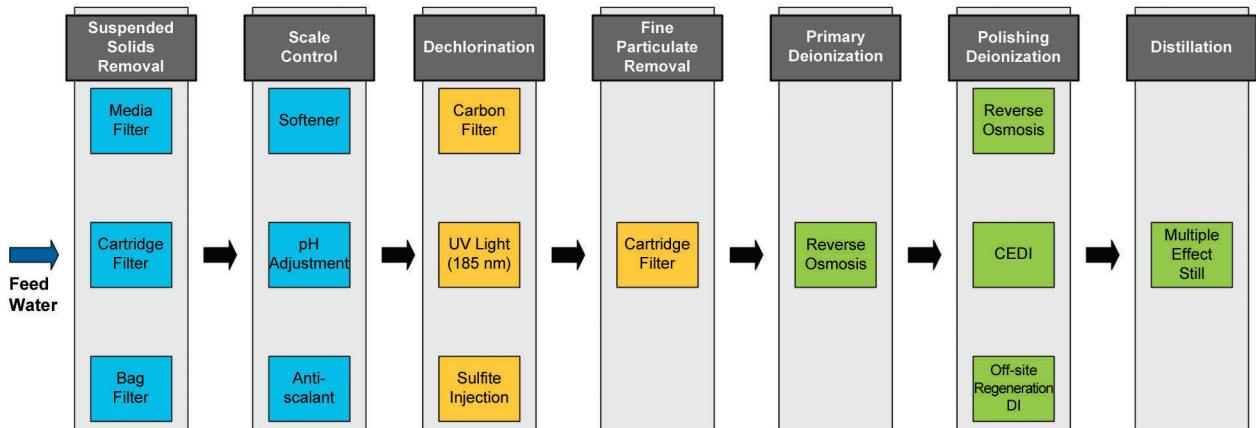
Membrane-based systems for WFI production can be viable alternatives where WFI production limitations do not preclude the choice (e.g., US, Ph. Eur., Japan etc. [4, 5, 6]). Although some membrane systems operate at continuous lethal temperatures, most do not. Therefore, proper system design for sanitization, hygienic design, materials of construction, multiple microbial/endotoxin barriers, and controls/instrumentation is critical. Membrane systems can be designed and implemented to do this as proven in many applications, but improper design/operation is possible.

Many regulatory documents exist with binding and nonbinding language regarding WFI system design. Complete system process designs are not mandated and significant flexibility in many areas of process design is available to system designers. Ph. Eur. 9.8 WFI Monograph (0169) states that the alternative production method to distillation is [5]:

> "Reverse osmosis which may be single-pass or double-pass coupled with other appropriate techniques such as electro-deionisation, ultrafiltration or nanofiltration is suitable."

The JP 17th Edition WFI Monograph states that the alternative production method to distillation is RO and/or UF either from the water which is obtained by appropriate pretreatment such as ion exchange or reverse osmosis on Water, or from Purified Water [6]. The 1993 FDA "Guide to Inspections of High Purity Water Systems" has language discussing the recommendation for two RO membrane arrays in series [40]. These documents and others may not specifically require redundant membrane element barriers but the concept is clearly stated in the language. The incorporation of redundant membrane microbial/endotoxin barriers in WFI systems is considered Good Engineering Practice (GEP) and will likely assist with regulatory compliance.

Additional non-membrane microbial-control processes such as UV light are often part of comprehensive membrane systems. Membrane system options shown in Figure 6.5 can be appropriate for WFI production with proper process configuration, construction, and operation. Systems typically implement two or more membrane passes for consistent water quality attainment. The most common configuration implements one or two passes of RO with CEDI and UF polishing, although alternative designs are not uncommon. UV sanitizers may be incorporated and on-site regenerated demineralizers may be substituted for CEDI in some instances. Two passes of RO also can meet the conductivity requirements although Stage 1 [4] conductivity attainment may not be consistent for some source water supplies.

Regulators recommend the availability of multiple sanitization methods for maximum microbial control in systems. Hot water sanitization is typically the primary sanitization method for membrane-based WFI systems and chemical sanitization may be used for extreme conditions such as biofilm removal if necessary. Hot water sanitization at sufficient frequency typically allows systems to meet the low microbial/endotoxin levels required.

Appropriate instrumentation and controls are necessary for all WFI systems. Stills have historically been provided with instruments for conductivity, pressures, temperatures, and flows as necessary. Properly designed membrane systems implement similar instrumentation. Rapid microbial monitoring methods are becoming increasingly popular as an effective process control tool for membrane-based systems. TOC instruments are also provided in some systems for confirmation of TOC attainment prior to distribution.

Figure 6.5: Membrane-Based Water for Injection System Technology Map
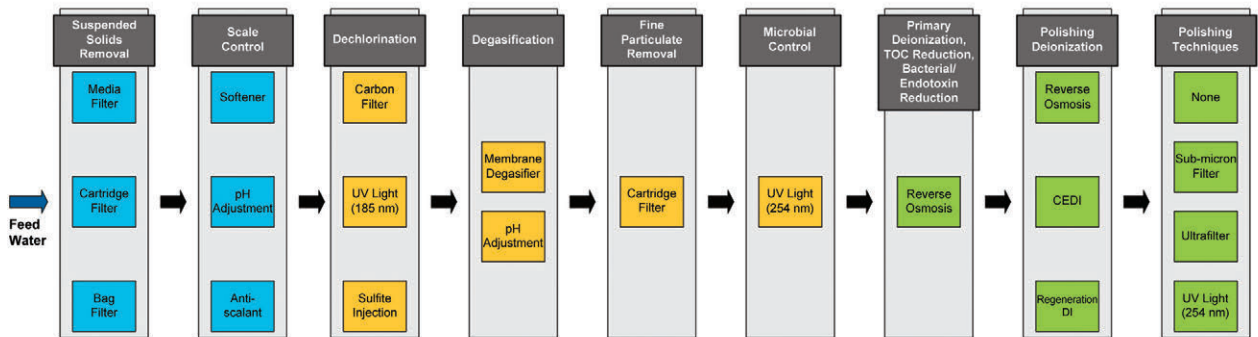
Robust sampling is an expectation for WFI membrane systems. Sampling for source water, points throughout the generation system and POU are suggested. Refer to the *ISPE Good Practice Guide: Sampling for Pharmaceutical Water, Steam, and Process Gases* for additional information [33].

6.3.2 Pharmacopeial Requirements

Most pharmacopeias require the source water to meet regional drinking water standards, stating additional specifications depending on the end water type, PW or WFI. See Chapter 9, Table 9.3 for a summary of various pharmacopeial water specifications.

6.4 Non-Compendial Waters

Non-compendial grade water often is produced and validated in a manner consistent with compendial water in the pharmaceutical industry. The most common use of non-compendial waters is in the laboratory, which is discussed in detail in Chapter 9.

Non-compendial water for pharmaceutical manufacturing is simply water that is defined by factors other than the compendial requirements. The water quality parameters may be more or less stringent than those of compendial waters. The lowest quality non-compendial water for pharmaceutical use is generally water meeting drinking water standards, such as US EPA NPDWR [29] or equivalent. Non-compendial waters can exceed the quality standards of PW or WFI where the product or process requires extremely pure water.

Systems for non-compendial waters may employ all of the pretreatment and final treatment processes used in compendial water systems. The logic used in risk-based system design is built upon CQA and CPP attainment as for compendial waters. Systems may be as simple as filtration and softening or may utilize most processes available for waters with CQA levels well below compendial levels. Refer to Chapters 3 and 9 for additional information.

7   Pharmaceutical Steam

7.1   Introduction

This chapter aims to simplify and standardize the process of selecting, programming, and designing pharmaceutical steam systems. Guidelines, information, and options of proven practices (as of publication) and technologies are provided, along with advantages and disadvantages.

There are few industry guidelines for the specification, installation, and QA of pharmaceutical steam. Guidance bodies (e.g., USP, EN 285, HTM 01-01 Part C:2016 [4, 41, 42]) provide requirements for the production and purity of Pure Steam, which are consistent with the guidelines for high purity water (WFI (Water for Injection)) used in the bioprocessing and pharmaceutical industries. These guidelines include material specifications, dimensions/tolerances, surface finish, material joining, and QA.

This chapter discusses standard definitions for terms commonly associated with pharmaceutical steam and provides information to help facilitate making correct and cost-effective decisions.

7.2   Common Steam Terms and Definitions

7.2.1   Plant Steam

Plant steam is a no impact steam (utility steam) produced by the feed of potable water or equivalent to an industrial type boiler. Corrosion control additives may be used in the maintenance of the boiler system. Typically, this steam is used for non-direct contact process heating.

7.2.2   Chemical Free Steam

Chemical Free Steam (CFS) is a no impact steam produced from pretreated water with non-volatile boiler additives. Non-volatile boiler additives should meet the FDA Generally Recognized as Safe (GRAS) [43] listed additives or an equivalent international standard where applicable. Typically, CFS is used for humidification and not for product-contact operations.

7.2.3   Process Steam

Process steam is a 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.

7.2.4   Pure Steam

Pure Steam is a direct impact steam produced by a steam generator. When condensed, the steam condensate meets the requirements of relevant compendial standards (i.e., USP, Ph. Eur. [4, 5]) for WFI, except for microbial content. Pure Steam is predominantly used for sterilization. Sterilization steam used in autoclaves for international manufacturing also should meet the requirements of EN 285 [41] for non-condensable gases, degrees of super heat, and dryness.

7.3   Types of Pharmaceutical Steam

Pharmaceutical steam is classified into two types based on their respective sources. These are:

•   Utility-boiler produced steam (plant steam)

•   Non-utility-boiler produced steam (Pure Steam)

7.3.1   Plant Steam

Plant steam is normally characterized by having:

•   Chemical additives to control scale and corrosion

•   Relatively high pressure with the potential of generating superheat during expansion

•   Relatively high pH

Chemical additives: Plant steam normally is produced using conventional steam boilers (water tube and fire tube are the most common types), usually of steel construction. Such boilers are commonly provided with systems that inject additives into the feed water to protect the boiler and steam distribution and condensate piping from scale and corrosion. The scale and corrosion inhibitors may include amines and other substances that may not be acceptable in steam used in pharmaceutical processes. The user must determine which additives to use and verify if they are acceptable in the particular application, that is, ones that do not add any impurities or create a reaction in the drug product. The creation of steam condensate that can meet the potable water specification may be possible.

Typically, plant steam is used for heating coils in HVAC applications and as the heating media in heat exchangers. Additionally, plant steam can be used for sanitization of non-product-contact equipment or biological destruction of solid or liquid wastes.

Plant steam can be filtered to remove particulate matter, but this process does not remove dissolved substances and volatiles such as amines.

Superheat: Superheated steam is produced by heating the steam beyond saturation temperature or by generating the steam at a higher pressure in a boiler and then reducing the pressure through a regulating valve.

Superheat may be dissipated downstream of the regulating valve because of heat loss in the lines. This excess of sensible heat must be removed before steam will condense. This makes steam more difficult to condense, as a portion of the heat exchange surface will be used to remove the sensible heat before a phase change can occur. This is beneficial to transport (less loss in the steam lines), but can be a problem in heat exchangers and sterilization processes.

Control of pH: To protect carbon steel from corrosion by the plant steam, additives are used to raise the pH to 9.5–10.5.

7.3.2   Pure Steam

Guidance documents from regulatory agencies include various definitions for these terms. The most commonly used terms are Pure Steam and clean steam. In this Guide, Pure Steam is used as referenced in USP General Information Chapter <1231> Water for Pharmaceutical Purposes [4].

Pure Steam is generated from treated water that meets applicable drinking water regulations and is free of volatile additives, such as amines or hydrazines. It is used for thermal disinfection or sterilization processes. It is considered especially important to preclude such contamination from injectable drug products.

Pure Steam is characterized as having:

*   No additives

*   Limited generated superheat except when the generated pressure is significantly higher than the use pressure of the steam

The condensate of Pure Steam should meet requirements of relevant compendial standards (i.e., USP and Ph. Eur. [4, 5]) for WFI, except for microbial content, has no buffer, and has a relatively low pH compared to that of plant steam.

7.4   Regulatory and Industry Guidance

The user has the ultimate responsibility for system design and performance and for ensuring that the proper type of steam is used for a given process.

7.4.1   USP Guidelines

The USP [4] provides guidance as to the generation, quality attributes, and uses of Pure Steam. The Pure Steam section of USP monograph <1231> provides direction for the feed water source, added substances, and testing condensate attributes. Pure Steam dryness and non-condensable gases, however, should be determined by the user based upon the specific application.

7.4.2   European Guidelines

European Guidance for Pure Steam is provided in EN 285 [41] and Health Technical Memorandum HTM 01-01 Part C:2016 [42].

EN 285 stipulates that steam for sterilization equipment meets the following physical quality attributes:

*   Contains no more than 3.5% v/v of non-condensable gases (contains no more than 3.5 ml non-condensable gases collected from 100 ml condensate)

*   Dryness value not less than 0.95

*   When steam is reduced from line pressure to atmospheric pressure, the temperature measured should not exceed 25°C (77°F) above boiling temperature for the atmospheric pressure at the test point (typically the measured value should not exceed 125°C (257°F)).

EN 285 and HTM 01-01 Part C:2016 provide guidance on the test methods for these attributes [41, 42].

7.4.3   Industry Guidance

Guidance documents, such as ASME BPE [37] govern the design and construction of Pure Steam generators and distribution systems. These guidance documents provide recommended practices for Pure Steam systems and high purity water systems in the bioprocessing and pharmaceutical industries. Comparable guidelines and standards in Europe and Asia include DIN 58950 (2011), JIS G 3452, and JIS G 4904:2017 [44, 45, 46]. These guidelines and standards contain material specifications, alloys, dimensions/tolerances, surface finish, material joining, and QA.

7.5 Background and Industry Practices

7.5.1 Purity of Sterilizing Steam

When steam or the resulting condensed water comes in direct or indirect contact with the drug product, the purity should be equivalent to the water purity acceptable for manufacture of the drug product.

Note: A continuous supply of dry saturated steam at the POU is considered necessary for efficient steam sterilization. Water carried by the steam in suspension may reduce heat transfer and superheated steam is considerably less effective than saturated steam when used for sterilization. Non-condensable gases, if contained in the steam, act as insulation by blanketing heat transfer surfaces, and may prevent the attainment of sterilization conditions in parts of the sterilizer load.

7.5.2 Steam for Humidification

When steam is used for indirect humidification, such as injection into HVAC air streams prior to final air filtration, the steam does not need to be purer than the entrainment air and suitable plant steam. Some plant steam is produced with softened water, without amines and corrosion inhibitors, and is suitable for HVAC humidification applications. When humidifying process areas, however, the potential level of impurities including amines and hydrazines should be evaluated to ascertain the impact on the final drug product. This is particularly important in areas where open processing takes place, such as aseptic filling suites and formulation areas. If the diluted water vapor is found to contribute to the contamination of the drug, a purer grade of steam should be selected.

7.5.3 Industry Best Practices for the Production of Steam

Table 7.1 represents typical uses for Pure Steam and the commonly accepted generation methods used to meet regulatory requirements in the pharmaceutical industry. The table is not intended to be definitive or all inclusive.

Table 7.1: Typical Uses and Generation for Pure Steam

Intended Use of Steam	Method of Steam Generation or Steam Type
Parenteral and Non-Parenteral Dosage form applications where steam is in direct contact with the drug	Pure Steam Generator (PSG)
Critical step in the manufacture of Active Pharmaceutical Ingredient (API) where steam is in direct contact with the API	PSG
Non-critical step in the manufacture of an API where added impurities will be removed in a subsequent step	Commonly PSG; however, Chemical Free Steam (CFS) may be acceptable
Sanitization or sterilization of a High Purity Water system	Commonly PSG; however; CFS may be acceptable followed by adequate flushing
Humidification for dosage form production where steam is in direct contact with the drug, where open processing occurs, or where chemical additives may be detrimental to the drug product	PSG
Humidification of non-critical HVAC systems such as rooms and areas where the drug product is not directly exposed to the room atmosphere	Commonly PSG; however; CFS or plant steam may be acceptable
Humidification of critical process cleanrooms	PSG
Heat source for non-critical and cGMP heat exchangers	CFS or plant steam
Deactivation of solid or liquid biological process waste	PSG or CFS or plant steam in a dedicated deactivation vessel; however, the use of PSG is not necessary to treat waste
Sterilization of direct product-contact production equipment, process vessels, containers, or packaged product	PSG

7.6   System Planning

Pharmaceutical steam system planning is the process of establishing system boundaries, limitations, and restrictions. Initial system planning should reveal primary boundaries that establish the foundation for design criteria. The system boundaries include:

- Steam requirements

- System design

- POU criteria

- Distribution system requirements

The limitations of these system boundaries establish specific operating strategies and ranges. To allow more flexibility in final planning and detailed design, the designer should always indicate ranges of acceptability, rather than a specific value or position.

7.6.1   Steam Requirements

The planning process starts with the listing of all steam requirements and applications, such as:

- Company standards including QA/QC requirements and established SOPs

- The categorization of POU by:

    - Type of application (humidification, contact with product, API, and dosage form applications)

    - Purity selection primarily based on the application and the endotoxin and chemical purity criteria set for the product with which the steam, or its condensate, will be in contact. The selection should consider underlying factors that impact purity control, installing and operating cost, maintenance, and practicality.

    - Steam quality (dryness, non-condensable gas limits, and maximum superheat)

7.6.2   System Design

Pharmaceutical steam is generated using different methods. The most appropriate method for each application should be selected; therefore, the second step in the system planning process is to evaluate the steam system requirements (generation) by considering the type of generation system that satisfies each category. For example:

- The types of generation systems available. If both Pure Steam and lower quality steam are required, the practicality and economy of producing only Pure Steam should be considered.

- The type and number of systems needed based on feedback from the distribution system evaluation

- The condensate sampling needs

- Safety concerns

7.6.3   Point of Use Criteria

The third step should define the specific delivery requirement ranges for Pure Steam at the POU:

- Utilization, which is determined from system peak demand(s), average demand, and the relationships between peak demand periods and their flow rates

- Pressures, flow rates, and sampling requirements

- Use periods and histogram analysis, if available

7.6.4   Distribution System

The fourth step concerns the distribution system evaluation, which includes:

- Condensate, non-condensable gases, and moisture removal (use of steam separators where applicable)

- Pipe size and insulation requirements

- Materials of construction, hygienic design requirements, and surface finish

- Physical location of each POU

- Heat and temperature losses

- Natural drainage (same as water slope 1/8" per 12" or 1/100 cm)

Note: With time, steam quality declines with condensate formation due to heat losses in relation to the efficiency of the insulation and the length of the distribution system. Therefore, the steam quality at the POU does not reflect the generation quality level. The inclusion of high-quality condensate removal traps that are strategically located and correctly installed can greatly reduce this effect.

7.6.5   System Planning Reevaluation

These sequential steps described in Sections 7.6.1 to 7.6.4 are repeated and reevaluated as information in the design process iterates, and further criteria about the overall system boundaries are identified.

In operations with a requirement for only one grade of steam, the steam system should be designed to meet the requirements of the product or process. Where more than one purity grade of steam is required, products and processes are frequently categorized to be fed by the most appropriate steam system. The number of types of steam generated is usually a function of the volume of steam consumed, economics, and variation of purity required.

Figure 7.1: Pharmaceutical Steam Purity Decision Flowchart
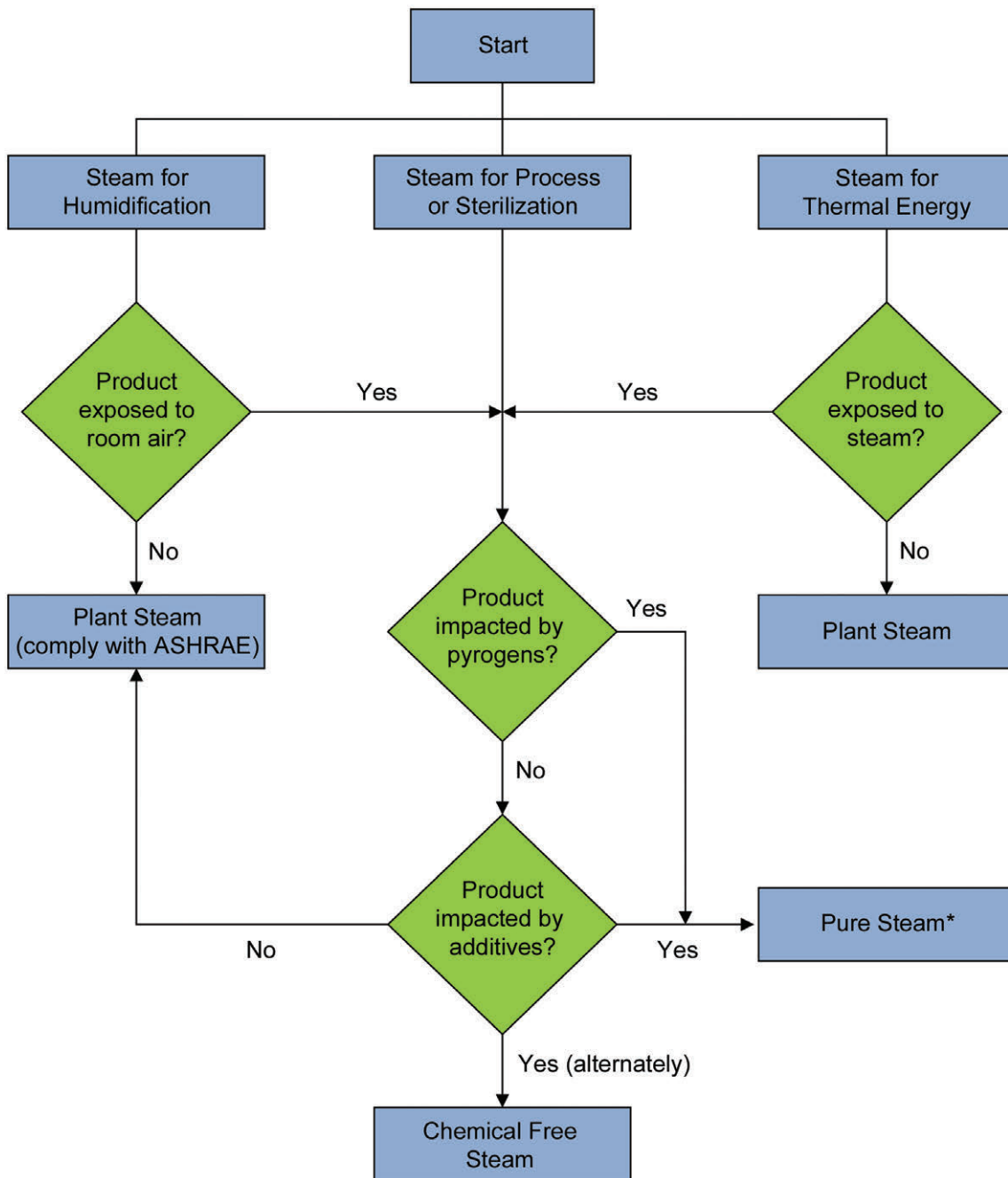
Note: *Pure Steam for humidification applications is a conservative approach. Alternatives may be acceptable dependent upon the application. See the *ISPE Good Practice Guide: Heating, Ventilation, and Air Conditioning* [47] for specific applications.

7.7   Steam Generation

7.7.1   Plant Steam (Utility Steam)

Plant steam is produced in conventional plant utility boilers (i.e., fire tube and water tube boilers) or electric heaters whose typical design and construction are outside the scope of this Guide.

7.7.2   Pure Steam

Pure Steam is produced in specially designed non-fired generators or from the first effect of ME WFI stills, which do not use scale or corrosion inhibitor additives. The generator is fed with water pretreated to remove elements that contribute to scaling or corrosion, and the materials of construction are resistant to corrosion by steam that has no corrosion inhibitors.

The dedicated Pure Steam Generator (PSG) is very similar in design and construction to an SE still or the first effect of an ME still. For further information, see Chapter 5.

7.7.2.1   Dedicated Pure Steam Generator

There are various designs of PSGs using the vaporization of feed water to produce Pure Steam. Typically, vaporization is accomplished in a steam-to-steam evaporator, which can be of the vertical or the horizontal type, depending on the manufacturer and the overhead space available.

The feed water disengagement space and the moisture separator may be housed in the same vessel as the evaporator or in a separate vessel.

Hygienic construction typically includes 316L SS material, orbital Tungsten Inert Gas (TIG) welded wherever possible, or mechanically welded with the inner surface ground smooth after welding. Movable connections normally use in-line hygienic fittings. Flanges and threaded connections on the Pure Steam portion are not considered hygienic and are not recommended. For further information, see ASME BPE [37].

Heat exchangers, using plant steam as the heat source, including the evaporator, should be of the double tubesheet, tubular design to prevent the contamination of the Pure Steam by the heating medium in the event of a tube-to-tubesheet joint failure or leak.

Most PSGs, except those with heated feed water or with lower capacity, are fitted with feed water heaters. In addition, a blowdown cooler typically is included to avoid discharge of very hot and flashing condensate.

A feed pump may be needed if the feed water supply pressure is inadequate. Depending on system design and the manufacturer, a feed pressure of approximately 10–15 psig (0.7–1.0 barg) above the maximum expected Pure Steam pressure is necessary. This allows for pressure drops in piping and valves.

A sample cooler fitted with a conductivity element is most often used to monitor Pure Steam condensate purity. Monitoring the conductivity of the condensate can alarm problematic operation and provide information regarding the suitability and applicability of the distributed steam for its final use.

7.7.2.2   Operating Principles of a Typical Pure Steam Generator

Pure Steam normally is generated in a double tubesheet, shell and tube heat exchanger-like evaporator. Feed water is introduced on one side of the tubes, while the heating medium is introduced on the other side. Heating the feed water to above the boiling point causes the water to evaporate, producing steam. The heating medium is normally plant steam, and does not come in direct contact with the feed water or with the Pure Steam. PSGs may be designed to use other heating media, such as electric immersion heaters.

Pure Steam pressure should be selected by the user. Typical units are designed for pharmaceutical applications at 30–60 psig (2–4 barg). Pure Steam pressure is maintained by a standard Proportional Integral Derivative (PID) control loop, which modulates the supply steam control valve. The evaporator feed water is independently controlled using a level sensor and a control loop to start/stop a feed water pump or open/close a feed water supply valve. The feed water level is controlled to protect against flooding the evaporator and prevent carryover of endotoxins. A high-level alarm and subsequent shutdown normally are incorporated into the design.

The plant steam supplied to the generator, typically 80–120 psig (5–8 barg), should be at a higher pressure than the required Pure Steam pressure. In general, for a given size generator, the greater the differential between the plant steam pressure and the Pure Steam pressure, the higher the Pure Steam production rate. Plant steam pressure should be > 30 psig (> 2.0 barg) higher than the Pure Steam pressure to optimize the heat transfer and production rate. Plant steam consumption will be approximately 10%–20% greater than the quantity of Pure Steam produced.

Moisture entrainment separators normally are designed to function over an optimum range of steam velocity. Caution should be taken if the volume of steam increases substantially beyond design capacity. The increase in steam velocity associated with the higher capacity could result in carryover of water/moisture and, therefore, endotoxins through the moisture separator. This condition also can exist if the steam pressure differential significantly exceeds design parameters. Under these conditions, the velocity of the steam through the separator also may be excessive. Specification of the PSG should be at the maximum output of the generator and at the highest possible pressure difference. An alarm and equipment shutdown are recommended and can be incorporated into the controls to protect against such conditions.

7.7.3 Pure Steam from Multiple-Effect Stills

The first effect of an ME still can be used to produce Pure Steam. The ME still may or may not produce Pure Steam when the still is producing WFI. A common practice is to increase the size of the first effect to provide the required Pure Steam capacity for distribution to POU plus the quantity to supply subsequent effects of the still. This design is commonly used if simultaneous production of Pure Steam and WFI is preferred.

Advantages:

• Does not require a separate PSG with the associated cost, space, installation, operation, and maintenance.

Disadvantages:

• Output may be limited to the capacity of the first effect of the ME still.

• May not produce WFI when using excessive quantities of Pure Steam. In an ME still, the steam generated in the first effect becomes the motive (power) steam for the second effect, which in turn produces motive steam for the third effect, etc. The impact of utilizing an excessive quantity of Pure Steam higher than the sizing of the first effect, therefore, drastically reduces the ability for WFI production.

The ME still manufacturer should be advised in advance if simultaneous production of WFI and Pure Steam is preferred.

7.7.4 Feed Water Pretreatment

Feed water pretreatment is an important consideration in the design and successful operation of the PSG. All generators are susceptible to scaling and corrosion if the feed water is not pretreated properly. The basic functions of the pretreatment are to minimize or prevent scale formation and to minimize or prevent corrosion. Additionally, the pretreatment system can remove objectionable volatiles, such as ammonia, which are not removed in stills and carry over into the distillate with adverse effects on distilled water quality.

The pretreatment of feed water for a PSG is similar to that of an ME still; therefore, the guidelines for feed water treatment for ME stills should be closely followed for a PSG. For further information, see Chapters 4 and 5. Additionally, with some pretreatment systems, if the Pure Steam is to meet the requirement of EN 285 [41] for non-condensable gases, then the PSG may need to be fitted with a feed water deaerator or heated break tank. Hot WFI or PW with 1.3 µS/cm conductivity or better, which has not been nitrogen blanketed, should not contain sufficient non-condensable gases to result in failure of the EN 285 test.

7.7.4.1 Common Practices for Feed Water

It is common practice to generate Pure Steam from water treated to remove impurities that may be detrimental to the operability of a PSG. Many manufacturers recommend the removal of particulates, chlorine/chloramines, and hardness ions as a minimum; however, additional levels of water treatment (e.g., RO, DI) usually are utilized to aid in the removal of impurities and extend the mechanical reliability of the PSG. A common practice for supplying the treated water is to use the same water treatment system as the facility's high purity water system. Water is supplied from the treatment system following the treatment step required by the PSG manufacturer or desired by the owner.

Another common practice for supplying water to a PSG is to use the facility's high purity water system (e.g., PW, WFI).

Note: The PSG does not require feed water meeting the PW or WFI monographs in USP<1231> [4]. This practice, however, ignores the ability of the PSG to remove impurities. A customary application for this practice is when the steam quantity is small and the cost and maintenance of a dedicated feed water system exceeds the cost of using high purity water.

7.8 Steam Attributes and Condensate Sampling

7.8.1 Treatment of Plant Steam

It may be necessary to filter or condition plant steam. In specific applications, it also may be necessary to change the steam boiler treatment and substitute additives that do not contain amines or hydrazine.

Given that the type and degree of conditioning are dependent on the application, as well as on the quality of the plant steam and additives present, in this Guide all possible scenarios are not addressed.

Prior to the elimination of amines and hydrazines by the substitution for standard boiler pretreatment additives, the plant steam boiler manufacturer should be consulted regarding the impact on equipment warranty, performance, and expected life. Substitute additives may not be as effective as those normally used.

7.8.2 Pure Steam Purity Sampling

Purity requirements for steam used in pharmaceutical manufacturing and product development normally are driven by the product characteristics, manufacturing process, and the intended use of the product. When required by the process, the steam purity should be monitored through acceptable sampling techniques. Typically, steam sampling is via a condenser/cooler, fitted with a sampling valve, and noted as condensate.

Sampling of the steam condensate should be part of C&Q using an established SOP for regular or periodic use.

If the sampling requirement is for endotoxin or pyrogen testing, the sample cooler, tubing, and valve should be of hygienic construction.

Sample coolers can be fitted to the PSG, located in the distribution line, or at the POU (recommended location), or a combination thereof. It is normal practice to fit a sample cooler with conductivity monitors and alarms on the outlet of the PSG. Additionally, sample locations typically are situated at sterilization equipment and at the farthest points in the distribution system. These sample locations can have permanently installed sample coolers or a portable cooler can be utilized. Reference the *ISPE Good Practice Guide: Sampling for Pharmaceutical Water, Steam, and Process Gases* for additional information [33].

Endotoxin removal: The condensate sample from a PSG with separator is expected to show 3-4 $\log_{10}$ level reduction in pyrogens compared to the level in the feed water (similar to reduction in WFI stills).

Though steam purity requirements are product specific, it may be impractical to produce special steam for each situation. Manufacturing operations typically generate and distribute only one or two steam purity grades. Although, for a given application, the condensate of Pure Steam may not be required to meet WFI attributes, it is important to note that, as a rule, if the condensate does not meet the attributes, the generator design/operation or distribution system should be evaluated.

7.8.3   Pure Steam "Quality" Sampling

The term "quality" when referring to steam indicates the degree of superheat, dryness fraction, and the amount of non-condensable gases in the Pure Steam. (The steam dryness fraction quantifies the amount of water within steam. If steam contains 10% water by mass, it is said to be 90% dry, or have a dryness fraction of 0.9). The quality of the Pure Steam should be established by the application and as required by the applicable regulatory guidelines. Steam with low moisture levels and little or no superheat is necessary for steam sterilization when it enters the sterilizer. EN 285 [41] and other international regulatory requirements commonly are adopted for Pure Steam systems globally.

Water can be generated and carried by steam within distribution piping systems in two ways:

*   In suspension as moisture when the steam dryness is < 100%

*   As condensate separated from the steam

Water vapor carried in suspension may be reduced by:

*   Reducing the pressure

*   Reducing the velocity

*   Adding a steam entrainment separator

The installation of a properly designed condensate trap is recommended immediately upstream of steam quality testing locations.

Steam "quality" sampling may be employed to determine the dryness, superheat, and non-condensable gases. The dryness of steam may be determined using a calorimeter to measure the dryness or saturation level.

7.9 Materials of Construction

7.9.1 Materials of Construction for Plant Steam Conditioning and Distribution

Chemical compatibility with the plant boiler generated steam and the carried over feed water chemicals normally are required for all materials used to condition the contaminated steam.

Based on the particulate levels in the steam and the required steam purity, more than one filtration stage may be utilized.

Distribution of plant steam following filtration follows similar practices as Pure Steam to control condensate buildup, non-condensable gases, and saturation levels as required for the application.

Acceptable materials should be relatively inert; the most common materials are carbon steel but can be SS or tin-coated copper.

7.9.2 Materials of Construction for Pure Steam Generators

Structural integrity and chemical compatibility with the contact fluid and its constituents are two of the more practical issues that drive construction material selection for Pure Steam systems.

The intrinsic corrosion potential forces PSG manufacturers to consider relatively inert metals, including SS or titanium. Hygienic piping and valves, considered unnecessary for plant steam boilers, often are standard features for Pure Steam systems based on the specific manufacturer and model. The materials chosen should not contribute to contamination of the drug product.

The most commonly used material of construction is 316 and 316L SS, except for the plant steam supply piping, which is normally carbon steel, as are the skid and structural supports and framework. Chlorine and/or chlorides combined with water will damage the SS generator and distribution piping regardless of the finish; appropriate selection of chloride-free insulation is recommended. Insulation also should be rated for the appropriate temperature to prevent material breakdown, which may contribute to chloride-induced corrosion of SS.

7.10 Distribution

Distribution systems for Pure Steam follow the same engineering standards commonly used for plant steam; however, contact materials should be inert to the aggressive nature of Pure Steam. Corrosion-resistant 304, 316, or 316L grade SS tubing or solid-drawn pipe normally are used. Surface finish is not critical because of the self-sanitizing nature of Pure Steam. Mill finish or mechanically polished pipe or tubing usually is sufficient. Orbital welding and post-installation passivation are considered appropriate for this application. Piping should be designed to allow for thermal expansion and to drain condensate. Piping should include minimum slope in the direction of steam flow to a low-point condensate trap for adequate removal of condensate.

Note: Sloping the distribution piping in opposition to the direction of flow is not recommended because of the possibility of condensate collection and moisture entrainment.

Hygienic high-pressure clamps or pipe flanges are frequently used where the piping should be joined, but welded connections are preferable where possible to eliminate safety concerns, maintenance costs, and the potential for leaks. Threaded connections may be suitable for instrumentation if positioned to drain condensate and remain hot; however, hygienic clamp connections are preferred. Ball valves are commonly used for isolation. Unlike water systems, ball valves in steam systems are permissible as there is no possibility of microbial issues. The use of diaphragm valves should be scrutinized and assessed because of the limited ability of the elastomeric diaphragms to hold up well in this service. Where diaphragm valves are used, PTFE-encapsulated EPDM or Viton diaphragms usually provide the best long-term performance. Gasket materials should be selected from PTFE-encapsulated EPDM or Viton or 316 SS impregnated PTFE.

Steam quality sampling should be included in the distribution design, and sample locations should be designed with condensate traps, entrainment separators, and vents. Condensate trap maintenance cannot be over emphasized because of the small orifices required in the separation of gas and liquid.

7.10.1 Line Sizing

Steam distribution headers are normally sized for a maximum velocity of 120 ft/s (37 m/s) to limit pressure drop and extend the life expectancy of the piping. Condensate line sizing should follow industry standards for utility condensate. A Pure Steam system including the PSG usually is not designed to provide the cumulative connected load requirement. A diversity factor should be established for the Pure Steam system consistent with the usage profile; however, consideration should be given to changes in the usage profile, otherwise increased usage may cause difficulties.

A common problem in established Pure Steam systems is the addition of equipment without consideration of the maximum supply capacity of the distribution system. The size of the distribution system should be evaluated along with usage diversity when new equipment or POU are added.

Designing Pure Steam main headers and main branches of a distribution system at lower velocities (e.g., 100 fps) can compensate for future connected loads or decreasing diversity.

7.10.2 Point of Use Design

Designs for a Pure Steam POU normally include an accessible isolation ball valve and an appropriately oriented condensate trap. The supply piping to the POU valve typically is designed as a branch of piping extending from the top of the distribution main to the condensate trap. The condensate trap usually includes an isolation valve, for trap maintenance, and outlet piping to a drain. The condensate drain piping should contain an air gap separation to the floor drain. Consideration should be given to the temperature and the aggressive nature of condensate versus the drain piping material. The POU valve should extend from the top of a horizontal run of the branch pipe prior to the trap preventing moisture entrainment at the POU valve. (See ASME BPE [37].) Where flexible connections are used to connect to the POU, consideration should be given to avoid low points where condensate can accumulate.

7.10.3 Instrumentation

Monitoring the pressure and/or temperature of the Pure Steam system is considered essential for proper operation and quality. Pressure and/or temperature monitoring is recommended at the PSG as well as at critical process locations in the distribution system. The pressure at the extents of the distribution system tends to drop if the system is poorly designed or inadequately sized. The drop in pressure corresponds to periods of high usage. Suitable pressure monitoring can provide information for establishing usage diversity for a system.

It is considered unnecessary to use a feed water conductivity monitor when the feed is from a USP Purified or WFI source.

7.10.4 Moisture Removal

Moisture forms in steam systems because of heat loss, causing a change in the liquid-to-vapor ratio or steam "quality."

Steam is dried by reducing the pressure just prior to the POU to coincide with the steam temperature of saturation at the reduced pressure.

Moisture entrained in the steam also can be removed by installing an in-line separator just prior to, or just after, the pressure control valve. If the moisture separator is located upstream of the pressure control valve, the piping should be designed to protect the valve from condensate damage. A sudden line enlargement combined with a change in flow direction and a condensate trap also can be used for moisture removal.

In-line separators remove moisture with a series of baffles on which the suspended water droplets impinge and fall out by gravity to the outlet trap, which should be piped to drain. Separators commonly have an efficiency of > 99% in the removal of condensate within the design range.

7.10.5 Condensate Removal

Condensate is the water that has separated from the liquid vapor mixture, and forms in steam systems because of heat losses and natural separation effects. Lines should be sloped in the direction of flow to a trap to prevent the buildup of condensate. The proper location of condensate traps can prevent dangerous water hammer and eliminate branches where condensate is allowed to collect. The following practices are commonly employed to minimize these concerns:

- Each line is adequately sloped/supported in the flow direction to avoid sagging and subsequent condensate accumulation.

- Steam traps are installed at points where condensate can collect (e.g., at least every 100 ft (30 m), upstream of control valves, at the bottom of vertical risers). Steam traps used for Pure Steam systems should be hygienically designed and self-draining.

- If the main distribution header is above the use points, the branches to the POU should be routed from the top of the header to avoid excessive condensate loads at the branch. Each branch should be trapped to avoid condensate buildup.

- An alternative is to run the main distribution header below the POU. The branches can drain back to the main distribution header, avoiding the need for additional traps; however, this design can result in condensate being discharged at the POU due to entrainment in the high velocity steam.

7.10.6 Non-Condensable Gas Removal

Air and other non-condensable gases should be minimized in pharmaceutical steam systems. Since air acts as an insulator, incomplete sterilization can occur in the process. Air in a system offers a highly effective barrier to the heat transfer, which may lead to a reduced temperature at the surface of a tube, system component, or process equipment.

When a steam system is pressurized for the first time, or following a PSG or partial-system shutdown, a repeatable procedure should be employed to slowly warm the distribution system to prevent thermal shocking and to remove the air from the system. Because air is heavier than steam, under very low flow rate conditions it will be removed by steam traps at the low points. However, it is also likely that with even low flow rates it will be forced to the end of systems and may accumulate there.

The removal of air can be achieved by inserting thermostatic steam traps at appropriate locations throughout the distribution system. These should be placed in positions where air is prone to collect, such as the terminal points of the main and large branches of the steam header. In the case of air and condensate discharge at the bottom of large vessels, the air and condensate should be separated by suitable piping practices.

8   Storage and Distribution Systems

8.1   Introduction

Appropriate design and operation of the storage and distribution system is critical to the success of a biopharmaceutical or life science water system. There are a considerable number of design options available. The differences in these designs are directly correlated to the user and manufacturing requirements.

This chapter provides an overview of common storage and distribution configurations, noting certain advantages and disadvantages of each alternative. Comparisons of the alternatives and a decision flowchart are provided to help choose the alternative that best suits the operating requirements. Microbial considerations are discussed, as they apply to alternatives for continuous and periodic sanitization of storage and distribution systems. Typical system components are also presented, along with alternative materials of construction, and common installation practices.

Hygienic design is the culmination of the use of components, fabrication, installation, operational and/or maintenance practices that each are hygienic. When implemented together they form a hygienic system; however, any single element that is non-hygienic can render the entire system unacceptable.

8.2   Purpose

The purpose of a storage system is to accommodate demand peaks without oversizing the purification system. A distribution system should provide water to POU at the required location, flow, temperature, and pressure. Additionally, the storage and distribution system should not cause the water quality to degrade from the appropriate quality for its designated end use.

Storage allows a smaller, less costly, water purification system to meet peak usage demand while enabling operation closer to the ideal of continuous, dynamic flow. Large manufacturing sites, with systems serving different buildings, may use storage tanks as a means to separate sections of the system and to minimize potential cross contamination. For sites that require continuous operation, an appropriately sized storage system allows the distribution system to remain in service and supply the POU while maintenance activities are performed on the purification equipment.

8.3   System Components

This section is intended to review many of the primary metallic and/or non-metallic components found in a typical storage and distribution system. It is not meant to be limiting or all inclusive, but to provide general information regarding the most common components. It is important to note that the trend in laboratory systems is to use non-metallic materials of construction. For further information, see Chapter 9.

As technology has improved, many design features such as storage at elevated temperature, constant circulation, use of hygienic components including 316L SS tubing and diaphragm valves, along with orbital welding and frequent sanitization have become commonplace. To incorporate all of these features into each new design typically leads to escalating cost with possible minimal reduction in the risk of contamination. Although each feature provides improvements to the system, it may be unnecessary to use all of them in every system.

A reasonable approach is to use designs that provide the greatest reduction in risk to operational and microbial issues at the most reasonable cost. The idea of selecting design features based on ROI, where return is defined as reduction in risk, can be very helpful in controlling system cost and in evaluating alternatives. The ability of a system to deliver water of the required quality may be used to determine the success of each design application. The challenge for the design engineer is to determine which features will achieve the required water quality with the lowest lifecycle cost.

8.3.1   Tanks

Tanks, for the purposes of this discussion, are appropriate containers used to store any volume of product water and are installed and validated as a permanent part of a storage and distribution system. Tanks can be any size and configuration to support proper system design. The term vessel is often used interchangeably with tank.

When properly designed, storage tanks offer a number of advantages over tankless systems, including reserve capacity during a purification outage, atmospheric air break for loop return, and/or facilitating the service of the upstream water purification equipment and minimizing purification system instantaneous demand capacity. Careful consideration should be given to sizing based on various factors including associated costs. The storage tank also may be used as a contact chamber for sanitization using ozone.

Ideally, tanks should be maintained under continuously sanitizing conditions using either elevated temperature or ozone, virtually eliminating microbial risk and biofilm development. Tanks that are periodically sanitized and operated predominantly at ambient temperature are at increasing risk as the time between sanitizations is lengthened.

Potential disadvantages of storage tanks are the capital cost and the cost of accessories such as pumps, vent filters, and instrumentation; however, this expense is usually less than the increased cost of larger water purification equipment sized to handle the peak demand in the facility.

Storage tank configuration may result in regions of slower moving water, which can, during ambient operation, result in the development of fragile biofilm structures that are easily disturbed by slight fluctuations in water flow. Hence, the sanitization regime chosen is an important consideration.

Generally, storage vessels are located near the purification equipment for ease of maintenance and to minimize cost; however, alternate locations may be suitable. Utility areas are acceptable for this purpose, if maintenance accessibility is provided, the area is suitably maintained, and personnel access is controlled.

8.3.1.1   Tanks – Sizing and Capacity

Criteria affecting storage capacity include the user's existing and future demand profile (or the amount of use), demand duration, timing, diversity (in the case of more than one user), and whether the system is circulating or non-circulating. Careful consideration of these criteria is necessary to optimize cost and water quality.

The storage tank should provide an adequate reserve to minimize cycling of the purification equipment and to offset maximum water usage. Average usage over time should be determined to approximate the purification system capacity. The storage tank size also should enable routine maintenance and orderly system shutdown in the event of an emergency, which can vary from a few to many hours, depending on the size and configuration of the system and maintenance procedures.

In heated systems, a sprayball serves to keep the top of the vessel wetted and at nearly the same temperature as the water. The use of sprayballs for high purity water storage vessels may not require the stringent cleaning requirements used for CIP applications, especially in hot systems. Tank sprayballs may be placed on:

•   The return of the distribution loop

•   A slip stream from the discharge of the distribution pump

•   A separately pumped recirculation loop

Connections on the top head of the storage tank (relief devices, instrument connections, etc.) should be kept as close to the head as possible to simplify the sprayball design and obtain the benefit of the spray action. An exception is the vent filter, which should be removed far enough to avoid direct contact from the water spray because it could blind the filter. If dip tubes or instruments project down from the head, multiple sprayballs may be selected to avoid creating a

shadow in the spray pattern, and vacuum-break holes may be necessary. For ozonated systems, sprayballs typically are not used, as the agitation increases off-gassing. Return flow should enter the tank below the liquid level in an appropriate location (often near the bottom) to maximize ozone contact.

The tanks may be vented to allow filling and emptying (especially for non-pressure or vacuum-rated vessels), and a sterilizing-grade filter should be used at the vent to avoid airborne particulate and microbial contamination intrusion.

If the change in conductivity resulting from absorption of atmospheric CO_2 (carbon dioxide) into the water proves problematic, a number of options can be considered including:

• Polishing deionization/CEDI

• Blanketing the tank head space with an inert gas (e.g., nitrogen)

• Using a CO_2 absorber with the vent filter

• Flushing/replenishing with fresh water

Gases added to storage tanks should be of appropriate quality to avoid objectionable contamination and typically require an uninterruptible source.

8.3.1.2   Tanks – Design Considerations

Tanks should be designed using appropriate standards and installed such that they do not compromise the water quality or system operation. Generally, a good practice is to minimize surface area per usable volume. Additional information can be found in the ASME BPE [37].

Horizontal tanks may be used to address space issues; however, vertical orientation is the most common based on the following advantages:

• Lower cost

• Less dead volume

• Simpler sprayball design

• Smaller footprint required

The turnover rate may be important for systems using polishing equipment. Storage tank turnover may also be important to improve mixing within the tank (during thermal and/or chemical sanitization), which may reduce time during sanitization. The turnover rate is less important when storage is under continuous sanitizing conditions, including hot storage or ozone. It also may be less important under conditions that limit microbial growth, such as cold storage (4°C–10°C (39.2°F–50°F)).

For circulating systems, tank design may include one or more internal sprayballs to ensure that all interior surfaces are wetted and as part of the microbial-control strategy. Horizontal tanks may be necessary if overhead space is limited. With a horizontal tank, there should be no unwetted surfaces during operation and multiple sprayballs are more likely needed. Tank jacketing or an external heat exchanger may be necessary in hot systems to maintain water temperature over long periods without makeup. Alternatively, these features may be used to cool high influent temperatures to reduce pump cavitation and possible rouge formation. Ozonated tanks are typically not equipped with spray devices as increased off-gassing occurs. Refer to the *ISPE Good Practice Guide: Ozone Sanitization of Pharmaceutical Water Systems* [34].

The maximum size of a single storage tank often is limited by the space available in the facility or by structural loading. Multiple tanks may be required to obtain the desired surge capacity or the desired maintenance redundancy. In this case, interconnecting tubing should ensure adequate flow through all supply and return branches. In addition, if elevations require lower than desirable pump suction head, vortex breakers may be required. When space within the facility does not allow storage of the volume desired, exterior storage tanks may be considered provided the design and operation is proper. Additional considerations include wind loading, height with lighted markers, snow loading, access, color and finish, security, vent design, temperature control with possible redundant freeze protection, and maintenance.

8.3.2 Pumps

Hygienic centrifugal pumps are commonly employed in high purity water distribution systems. Performance curves and suction head requirements should be reviewed carefully to preclude pump cavitation and possible resulting rouge (refer to Chapter 10 for additional rouge information), contamination, and corrosion within the pump head. The generation of pump heat (and other heat sources) over extended periods of low or no draw also should be considered, since a significant temperature rise in cold systems or cavitation caused by low vapor pressure in hot systems could occur. Where the pumps are at the low point of the distribution, casing drains allow for full system drainage. The installation of dual pumps, for standby purposes, may be considered if properly designed to avoid dead legs and suitable pump switching procedures are implemented. Additional information can be found in ASME BPE [37].

8.3.2.1 Pumps – Sizing and Capacity

High purity water distribution pumps should be designed to deliver the required capacity/flow rate and pressure to support usage. Typically, this includes a usage diversity factor, that is, only a percentage of the POU that are part of the distribution system may require flow at any time. The flow and pressure capacity of a distribution system should adequately meet the diversified usage requirement with additional capacity to meet minimum specified return velocity and pressure during maximum usage, while maintaining fully flooded tubing. Centrifugal pumps whenever feasible are selected for operation at less than the maximum pressure and flow capacity. The use of Variable Frequency Drives (VFDs) and/or back pressure control valves ensure positive pressure in the loop return and can be used separately or in combination if properly designed.

VFDs are most commonly used to vary pump flow and associated pressure (using the output signal of a flow meter or pressure transmitter) to meet system demand requirements while reducing energy consumption. They are also used to soft start motors, reducing water hammer and pressure surges on start-up. This feature may result in slightly increased capital cost, but reduces operating and maintenance cost because the pump will only operate at the speed required to meet the system demands.

Similarly, a pressure control valve modulating system pressure can impose pressure on a constant speed pump, which will allow similar performance at slightly higher energy costs.

Distribution systems often are hydraulically modeled to closely predict performance under various usage conditions. Hydraulic modeling can be used during the design process to evaluate the design against user requirements. Moreover, in existing distribution systems, a hydraulic model can be used to evaluate modifications or additions that may affect pump performance. Flow velocity is an important criterion used in distribution system design and necessitates that pumps be adequately sized.

8.3.2.2 Pumps – Design Considerations

Common practice is to design circulating loops based on:

• Flow

• Pressure

- Temperature

- Velocity

Pump selection should include considerations for excessive pressure surges (i.e., water hammer) and adequate suction pressure to avoid cavitation. Net Positive Suction Head available (NPSHa) should always exceed the Net Positive Suction Head required (NPSHr).

Pump seal materials should be suitable for the application with consideration given to wear and particle generation. Materials such as silicon carbide and tungsten carbide are preferred over carbon. Pumps equipped with external single mechanical seals typically are used for high purity water applications and minimize the possibility of contamination. Double mechanical seals, using product water as the flushing fluid, are less frequently used than in the past.

The pump casing and impeller generally is recognized as a predominant area for the formation of rouge. (For further information on rouge, see Chapter 10.) This is speculated to be caused by the highly turbulent conditions inside the pump head and exacerbated if low-pressure conditions exist. Therefore, the use of not less than 316L SS is recommended for these components and even higher-grade alloys may reduce rouge formation (ex: Hastelloy®, AL-6XN®) and improve system performance. Forged materials offer better service life than cast.

It is common for distribution pumps to have the discharge oriented at 45° for complete venting of the casing along with a bottom fitting to allow for complete drainage, although other orientations may be suitable depending on design conditions. Pump casing drains should be minimum in length. Suction issues should be reviewed based on height requirements necessitated by the casing drain.

Given that distribution pumps require routine maintenance, the design of pharmaceutical water systems may include redundant or standby pumps. These secondary pumps may be in a primary and standby configuration with one pump always running and the second pump ready for operation in standby mode. The standby pumps may require flushing or sanitization prior to being put into service or can be included in the continuously circulating system for immediate operation without sanitization. Conversely, if it is acceptable for the system to be sanitized following pump change out, use of an uninstalled spare may be considered. A less common practice is to include hygienic check valves each with a small hole that allows hot or ozonated water to circulate through the idle pump when not in service.

8.3.3   Vent Filters

There has been considerable debate over many years associated with the use of vent filters on compendial water storage tanks. Ostensibly, the purpose of vent filtration is to avoid particle and/or microbial intrusion into the water stored in the vessel. The primary point of discussion revolves around the concern for microbial contamination since the need for the elimination of particulate is commonly agreed.

Filter elements used for air (gaseous) filtration are typically more efficient in particulate removal than those used for water because the additional electrostatic particle removal does not occur with liquid filtration. As a result, a filter rated for 0.45 μm in water may be able to remove particulates < 0.2 μm in gases. However, very often filters specified as sterilizing grade 0.2 μm or 0.22 μm are used as vent filters, even though compendial water is not required to be sterile. This situation is compounded since many believe that all sterilizing-grade filters, regardless of their purpose, must be integrity tested.

Although it is often prudent to employ conservatism, sterile filtration with integrity testing may not be necessary or cost justifiable given the requirements and risks. Users should determine the level of filtration needed along with the associated methodologies to be employed, with the obvious understanding that the microbiological control requirements for WFI are far more challenging than for PW, with greater associated risk. It should also be understood that a regulatory risk exists beyond the technical risks discussed. If regulatory expectations include the use of sterilizing-grade filters (complete with integrity testing), users who choose alternate methods may need to address possible scrutiny and associated challenges.

The following discussion is intended to provide information relative to vent filtration design, application options, and current practices.

Vent filters are commonly used on high purity water storage tanks to serve as a particulate and microbial barrier between the surrounding environment and the water. The headspace of the storage tank takes in and expels air proportional to the rise and fall of the water level. Vent filters suitable for microbial-retentive gas filtration typically are constructed of compatible materials, such as hydrophobic PTFE, PP, or PVDF to prevent wetting. Alternatives, for instance sintered metal, may be suitable based on risk assessment. Filters should be capable of withstanding sanitization processes (i.e., heat, ozone) and be sized based on vessel design characteristics (e.g., pressure and vacuum rating), and system maximum fill or draw-down rates.

Areas of concern for gas filtration include:

- Proper sizing (surface area and µm rating)

- Blockage of the filter caused by condensed water vapors or particulates

- Leakage caused by improper filter installation or damage

- Materials incompatible with water system and sanitization methods

- Defective filter cartridges

- Filter element integrity testability *in situ,* including seals if required

The filter cartridges should be compatible with the filter housing. When required or desired, in order to mitigate risks of non-integral filtration, vent filters for compendial water storage tanks should be integrity tested following installation in the housing. Similarly, integrity testing and visual inspections should be performed at the end of service life. Alternatives such as multiple replaceable housings, parallel housings, and other options may be desirable for testing under controlled conditions in a laboratory rather than under field conditions.

The purpose of the integrity testing is to verify that the filter is not plugged or is not leaking at the time the filter is removed from service, and to provide assurance that the preventive maintenance schedule is appropriate. Common filter integrity testing methods include bubble point, diffusion, and water intrusion, which vary based on the filter manufacturer, application, and type of cartridge. Adequate protocols should be developed for possible failure of filter testing following removal from service. Additional information can be found in ASME BPE [37].

8.3.3.1   Vent Filters – Sizing and Capacity

Microbial-retentive hydrophobic vent filters typically have a 0.2–0.22 µm absolute rating. (Absolute rating does not mean all particles 0.2 µm and larger are excluded). When sizing vent filters, the filter should allow gas to enter or escape at a rate comparable to the water entry or removal. This is to avoid creating a vacuum or positive pressure condition that could exceed the vessel rating, or that could impact operation of other devices such as rupture disks, level controls, or ozone injectors. For high flow rates, multiple vent filters may be needed to avoid exceeding the recommended maximum flow rate or pressure drop across a single filter, recognizing the risks associated with additional hardware. The expected life of the vent filter varies based on the operating conditions. The flow, differential pressure, and life expectancy values of filter cartridges typically depend on the air temperature, air quality, materials of construction, and filter manufacturer. For example, a filter cartridge that is periodically heat sanitized could last longer than one operated continuously at elevated temperatures.

8.3.3.2 Vent Filters – Design Considerations

The design of vent filters for high purity water storage tanks can be as simple or as complicated as needed to satisfy system operational requirements. This can range from a single disposable cartridge/housing combination to parallel heat-traced housings with *in situ* sanitization and integrity testing capability. Consideration may be given to installing redundant parallel filters or valves that allow for filter replacement and integrity testing without exposing the contents of the tank to the environment or reagents. The design of the vent filter(s) depends significantly upon the operating parameters of the associated storage tank and the flexibility for periodic maintenance.

Pressure safety devices (for example, rupture discs) should be used for tank over/under-pressurization protection based on tank design and rating, because vent filters can plug during operation or valves installed on vent filters could be inadvertently closed. Tanks rated for the appropriate pressure and vacuum offer the safest and most trouble-free operation. Typically, only over pressure protection (not vacuum relief) is used for tanks rated for full vacuum. These devices should be installed with suitable indication of their status (for example, rupture indication).

Where filters are used, care should be taken to prevent wetting of the filter. If the tank contains a sprayball, the vent filter should be located on a tank nozzle, such that the spray will not wet the element, and where it is easily accessible for maintenance. Consideration also should be given as to the source of air for the tank. It is desirable to avoid placing the vent filter in a location where organic vapors or other undesirable vapor sources could enter the tank, causing contamination or damaging the filter element.

Control measures to avoid accumulation of condensed vapors in the vent filter housing include electrical or steam heat tracing and a self-draining orientation. If heat tracing is used, the temperature should be set above the dew point temperature of the vapor space and below the manufacturer's maximum temperature rating of the cartridges.

Steam tracing of vent filter housings is more commonly used but poses the added maintenance issue of steam and condensate disconnection whenever an element requires changing, or using flexible steam and condensate hoses. Electric heating elements have become popular more recently due to the simplicity of removal and the more precise control available.

An alternate practice is to blanket the tank head space with a suitable non-reactive or inert gas (for example, nitrogen) to prevent water conductivity changes caused by CO_2 from ambient air. It also ensures the tank contents are under positive pressure at all times to avoid particle, organic vapor, and/or microbial intrusion. Blanketing design must take into consideration issues including:

- Maximum feed water in-rush and system draw-down rates

- Tank pressure and/or vacuum rating

- Venting of gas

- Potential for condensation

- Gas quality

- Hardware required

- Controls and interlocks/alarms

- Continuous uninterruptable source of the gas supply

8.3.4 Heat Exchangers

Heat exchange equipment is used to heat or cool high purity water to desirable levels or to maintain temperatures. Design configurations often include:

- Shell and tube

- Plate (also called plate and frame)

- Jackets applied to tanks

Within each group there are design variations that may, when properly applied, improve reliability or reduce risk. Shell and tube heat exchangers typically are constructed of an outer cylindrical shell, with one or more smaller tubes installed inside. High purity water flows through the inner tube(s), while heat transfer media contacts the exterior, contained between the product tube exterior(s) and the outer shell.

Plate heat exchangers are constructed of specially formed plates that when assembled create a stack with precise gaps between each plate. The stacks usually are mounted within a support frame, hence the alternate name plate and frame. High purity water and heat transfer media flow through these gaps in an alternating arrangement.

Tank jackets commonly are constructed by adding a secondary layer to the outer wall of the vessel. The gap created between the outer wall of the vessel and the jacketing is the space through which heat transfer media travels. Jackets can be applied to the sidewall and heads of a tank and can be configured in a variety of ways. Additional information can be found in ASME BPE [37].

8.3.4.1 Heat Exchangers – Sizing and Capacity

Heat exchangers are available in a large number of standard and custom sizes. The capacity of tube and shell or plate heat exchangers is determined primarily by the size and number of tubes or plates. The capacity of a tank jacket is limited by the tank dimensions. Tube and shell or plate heat exchangers often can be configured by the manufacturer to suit an application, such that the size and number of tubes or plates can be selected for the best fit. The details of the heat transfer media will have a significant impact on the heat exchanger sizing, along with the thickness of the materials of construction and resulting heat transfer coefficient. Sizing can be based on a once-through design or on a batch basis, as needed for the application. A once-through design generally results in a larger unit with higher utility demand requirements. Utility systems that provide heat transfer media including overall capacity, demand cycles, supply and return temperatures, pressures, and flow rates should be considered.

8.3.4.2 Heat Exchangers – Design Considerations

Heat exchange equipment that will be in contact with high purity water should be specified with appropriate materials, finishes, and connections, etc. The principal concern with properly sized heat exchangers is the possibility of contamination from the heat transfer media into the high purity water. This possibility is compounded by the thermal expansion typically endured by heat exchangers used in systems with significant temperature variations, or if used for both heating and cooling applications in the same exchanger. Thermal impacts on related utilities (e.g., the coolant in a cooling exchanger during sanitization) also should be considered.

A variety of schemes to minimize this risk can be employed. One method is to ensure there is a higher pressure on the product side than on the media side, which requires the inclusion of pressure monitoring devices, as well as procedures for ensuring proper operation; however, this technique may not be able to overcome venturi action if a leak develops in an area of high velocity. Another method uses double tubesheets for tube and shell exchangers. Double tubesheets with an air gap between reduce the risk of contamination if the leak occurs at the tube-to-tubesheet seal; however, this feature does not eliminate the risk if a tube ruptures. Conductivity sensors, installed at the outlet of exchangers, commonly are used as a method of detecting a tube rupture and the entrainment of media in the high purity water.

Alternatively, double wall heat exchangers can further minimize the risk of contamination, especially if other scenarios described in this section are employed. Double wall heat exchangers contain an added layer of material to further isolate the media from the product. These designs can be effective, but usually at a significant loss of efficiency. For example, in the simple tube and shell heat exchanger with a single tube within the shell, the product is contained within the inner tube while the media is contained between the shell and the inner tube. Employing a double wall design requires a third concentric tube, where the product remains within the inner tube, but now the media is contained between the shell and the intermediate tube. The gap between the intermediate tube and the inner tube serves as a barrier in the event of a leak and is vented to provide a method of detection. For plate heat exchangers, the plates can be doubled to accomplish the same goal; however, the added gaps result in lower heat transfer efficiency.

Shell and tube heat exchangers can be made completely drainable, either using slope or for U tube (multi-pass) units, by adding weep holes at the low point of each chamber. Plate heat exchangers typically are more compact and also can be less expensive and more efficient; however, they are usually not fully drainable, making them less desirable for many applications. Gasketed units can be drained with full disassembly. Appropriate construction is important including proper welding; for double tubesheet units, the inner tubesheet should be torque-rolled while the outer is normally welded and polished. Sanitization of shell and tube exchangers is simple and straight forward with no need for special treatment when sanitized as part of an entire storage and distribution system. Alternatively, plate and frame heat exchangers sanitized with heat pose no greater concern but when chemically sanitized, they can require additional rinse out to remove all chemical residues.

Plate and frame type heat exchangers used for pharmaceutical water applications are compact in size, and often lower cost; however; these benefits are commonly outweighed by the challenges posed by their use. Standard single wall plate and frame exchangers consist of multiple plates with a large surface area gasketed around the entire periphery, often with gaskets attached using glue. The large gasket surface area can lead to leaks that are difficult to locate and repair. The plates are also subject to pinholes. Additionally, the flow path through the heat exchanger stack is serpentine with areas that see less flow turnover experiencing a potential for lower velocity and turbulence. Double wall plate and frame designs eliminate some of these issues but are significantly more costly and challenging to service. As a result, these types of heat exchangers are more commonly utilized in pretreatment and non-compendial systems than for hygienic or compendial applications.

Heat exchanger service is an often-overlooked activity that can result in system contamination and significant downtime and remediation. For shell and tube exchangers, periodic disassembly and inspection along with pressure testing is most suitable. Pressure testing of the interstitial space between the shell and tubes will serve to determine if there is a leak in either simultaneously. Pressure testing of the tube-side only will verify gasket integrity as well as tubesheet seals. Similar testing for plate and frame units may be less conclusive and failures will be more challenging to locate, necessitating complete disassembly for inspection of plates and gasketing.

Appropriate space for service is required, such as pull-out tube bundles for tube and shell units. It should be noted that inclusion of all design features is unlikely to remove all potential scenarios for contamination. An evaluation of the overall installation of any exchanger to ensure safe and proper operation, including the use of pressure relief devices as necessary, should be conducted. Hygienic heat exchangers also can become part of an economizer circuit to reclaim energy where appropriate and justifiable, provided proper design standards are applied.

8.3.5 Piping/Tubing/Fittings

Piping and Tubing: Extruded seamless and longitudinally welded tubing (designated and sized by the OD) (ASTM A270) [48], commonly is used. Longitudinally welded tubing is similar to seamless in appearance and performance and can be significantly lower in cost, especially in larger sizes. Pipe is nominally designated and sized by the inner diameter and is seldom used for hygienic applications due to the dimensional irregularities, and limited availability of polished material and fittings. The terms pipe and tube are often erroneously used interchangeably. See Appendix 2 (Glossary).

Thermoplastics such as PVDF and PP have been shown to be viable alternatives with proper design. System temperature, extractables, and chemical compatibility are a concern when using thermoplastics. Continuous support is typically required.

Fittings: Detailed information on hygienic fittings is found in ASME BPE [37]. Hygienic clamp connections in a range of designs are available in a large number of sizes and are used frequently. Clamp joints are usually minimized to reduce microbial and maintenance concerns.

Tube/Fittings – Sizing/Capacity

The flow of water in tube and fittings in ambient distribution systems should be turbulent to help control partial biofilm dislodgement. It is also necessary for thorough mixing and dispersion of sanitizing agents/conditions throughout all components of the distribution system (see Chapter 13). Turbulent flow can be achieved at relatively low velocities and is dependent on water temperature and the diameter of the tube. The capacity of the system should be such that the desired amount of water can be used at all times without risking the loss of return pressure. The size of the tube is then decided based on maximum pressure drop at maximum flow rate in the system.

Designing to obtain a velocity in the tubing of at least of 0.9 m/s or 3 ft/s for an ambient pharmaceutical water system is considered outdated. Based on data prepared by the Public Health Service/Dairy Industry Committee 3A [49], older distribution systems were designed with a minimum velocity of 5 ft/s. Over the years, many users accepted lower velocities (3 ft/s or 1 m/s) without significant repercussions. Recently the trend is to design for not less than turbulent flow based on Reynolds number (see Section 8.6.2 Distribution Loop Velocity) with various minimums accepted. It should be noted that these lower velocities may have a significant impact on biofilm consistency such that partial biofilm dislodgement may occur more easily at lower velocity. A risk-based approach to the selection of a suitable minimum velocity should be followed, giving consideration to the sanitization regime, to ensure acceptable system operation and qualification.

Tube/Fittings – Design Considerations

The installation of a distribution system that is fully drainable is a common industry practice, but not a GMP requirement. Systems that will be steam or chemically sanitized should be fully drainable to assure complete removal of condensate or waste. Systems that are not steam sanitized may not need to be fully drainable, as long as water is not allowed to stagnate in the system and no unacceptable dead legs (see Appendix 2 (Glossary) and Chapter 13) exist. These systems are commonly designed for continuous circulation, or for water to be dumped/flushed periodically to avoid microbial contamination. The drainability of a system may allow for more rapid access during maintenance. Other methods, such as a suitably treated and filtered compressed air-blow of the system may work equally well, although most guidance suggests a minimum pitch for drainage. This subject should also be evaluated based on risk. Since hot water sanitization of storage and distribution equipment is almost universally adequate, steam sanitization is typically discouraged.

It is common practice to allow for the complete draining of equipment and associated tubing, facilitating system maintenance or system flushing. Drain points in non-controlled areas should be evaluated based on a possible risk of contamination from uncontrolled air entering the system. Vent valves also may be needed at the high points in complex or larger systems to allow filtered air into the distribution system as an aid to complete drainage. In addition, it may be acceptable to include partial disassembly of the system for complete drainage.

When hygienic fittings are employed, gaskets are needed. Table 8.1 describes some materials that can be used. It should be noted that various formulations of nearly every compound used as a gasket exist with significant variance in the chemical compatibility and serviceability. Users are advised to confirm that the formulation selected is suitable for the application, especially when subjected to passivation, sanitization chemicals including ozone, high temperatures, etc.

It should also be noted that alternate gasket styles are available (for example, standard, flanged, etc.). Gaskets used in the joining of distribution system components should be sourced from reliable providers whose formulations have a proven track record in the application. Specification of gasket materials simply by name (e.g., EPDM) may result in failure as multiple formulations of EPDM exist.

Clamps used for the assembly of hygienic joints also have various configurations, styles, pressure ratings, and methods of assembly. Users should ensure care is exercised to assure gasket and clamp styles are compatible, and that both are suitable for the application.

The length of the dead legs should be minimized; a dead leg of any distance is problematic if it results in a microbial issue. There are various regulatory guidance documents that limit dead legs to less than 6, 3, 2, or even 1.5 branch tube diameters. For example, the FDA Guide to Inspections of High Purity Water Systems of 1993 [40] 6D (six diameter) rule describes the distance from the center line of the tube to the end of the dead leg. Other industry practices suggest using two diameters or less. It should be recognized that a one-way tube may not constitute a dead leg if it is continuously used, frequently flushed, or frequently sanitized. The discrepancies in the guidelines can cause confusion. Operations to control microbial concerns, such as periodic flushing for known sanitizing durations or other remediation activities, may be considered. For additional information on dead legs, refer to ASME BPE [37].

Dead legs should be minimized or eliminated where possible. A turbulent condition may be maintained in short dead-ended tube stubs, if the length of the stubs is limited. Thorough mixing is desired at these locations to facilitate sanitization. This limited length varies with the tube stub diameter and to a lesser degree with the main branch diameter. A specified minimum dead leg may be difficult to achieve in large mains with small branches, and may result in unacceptably long dead legs in large branches. Rather than universally applying "dead leg rules," it is important to recognize dead legs as areas of concern and take appropriate steps to prevent them in the original design or implement special provisions to address them if unavoidable. Factors to consider include:

- Operating temperature

- Velocity in the main

- Frequency of use of each outlet

8.3.6   Valves and Other System Components

Diaphragm valves predominantly are used in high purity water systems because of their enhanced ability to be sanitized. Other types of valves, such as ball, butterfly, plug, disk, and needle that have internal areas that harbor water, potentially facilitating biofilm development, typically are not used.

Hygienic valves such as the tapered stem-and-plug valves used in other hygienic industries are also acceptable for use in pharmaceutical water systems based on proper operation. These valves are extremely well suited for throttling, modulation, and back pressure control applications. Multiple types of self-contained pressure regulating valves, safety relief valves, and other specialty valves are available and should be evaluated per application.

System components such as spray devices, rupture disks, venturis, etc. should be selected based on a risk assessment. UV sanitization units are often installed in storage and distribution systems. Although frequently referred to as sterilizers, these units only help to reduce microbial populations and are not capable of sterilization. UV lights may also be utilized for ozone elimination, chlorine/chloramine and organic materials reduction if properly sized by the manufacturer and provided with performance assurance. Use of UV lights should be based on risk assessment, emitted wavelength and intensity, consideration of the possibility of heating the water, and the amount of required maintenance.

The use of in-line filtration has for many years been discouraged based on alleged FDA comments that have since been disproven [50]. Hence, the use of suitably sized and selected filtration equipment that is properly maintained and operated may be appropriate when circumstances dictate and based on risk assessment. A significant concern remains when sterilizing-grade filters are used to facilitate the use of a system that has not been shown to be under control and able to produce suitable water.

As noted elsewhere in this Guide, the use of hygienic components may not be limited to only hygienic sections of the system. For example, when sampling for microbial growth in the non-hygienic section of the system, hygienic sample valves are more suitable for proper hygienic sampling techniques, reducing the potential for false positive results. This approach may be appropriate for the application of other components as well.

Additional information can be found in ASME BPE [37].

8.3.7 Instruments

Appropriate instrumentation should ensure proper operation of a high purity water system and provide a means for obtaining suitable data to document operation. Components may range from local visual indicators to devices capable of integration with electronic systems offering control, alarming, trending, and more. Typical operational parameters commonly monitored by instrumentation in a pharmaceutical water system are temperature, pressure, flow, TOC, and conductivity. Additional parameters can include tank level, pump speed, and other parameters of interest, depending upon the level of sophistication and monitoring desired.

Critical instrumentation should be calibrated and be part of the preventive maintenance program to ensure the reliability of the data obtained. Instrumentation should be installed such that it is accessible for data gathering or maintenance. Instrumentation used for quality release of the water may require additional QA oversight. Data recording equipment must be carefully evaluated and where appropriate should be 21 CFR Part 11 compliant [51]. Additional information can be found in ASME BPE [37].

8.3.7.1 Instruments – Sizing and Capacity

Monitoring components should be appropriately sized. Accuracy should be considered at normal operating ranges as well as operational extremes, such as during sanitization, which may result in excessive pressures, temperatures, and/or chemical/ozone concentrations. Concerns include material compatibility (such as temperature and chemical/ozone) and physical compatibility (e.g., steam sanitizing of a pressure-based level transmitter). Pressure monitoring devices should be selected bearing in mind water hammer effects that may occur as a result of closing valves or abruptly starting a distribution pump.

8.3.7.2 Instruments – Design Considerations

Instrument location during system design helps to ensure proper performance and contamination avoidance, as well as accessibility for removal, service, and calibration. Pressure monitoring devices should be of hygienic design and include a diaphragm barrier to isolate the internal components of the device.

The recommended installation configuration for temperature and conductivity elements opposes the water flow. This ensures continuous contact with the water and proper flushing of the area around the element. Additionally, instrument connections can be oriented horizontally to the main tube to avoid trapping air. This is particularly important for conductivity elements, which can give a false reading in the presence of air. Care should be given to ensure proper hygienic installation.

High purity water storage tanks typically use differential pressure to monitor water level; however, there are several commonly used hygienic methods of monitoring tank level. Additionally, storage tanks should be equipped with a pressure safety rupture device. A rupture disk with burst indicator that will alarm upon a failure of the disk with resulting exposure to the atmosphere is strongly recommended.

Some instrumentation requires specialized connections to ensure proper installation and operation without undue risk of microbial contamination. Bottom mounted tank-level transmitters are one example of these types of unique fittings.

For further information, see Chapter 11.

8.3.8   System Components Comparison

Table 8.1 shows a summary of water system components, listing common industry practices and advantages and disadvantages. Table 8.1 is not intended to be all inclusive. Also see ASME BPE for further discussion of materials [37]. Components not listed should be evaluated for appropriate use. It remains paramount to select and utilize appropriate quality suppliers and components.

Table 8.1: System Components Comparison (major components only)

Item	Type	Industry Practice	Advantages	Disadvantages
Tube and Fittings	Welded or seamless ASTM A270 [48]	Standard for polished hygienic application and orbital welding	Mechanical tolerances including wall thickness and finish	Cost
Pipe and Fittings	Welded or seamless ASTM A312/A312M [52]	Industrial, non-hygienic application	Cost	Crevices, quality
Connection Methods	Hygienic (various types)	Common in hygienic equipment	Minimal crevice, ease of inspection, ease of disassembly	Cost, pressure limit in sizes above 4" OD
	Welded-Automated (hygienic)	Common in hygienic distribution	Highest reliability	Cost
	Compression (industrial)	Infrequently used in pretreatment	Skilled labor not required	Cost, crevices
	Flanged (industrial)	Common in pretreatment	Cost, disassembly	Alignment, crevices
	Threaded (industrial)	Common in pretreatment	Cost	Crevices
	Welded-Manual (hygienic or industrial)	Common in pretreatment	Cost	Quality, repeatability
Gaskets	BUNA (Nitrile)	Used for ambient temperature applications (i.e., pretreatment) (Rated by some vendors to 121°C (250°F))	Suitable for non-Pure Water and Steam applications, temperature range, resilience, cost	Compatibility (not Class VI), extractables, ozone incompatible
	EPDM (Ethylene Propylene Diene Monomer)	Used for both higher temperature and ozonated applications (i.e., heat or ozone-sanitized components and distribution) (Rated by some vendors to 148.8°C (300°F))	Suitable for Pure Water and Steam applications, temperature range, good ozone compatibility with proper formulation, resilience, cost	Several formulations are available Care should be exercised in formulation and vendor selection since some may have limited steam or ozone compatibility
	Silicone (Peroxide Cured, usually for Compression Molded Applications)	Used for ambient and higher temperature applications (i.e., heat sanitized components and distribution) (Rated by some vendors to > 204.4°C (> 400°F))	Suitable for Pure Water and Steam applications, temperature range, resilience, cost	Ozone incompatible

Table 8.1: System Components Comparison (major components only) (continued)

Item	Type	Industry Practice	Advantages	Disadvantages
Gaskets (continued)	Silicone (Platinum Cured, usually for Injection Molded Applications)	Used for ambient and higher temperature applications (i.e., heat sanitized components and distribution) (Rated by some vendors to > 204.4°C (> 400°F))	Suitable for Pure Water and Steam applications, temperature range, resilience	Ozone incompatible
	PTFE (Polytetrafluoroethylene) (solid)	Used for higher temperature application (Rated by some vendors to > 204.4°C (> 400°F))	Inertness, suitable for Pure Water and Steam applications, temperature range, excellent ozone compatibility	Cold flows, non-elastic, difficult for cyclic temperatures, requires higher sealing forces
	PTFE (envelope)	Used for ambient and higher temperature applications (i.e., ambient or hot systems typically when not heat sanitized) (Rated by some vendors to > 204.4°C (> 400°F))	Suitable for Pure Water and Steam applications, temperature range, good ozone compatibility	Cost, creasing, cracking, difficulty sealing
	PTFE/SS (Stainless Steel) composite or PTFE/elastomer laminates	Used for higher temperature applications (i.e., heat sanitized components and distribution) (Rated by some vendors to > 204.4°C (> 400°F))	Suitable for Pure Water and Steam applications, extended life, flexibility, high temperature	Cost, limited number of suppliers, higher sealing force required, possible delamination
	Viton	Used for both higher temperature and ozonated applications (i.e., heat or ozone-sanitized components and distribution) (Rated by some vendors to > 176.7°C (> 350°F))	Suitable for Pure Water and Steam applications, temperature range, good ozone compatibility, resilience	Cost Several formulations are available Some formulations may have limited steam or ozone service
Heat Exchangers	Concentric Tube (tube in tube)	Common in hygienic applications	Simple design, low-pressure drop	Limited surface area
	Plate and Frame (single wall)	Common only in pretreatment (non-hygienic)	Cost, large surface area	Drainage, not first in first out, gasket
	Plate and Frame (double wall)	More common in hygienic applications	Improved integrity	Cost, lowered efficiency
	Tube and Shell-Single Tubesheet	Common in pretreatment	Cost	Contamination potential
	Tube and Shell-Double Tubesheet	Common in hygienic applications	Highest integrity	Cost
Pumps	Centrifugal with Single Seal	Common for Purified and WFI	Cost, simplicity	Seal integrity
	Centrifugal with Double Seal	May be applicable for WFI	Seal integrity	Cost, maintenance
	Positive Displacement-Rotary	Can be used for high pressure 200 psi	High pressure	Cost, pulsation
	Positive Displacement-Diaphragm	Can be used for suction lift	Suction lift/priming	Limited flow, pulsation

Table 8.1: System Components Comparison (major components only) (continued)

Item	Type	Industry Practice	Advantages	Disadvantages
Tanks	Single Shell	Common for ambient temperature operation No heat sanitization	Cost, easy inspection	Sweating, flexibility
	Insulated with Sheath	Common for cold or for ambient temperature Operation with heat sanitization	Energy, safety	Cost, Difficult to Inspect and Repair (DTI&R)
	Jacketed 1/2 Pipe (and alternative)	Common for hot applications and/or heat sanitization	Thermal efficiency	Welding, cost, DTI&R
	Jacketed-Dimple Wall	Common for hot applications and/or heat sanitizations	Cost, less welding	Thermal efficiency, DTI&R
Relief Devices	Rupture Disc	Common for hygienic applications	Monitorable, integrity, suitable for pressure and/or vacuum service	Cost, failure causes shutdown
	Relief Valve ASME [19]	Common for hygienic applications	Certified	Cost, not monitorable and can result in contamination Suitable for vacuum-rated tanks only, unless used with vacuum relief device
	Relief Valve – Adjustable, Non-ASME [19]	Common for hygienic applications	Cost	Can be improperly adjusted, not monitorable and can result in contamination Suitable for vacuum-rated tanks only, unless used with supplemental vacuum relief device
Valves	Diaphragm	Common for hygienic systems	Integrity	Cost, not suited for steam
	Rising Stem Hygienic	Common in hygienic throttling	Integrity, leak detection, performance	Angle body design
	Butterfly	Common in pretreatment	Cost	Stem, crevices
	Ball	Common in pretreatment and Pure Steam	Cost, Pure Steam service	Stem, crevices
	Plug, Gate, Globe	Common in pretreatment	Cost	Stem, crevices
Vent Devices	Vent Filter – Unjacketed	Common for ambient systems and ozonated (with proper materials)	Cost, easier service	Costly if ozone compatible.
	Vent Filter – Steam Jacketed	Common for hot applications and/or heat sanitization	Eliminates blinding	Energy, must disconnect steam and condensate piping to change filter element
	Vent Filter – Electric Traced	Common for hot applications and/or heat sanitization	Eliminates blinding	Energy, must unplug/ disconnect electrical wiring to change filter element
	Ozone Destruct Vent – Thermal	Common for ozonated systems	Eliminates catalyst, non-hygienic	Energy, high heat
	Ozone Destruct Vent – Catalytic	Common for ozonated systems	Lower cost and energy, non-hygienic	Energy, catalyst can solidify and block vent

Table 8.1: System Components Comparison (major components only) (continued)

Item	Type	Industry Practice	Advantages	Disadvantages
Flexible Hoses	Elastomer (hygienic)	Used for lower temperature and pressure	Cost	Cost, when used in conjunction with hygienic vent filter
	Elastomer (industrial)	Common in pretreatment	Cost	Durability, when used in conjunction with hygienic vent filter
	Plastic (hygienic)	Used for moderate temperature and pressure	Cost	Cost, when used in conjunction with hygienic vent filter
	Plastic (industrial)	Common in pretreatment	Cost	Durability, when used in conjunction with hygienic vent filter
	Metallic (hygienic)	Used for higher temperature and pressure	Strength	Cost, flexibility, when used in conjunction with hygienic vent filter
	Metallic (industrial)	Common in pretreatment	Cost, strength	Flexibility, used in conjunction with hygienic vent filter
In-Line Filters	Disposable element	Used in both hygienic and non-hygienic sections of systems	Elements can be selected for specific removal ratings and applications Hygienic units vary for specific required application	Cost of operation, labor required for element change, disposal may have associated cost
In-Line Filters	Cleanable	Common in non-hygienic sections of system	Cost, excellent for removal of large particulates, low maintenance	Typically not hygienic, best for coarse removal
UV Irradiators	185 and 254 nm	Used in both hygienic and non-hygienic sections of systems	Microbial reduction, can be sized for chlorine, ozone, and TOC reduction	No removal of bacteria or by-products Cost, maintenance, water temperature increase

8.4   Materials of Construction/Finishes

Pharmaceutical water system equipment and distribution networks rely extensively on SS (typically 316L) to provide the non-reactive, corrosion-resistant construction material needed to meet operating conditions and sanitization methods (see ASME BPE [37]). 304 SS also has been used, but is not recommended for new installations because its alloy characteristics are more susceptible to the corrosive nature of high purity water. However, suitable thermoplastics (e.g., PP and PVDF) may offer alternative benefits.

Different assembly techniques lead to different internal surface finishes in assembled plastic piping systems. Assembly by socket fusion may create internal gaps or beads. The use of joining materials, glue, epoxies, etc., for thermoplastics should be avoided due to elution of TOC into the water system. Butt fusion techniques (bead and crevice free is most hygienic) should be employed for joining non-metallic piping. At elevated temperatures, structural integrity, support, and thermal expansion of the distribution systems becomes a concern. These concerns increase when using thermoplastics and need to be addressed. Thermoplastics also may be susceptible to degradation by UV irradiation; hence, it is common to install SS tubing immediately adjacent to a UV light.

Material selection should be appropriate throughout the distribution, storage, and processing systems. Materials of construction:

> *"…shall not be reactive, additive or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements"* (21 CFR 211.65) [53].

Sanitization procedures should be considered when selecting materials. Sanitization with heat, UV, chemicals, or ozone should be carefully managed with regard to concentration, pH, pressure, and temperature to avoid corrosive effects or damage to distribution systems.

High purity water distribution systems, using the material and finishes specified by the design, should be joined using acceptable welding or other hygienic techniques. For high purity water systems using a thermal sanitization method, 316L SS normally is used. Orbital autogenous (automated) welding is the preferred method for joining hygienic tubing systems because of the greater control over critical weld parameters and the smooth weld bead characteristics of the process. However, manual welding may still be necessary in specific situations, and should have increased quality inspection of the welds. The distribution and storage systems should be installed using GEPs and fabricated, manufactured, procured, and installed in strict accordance with explicit procedures (e.g., in-house specifications or industry standards) and consistent with GMPs. While the use of higher-grade materials and finishes may yield benefits in specific applications, the additional expense should be evaluated against the advantages.

There are numerous industry guidelines for the specification, installation, and QA of pharmaceutical-grade tubing and components. Guidelines for high purity water systems include the ASME BPE [37], which provides the requirements applicable to the design of distribution, equipment, and systems used in the bioprocessing and pharmaceutical industries. Comparable guidelines in Europe and Asia include DIN [44] and JIS G [45, 46]. These guidelines include topics such as:

- Material specifications

- Dimensions/tolerances

- Surface finish

- Material joining

- QA

Gaskets and seals used in high purity water systems should be reviewed for compatibility with the sanitization methods and chemicals. A variety of materials and designs are available, including solid one-piece molded elastomers, machined gaskets, and multipart envelope gaskets. A range of grades of elastic and inelastic polymers may be applicable, but should be selected based on their sealing and compatibility properties. Care should be exercised to avoid extractables and leachables (e.g., USP Class VI [4]), and to ensure suitability with sanitization methods, including heat, chemicals, and ozone.

See Table 8.2 for additional information.

8.4.1   *Hygienic Tubing and Piping*

Piping and tubing fabrication and installation should meet applicable specifications and/or standards (e.g., ASTM [18], ASME BPE [37], ISO [20], DIN [44], SMS [54], BSi [55], JIS G [45, 46]). The use of tubing for hygienic applications is most common.

All welds should be documented and inspected and an isometric or other suitable routing drawing should be maintained, identifying each weld with a unique number corresponding to the weld inspection log and including data such as the welder ID number, material test reports, and date.

The tube support type and its spacing should be designed and installed in accordance with supplier recommendations or tubing specifications and drawings. If necessary, the slope should be checked and documented. The installed distribution system should be pressure tested according to the requirements of the fabrication specification. Pressure tests can be performed pneumatically with proper safety precautions, particularly on thermoplastic systems. Pressure tests performed hydraulically should be evaluated based on possible residual microbial concerns. In both cases, the media should be of a quality to avoid contamination concerns. If hydraulic pressure tests are to be performed, they should coincide with system start-up to avoid microbial issues.

Although it has been a common requirement for all hygienic tubing to be installed with a verifiable slope (commonly 1%) for full drainability, this requirement may be unnecessary or excessive for every system, especially at the levels of validation typically required. The majority of water systems are operated continuously with minimum downtime. Chemical sanitization is avoided whenever possible leaving only periodic cleaning, de-rouging, and passivation procedures as drainability concerns. Recognizing that there are alternate methods to ensure the removal of water and residual sanitizers, the ability to relax pitch requirements should be evaluated for each system on a risk basis rather than enforcing unnecessary and overly rigid requirements that are unjustified.

8.4.1.1 Stainless Steel Distribution Tubing

SS tubing, commonly used for hygienic high purity water distribution, is available in seamless drawn or the more common welded construction. Material quality is critical, such that levels of both carbon and sulfur should be precisely controlled, especially when using orbital welding. Levels too high or too low can result in unsuitable welds and increase the probability of weld failure. Tubing recommended for a high purity water distribution system should conform to ASTM A270 [48].

SS is susceptible to chloride attack from sources such as chloride-containing insulation, prolonged contact with chlorinated or chloride-containing water, or some sanitizing agents. Temperature cycling can exacerbate the problem. Supports for the SS tubing, which incorporate isolators, should be used to preclude galvanic corrosion.

The use of SS tubing for high purity water distribution requires close attention to maintaining a passive layer on the water-contact surface to minimize concerns with rouge development. For further information, see Chapter 10.

8.4.1.2 Types of Non-Metallic Materials

Few compatible non-metallic piping materials are available that will withstand the rigors of a pharmaceutical high purity water system, including:

- 65°C–90°C (149°F–194°F) operation or periodic sanitization

- 121°C (249.8°F) steam (or superheated water) sanitizing temperatures

- Ozone contact

One such material that supports these conditions and limits inorganic extractables to a minimum level comparable with SS is PVDF. This material is available in a compatible range of pipe diameters, surface finishes, and fusion welding capability. PVDF is inert and does not exhibit surface corrosion when in contact with 90°C (194°F) high purity water or commonly used oxidizers. The surface finish of PVDF is comparable or better that polished SS, and the fusion bead and crevice-free welding equipment and capabilities are similar to SS orbital welding. Weldable fittings, elbows, tees, reducers, adapters, diaphragm valves, zero static valves, flow meters, regulators, etc., are available for PVDF pipe.

Maximum operating pressures for PVDF piping typically are less than those for SS tubing; therefore, the pressures should be evaluated and associated with pipe diameter and operating temperatures. Caution should be observed when using PVDF in combination with SS, because of differing thermal expansion characteristics, structural strengths, connection types, and applied stresses. Continuous support is recommended for systems operated ≥ 65°C (149°F), because of softening at elevated temperatures. Generally, the installation cost is greater, and the amount of support needed for non-metallic tubing is higher than for metallic tubing to avoid sagging.

PP is an additional non-metallic piping material typically used in laboratory systems. This material often is joined using heat fusion; however, hygienic flanged joints are readily available. These systems typically use chemical sanitization. For further information, see Section 13.4.2.

The use of PVC and CPVC for new distribution systems in the pharmaceutical industry has become uncommon; conversely, where non-metallic materials are used, the use of PP and PVDF has increased.

8.4.2 Materials Comparison

Table 8.2 is a comparison of the relative values of key factors for various materials in the design and installation of water systems.

Table 8.2: Materials Comparison

	Polyvinylidene Fluoride (PVDF)	Polypropylene (PP)	316L Stainless Steel
Material Cost	High	Medium	High
Installation Cost[1]	High	Medium	Medium
Steam Sanitizable	Yes[2]	No	Yes
Hot Water Sanitizable	Yes[3]	No[3]	Yes
Ozone Sanitizable	Yes	Yes[4]	Yes
Chemical Sanitizable	Yes	Yes	Yes
Rouging Susceptibility	No	No	Yes
Corrosion Resistance	High	High	High
Availability	Medium	Medium	High
Extractables	Low	Low	Low
Degree of Thermal Expansion	High	High	Low
Joining Method • **Hygienic Clamp** • **Solvent/Glue[5]** • **Thermal Fusion/Weld**	Yes No Yes	Yes No Yes	Yes No Yes
Support Requirements	High	High	Low
Typical Usage	Medium	Medium	High

Notes:
1. Based on skilled labor requirements, ease of welding, ease of visual inspection, shop fabrication requirements, etc.
2. Steam pressure and temperature control are critical and need to be kept below the manufacturer's ratings.
3. Sanitization of PP can only be performed at low temperatures (e.g., 60°C (140°F)). For PP and PVDF nearly continuous support along the entire length is needed.
4. Limited tolerance; may be beyond manufacturers recommendations.
5. Materials using solvents and glues are not recommended and may result in elevated TOC.

PE, having properties similar, but not identical to PP, is also used in some systems but typically for fabricated components such as tanks due to its fabrication characteristics.

It is uncommon for FRP to be used for hygienic applications due to the potential for extractables and leachables and the industrial methods of joining used. Lined vessels may prove acceptable if a suitable liner is selected and lining integrity is routinely confirmed; however, the risk may be higher for this design option and should be evaluated carefully.

It is also extremely uncommon to use Polyvinyl Chloride (PVC) and CPVC for distribution systems and/or hygienic application for the same reasons as FRP, except in pretreatment (see Chapter 4). Pigmentation, stabilizers, glues, and other additives can pose significant challenges to use in storage and distribution systems. Certain grades of PVC and CPVC may offer reduced extractables; however, these employ solvent-welded non-hygienic joints and generally are not suitable for application in high purity water distribution systems. These materials also require greater support to avoid sagging and drainability issues. Lined vessels are also relatively uncommon due to issues related to liner integrity testing and the risks associated with liner failure.

8.4.3 Process/Product-Contact Surface Finishes

SS (300 series) typically is produced by cold rolling, which imparts a granular finish to the material based on the rolling mill used, hence the term "mill" finish. This finish is not precisely controlled and as a result, typically is not acceptable for high purity water applications and usually is subjected to subsequent enhanced finishing processes. Industry guidelines such as ASME BPE [37], or comparable guidelines in Europe and Asia (e.g., ISO [20] and JIS G [45, 46]) should be used.

It is common industry practice to use hygienic tube OD sized materials for high purity water applications with process/product finishes ranging from 30 μin (0.76 μm) Ra maximum to mirror-like surface finishes of < 15 μin (0.38 μm) Ra maximum. Two primary methods of interior polishing are used; mechanical polishing (using abrasives) and electropolishing (electrochemical). After either method, any polishing materials should be confirmed to have been completely removed so as not to accelerate corrosion or contaminate the water. Polishing materials should be free of animal-sourced materials. Some believe it is better to discourage the use of polishing compounds altogether.

The benefits of a specified finish should be weighed against the application and the risks associated with using a lower quality finish.

Systems operating at ambient temperature or with infrequent sanitization may benefit from a smoother surface finish. The interior surfaces of stainless tubing systems in high purity water service typically are polished to achieve a smooth surface with minimal roughness to enhance sanitization efficacy.

Historically, various terminologies have been used to refer to finish qualities, for example numeric systems, as well as systems that attempt to measure the average grit particles per inch for the polishing abrasives. These measurements have been superseded by the use of Roughness average (Ra) expressed in appropriate units (i.e., μin and/or μm) as the industry standard. Ra reflects the arithmetic mean of the surface deviations. Industry guidance documents (e.g., ASME BPE, ISO [37, 20]) define grades of surface finish with associated Ra values and provide recommendations for application.

Mechanical polish is frequently used and provides a suitable surface for most applications; however, this type of abrasive polishing has particular inherent deficiencies, including the tendency to enlarge the exposed surface area, mask surface imperfections, and require multiple steps to apply properly.

Mechanical polishing however typically reduces the size of voids, scratches, crevices and other surface anomalies and often improves cleanability (i.e., penetration and rinsing of chemical sanitizers). Refer to Chapter 5.4.

Electropolishing is a controlled electrochemical process (reverse of plating) that utilizes an acid electrolyte, DC current, anode, and cathode to smooth the surface of SS by removing metal. Electropolishing also improves corrosion resistance. This process normally occurs after a specified surface roughness is achieved through the application of progressively finer mechanical polishing abrasives to the material surface.

Electropolishing is primarily utilized on parts or components (e.g., tubing, fittings, valves, tanks – see ASTM A967 [56]) as the final fabrication step. Electropolishing of entire field welded distribution systems is most often impractical. It should be noted that surface passivation occurs simultaneously with electropolishing under proper conditions; however, the quality of passivation depends on the type of SS and the formulation of the electropolishing solution.

Welding (whether field or shop executed), mechanical cleaning, and certain chemical cleaning procedures can damage electropolished surfaces. Using common installation techniques that employ orbital welding, the relative surface area impacted is typically very small (< 1%).

For further information, see Chapter 10.

The advantages of electropolishing include:

•   Reduction of the height variations of the surface

•   Improved cleanability of the surface

•   Increasing the chromium to iron ratio (enhanced passivity) at the product-contact surface of SS

•   Revealing defects hidden by mechanical polishing

•   Removing impurities trapped below folded layers of mechanically formed ridges

•   Potential for delay of initial cell attachment and biofilm development

•   May allow for improved visual detectability of cleanliness (i.e., surface residues)

Smooth hydrophobic non-metallic surfaces have reportedly provided a benefit regarding slower initial cell attachment and biofilm development; however, current information is inconclusive and this option may not offer the same benefit as electropolished SS in this regard.

Non-metallic materials appropriately used for hygienic systems such as PVDF and PP are typically molded, drawn, or formed using dies that have been highly polished and impart that same finish to the parts made using them. These finishes are often equal to or better than the finishes on comparable SS parts. It is interesting to note however that SS parts are individually fabricated and finished, whereas non-metallic parts made from a common mold or die will carry the same finish as the die. If the die has a scratch, each fitting produced will carry the identical flaw.

8.4.4   Fabrication/Installation

The distribution network and storage systems should be installed in accordance with GEPs and should be fabricated, manufactured, procured, and installed in strict accordance with explicit procedures. Fabrication of the distribution system requires extreme care and precision to ensure a smooth process/product finish so as to minimize crevices, which may support or promote bacterial growth, corrosion, or particulate generation.

Gasketed hygienic joints properly assembled will typically not create an objectionable crevice. However, improperly assembled hygienic joints, especially if overtightened, create significant problems, including gasket extrusion into the process stream resulting in interference with drainability, possible flow restriction, gasket tears and resulting particles, crevices, etc.

When work is performed in a shop, areas dedicated to the fabrication of SS (or higher-grade alloys) are important, using either segregated facilities or adequate controls, to avoid contamination by carbon steel or other materials. All fabrication should be performed by certified welders in a controlled environment or under appropriate environmental conditions (e.g., wind, humidity, ambient temperature) to preclude contamination of equipment and material surfaces and to enable the welding process. Fabrication should follow an approved quality plan. There should be adequate documentation in the design and construction of the system, including up-to-date Piping and Instrumentation Diagrams (P&IDs), system isometrics, weld test reports, etc. A traceability matrix for validated systems, including all material certifications, should be included.

Bending SS tubing should be closely evaluated because of possible damage to the surface finish (see ASME BPE [37]). Additionally, bending SS tubing introduces areas of reduced wall thickness, which may result in lowered pressure capability or possible stress cracking.

Tubing welds, whether orbital or manual, should have a smooth internal diameter contour without excessive concavity or convexity, bead wandering, misalignment, porosity, or discoloration. One hundred percent photographic or radiographic analysis may not be cost effective or justifiable for every high purity water system. Appropriate sampling is strongly recommended. A defined weld inspection program should be established to ensure the quality of welding. This program should include the process for reworking or replacing rejected welds. In the EU, the welding procedures should comply with ISO 15607 and the welder should be qualified according to ISO 9606 and ISO 14732 for orbital welding [57, 58, 59].

When specified, appropriate non-metallic piping should be installed in accordance with the manufacturer's recommendations and with ASME BPE [37], following the guidelines for inspection and QC.

8.5 Microbial-Control Considerations

Given that microorganisms grow almost exclusively on surfaces, every wet surface associated with a water system is at risk of biofilm growth. For further information, see Chapter 13.

In the storage and distribution system, the impact of biofilm growth is in the final water quality as there is contamination from bacteria and the cellular components shed by that biofilm; therefore, consideration should be given to microbial control in all aspects of storage and distribution, including the following elements:

- The compatibility of the materials of construction with the various planned or even unplanned sanitization approaches

- Mechanisms for minimizing influx of planktonic organisms from upstream

- How it is designed and operated to minimize locations that facilitate biofilm development

- How it is designed and operated to effectively apply, distribute, and remove the sanitizing physical or chemical conditions that periodically kill and remove the developed biofilm, or continuously keep it from developing

8.5.1 Hygienic Design and Operational Controls

External contamination of a water system may be avoided by design and maintenance features such as:

- Air breaks at drains

- Functioning vent filters

- Rupture disks that are properly maintained and monitored

- Maintaining a relative high positive pressure on the distribution system to prevent the influx of contaminants

Distribution system components should be designed, fabricated, installed, maintained, and operated to ensure the chemical and microbial purity of the water. The water flow should be fully turbulent and well mixed to assist in maintaining system-wide uniformity in temperature and chemical content during sanitization. The resulting high flow rate also helps the development of only a tenacious type of biofilm that is minimally released or shed into the turbulent water when sanitizing conditions are not present.

Microbial control may be achieved by a comprehensive program involving multiple design features, routine operational and maintenance approaches, and sanitization activities that work together. Design and operational elements should combine to make water of an acceptable microbiological quality. If a program feature is deficient, microbial issues could be a recurring issue. The capital cost of appropriate design features and the operational cost of routine maintenance and sanitization typically are less than the cost of repeated remediation and investigation (as well as potential product loss and regulatory scrutiny). For further information, see Chapter 13.

8.5.2   Sanitization Designs

A distribution system should be designed with the capability of being sanitized using several methods in case one approach proves to be ineffective. For further information, see Chapter 13. Materials should be compatible with the sanitizing agent or condition. See Table 8.1 for various distribution system material compatibilities with common sanitizing agents and conditions.

Sanitization of a storage and distribution system using steam was a common practice 20–30 years ago. However, it resulted in increased equipment cost, greater component wear, and often extended downtime during sanitization cycles. Hence, the practice of hot water sanitization (in lieu of steam) has become most common because it is as effective (or in some cases more effective) than steam and can be implemented at lower equipment and operating cost. Hot water sanitization also eliminates the need for steam traps and related hardware as well as the associated intervention, making it easier to operate and far less costly to fully automate (see Chapter 13 for additional discussion).

Removal of the sanitizing agent or condition should be accounted for in the sanitization design. With the exception of heat and ozone, which can be neutralized or removed *in situ,* all other sanitants should be removed by flushing from the distribution system. A sloped and fully drainable system could facilitate more rapid removal of the sanitant, possibly using less rinsing water.

Rinse water should be available in an amount suitable for complete sanitant purging and of a chemical and microbiological purity that will not re-contaminate or re-inoculate the newly sanitized water system. This water can be provided from a reserved quantity of high-quality distribution system water stored prior to the sanitization procedure or may be freshly generated by the water purification system if available at a sufficient rate. The valves should be designed such that the sanitizing agents or conditions are able to contact all system surfaces, including bypass tubing and valves and associated components, and if needed, the internal surfaces of POU valves exposed only while the valves are open.

When post-sanitization system rinsing occurs, the flow path should allow sanitant purging from the system without the influx of contaminated air, as well as efficient rinsing to drain (or to a neutralization tank, depending on the sanitant employed and local plumbing codes), such that no tube section or valve is allowed to retain any unflushed sanitant.

8.5.3   System Sanitization

Microbial control usually can be achieved through a combination of distribution system design features, as well as effective periodic or continuous sanitization. For further information, see Chapter 13.

8.5.4 Monitoring for Sanitization Effectiveness and Ongoing Microbial Control

Microbial monitoring should be used to confirm the effectiveness of the sanitization process on an ongoing basis, including where the process has been validated as effective. Over time, biofilm development in a water system can affect a validated process unpredictably. If contamination is present immediately or very shortly after sanitization, then either there is an upstream source of ongoing contamination or an untreated area existed during the sanitization, such as a dead leg, unflushed port, or tank head space. If a subsequent large rebound in microbial counts is experienced about a week after sanitization, this may be an indication that the full depth of biofilm was not killed and the survivors rapidly regrew, for example, from the nutrients in the dead biomass. A more stringent or more frequently applied sanitization approach should be considered and documented via change control. For further information, see Chapter 13.

8.6   System Designs

This section provides information that may be useful in evaluating the advantages, disadvantages, and cost effectiveness of different designs commonly used to store and deliver water to use points. In addition, a method of selecting/optimizing system storage and distribution design is discussed.

System designs should meet defined user requirements, while providing reliability robustness and appropriate lifecycle cost. Examples of common storage and distribution design approaches are presented to help demonstrate the concept of optimal system design. Alternatives provided are intended to demonstrate key concepts, which when applied and properly operated, can result in an acceptable storage and distribution system. They are **not** intended to indicate that these are the only suitable designs.

8.6.1   General Considerations

Numerous criteria should be considered when evaluating alternative designs for storage and distribution systems. The design advantages and disadvantages should conform to the user requirements for the water. The optimal design of a pharmaceutical water storage and distribution system should accomplish the following:

•   Maintain the chemical and microbial quality of the water within acceptable limits

•   Minimize the conditions and locations that favor microbial growth

•   Deliver the water to the POU at the required flow rate, pressure, and temperature

•   Accommodate a suitable total instantaneous demand of water (i.e., diversity) to multiple POU

•   Minimize capital and operating costs

•   Ensure reliability while minimizing potential disruptions to operations

•   Account for the possibility of future expansion

Potential disruptions to water availability may be acceptable for brief periods of time (e.g., non-intrusive maintenance, utility outages) based on limited impact on microbial growth potential. However, the intrusion of external contamination during these brief periods may be of concern if the system were opened. Extended disruptions may increase the risk of contamination.

Continuous sanitizing conditions, such as with heat or ozone, minimize the potential for biofilm development.

8.6.2   Distribution Loop Velocity

The primary purpose for recirculated distribution is to reduce the release of biofilm organisms into the water by forcing them to tightly adhere to the interior surfaces of the distribution system. This is discussed in Chapter 13. Although the mechanisms are not universally agreed upon, it is thought that the velocity that meets or exceeds minimum turbulent flow standards reduces:

•   Initial attachment of bacteria to interior surfaces

•   Development of fragile biofilm structures that could easily slough-off

It is generally recognized that turbulent flow is indicated by a Reynolds number > 4000. Distribution systems have often been designed to operate with nominal flow velocities of ≥ 3 ft/s, which greatly exceeds the turbulent flow threshold, and therefore, may have a greater detriment on biofilm fragility and development. Selection of a design nominal velocity should be based upon reasonable specifications taking into account capital/operating cost, and assuming a fully flooded tube. The turbulent mixing effect can assist in minimizing dead legs but may not prevent fragile biofilm formation within the branch. In general, velocity may drop off for short periods of time during high use without adversely affecting performance, so long as positive pressure is maintained in the system. Circulation at higher velocities also helps to maintain a uniform temperature throughout the distribution system.

8.6.3   Storage and Distribution Decision Flowcharts

Decision flowcharts are presented to aid in determining which of the alternative designs best suits a particular application. In evaluating which configuration is optimal for a given situation, designers should comply with the user requirements. There may be multiple designs that will satisfy a particular application; designers should investigate the advantages and disadvantages of each option to support a decision.

The decision regarding storage alternatives can be made by evaluating the requirement for QA release of the water prior to use (Figure 8.1). If QA release is required, a batch storage approach may be most suitable. If the water can be utilized while quality analyses are ongoing, as is most often the case, a dynamic/continuous storage and distribution concept is most appropriate. Following the decision of the storage alternative, a designer can use the decision flowchart (Figure 8.2) to decide on additional attributes and the type of distribution system that best fits the application.

Figure 8.1: Storage and Distribution Decision Flowchart
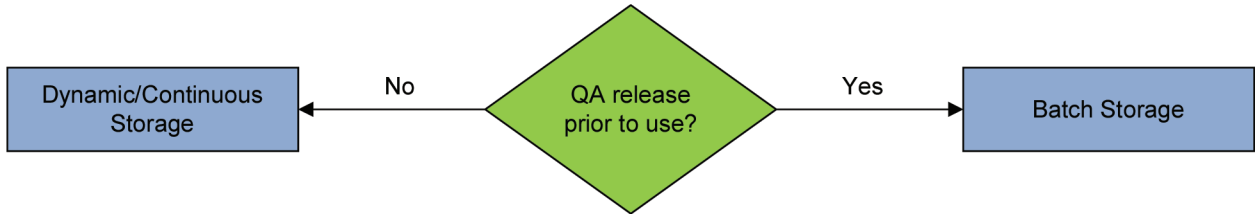
Figure 8.2: Distribution Decision Flowchart
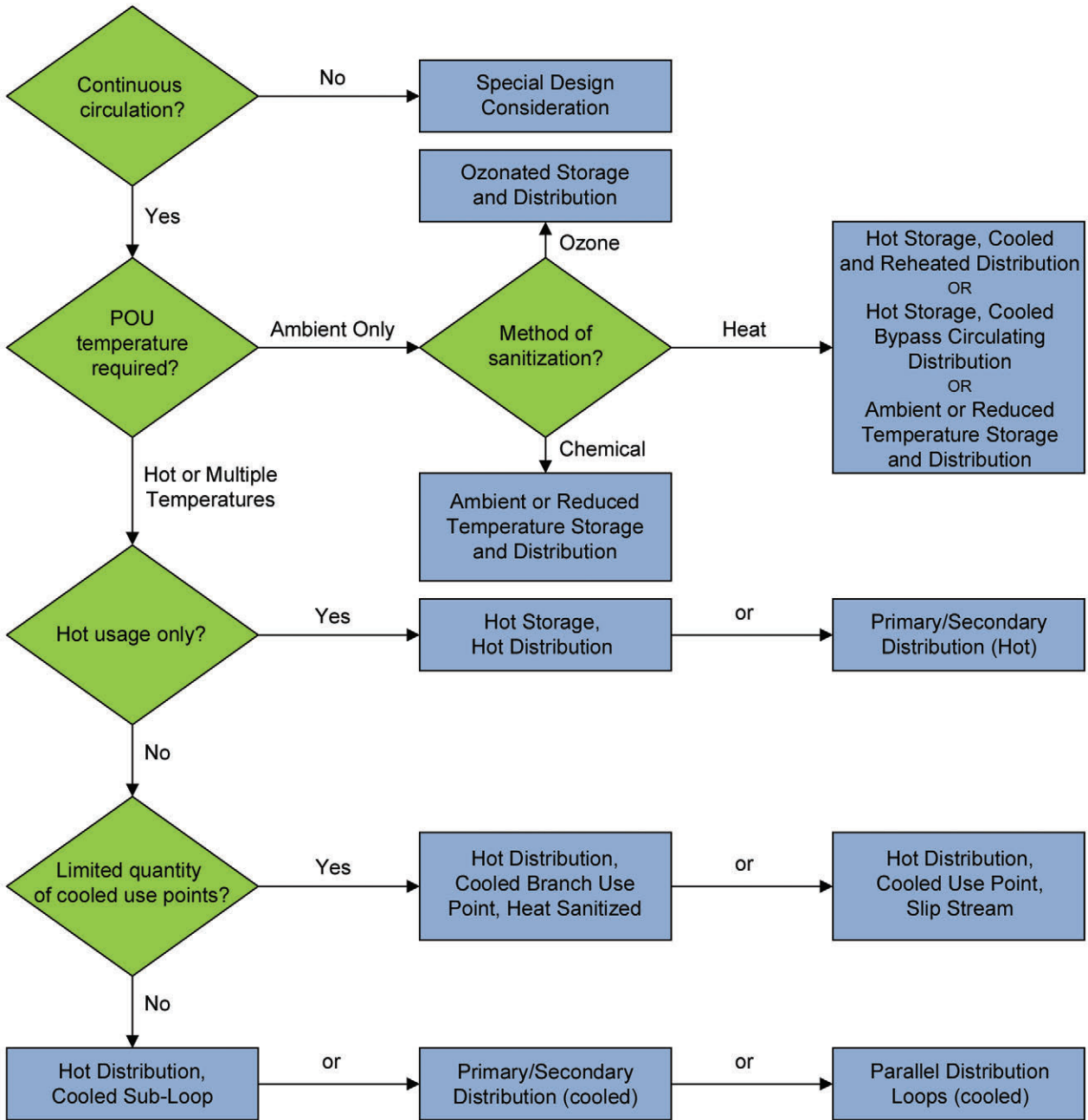
8.6.4   Storage and Distribution Design Concepts

The batch concept may use one or more storage tanks. With a single tank system, the vessel is filled with water that is then quality tested. With multiple tanks, one or more tanks may be filled and the water quality tested, while another is in service providing water to users. As batches are released and the in-service tank is emptied, tanks are rotated as necessary to meet demand. Batch systems limit production capability and are not common designs.

The dynamic/continuous storage and distribution concept offsets the peak instantaneous water demand put on the overall water system through use of a single water storage vessel. This vessel holds the generated and recirculated high purity water, and ultimately supplies it to users via the distribution system.

The advantages of the dynamic/continuous storage and distribution concept include continuous makeup, constant recirculation, and a significantly more efficient operation.

A storage and distribution system also may include equipment designed to maintain or modify attributes of the water, including heat exchangers for heating and/or cooling, UV lamps for microbial reduction, vent filters for microbial and particulate protection, and polishing equipment to maintain quality.

During storage and distribution design, the following additional considerations should be evaluated:

*   Loop configuration, including whether series or parallel loops are required, distribution loop POU, cooling requirements (steamable, sub-loop, or multiple branched heat exchanger assemblies), reheat requirements, secondary loop considerations, etc.

*   POU details including temperature, pressure, and flow rate (e.g., heat exchangers, pumps, flow devices)

*   Installation details (alcove, surface, direct, or cabinet mount) for POU protection/accessibility and room cleanability

*   Sanitization method (steam, hot water, ozone, or chemical)

8.6.5   Design Concepts

The figures that follow describe the systems that correlate to concepts in the accompanying decision trees (Figures 8.1 and 8.2) to successfully to store and distribute high purity water.

The concepts present simplified schematic diagrams (not meant to be P&IDs) of each configuration. System details including valves, instruments, and redundancy are not included unless specifically required for describing the system. Hot storage tanks (≥ 65°C (≥ 149°F)) typically are represented with steam jackets, but alternatively can use external heat exchangers in a circulating water loop. Vent filters are not shown with heating for simplicity, see Section 8.3.3. Advantages and disadvantages listed are not all inclusive.

Ambient or Reduced Temperature Storage and Distribution (Heat or Chemical Sanitization)

This system is most advantageous when the water is generated and used only at ambient temperature, and when there is adequate time for sanitization.

Configured in this manner (see Figure 8.3), water is stored and distributed at ambient or reduced temperature, with periodic sanitization accomplished by heating to sanitization temperature and circulating for an adequate amount of time, or operated hot for extended periods and cooled for use. Heat can be supplied to the water through the use of a tank jacket, or by a heat exchanger in a circulating loop. Alternatively, a sanitization chemical can be added to the system and then flushed, allowing the elimination of the sanitizing chemical. UV irradiation also can be included for reducing or impeding microbial growth. Cooling can be used to prevent temperature increases from pump and UV energy, for cool down after sanitization, and as a means for reducing or impeding microbial growth.

Figure 8.3: Ambient or Reduced Temperature Storage and Distribution (Heat or Chemical Sanitization)
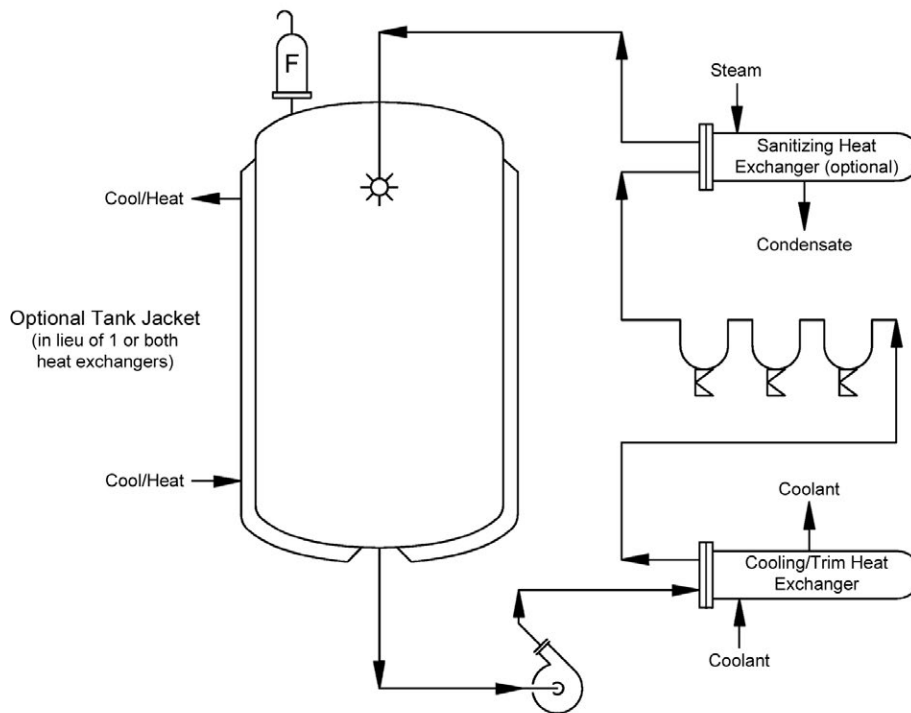
Advantages:

*   Well suited if water is generated and used at ambient temperature
*   Well suited for small systems
*   Reliable microbial control based on heat sanitization
*   Moderate capital and operating costs
*   Non-metallic materials of construction may be suitable based on the sanitization approach

Disadvantages:

*   Microbial control is a concern with chemical and/or infrequent sanitization
*   Cost of heat sanitization
*   Sanitization frequency and duration can limit water availability
*   Additional equipment may increase capital cost
*   If the water is generated hot, then this design increases operational costs and may not be energy efficient

Storage and Distribution with Continuous Polishing

Continuous polishing (maintaining or improving the quality of the water) can be included in the design of a storage and distribution system as a water QC mechanism. See Figure 8.4. The method of polishing includes technology common to purification (e.g., RO, DI, filtration, UF, etc.). Polishing the water may be achieved using a separate circulation loop off the storage tank that includes additional polishing equipment, or may include a POU that returns water for re-treatment by the primary generation system. The water source for the separate loop can be a separate pump or may be a branch off the main distribution loop. Flow balancing may be required to avoid over filling the storage tank or wasting polished water.

Figure 8.4: Storage and Distribution with Continuous Polishing
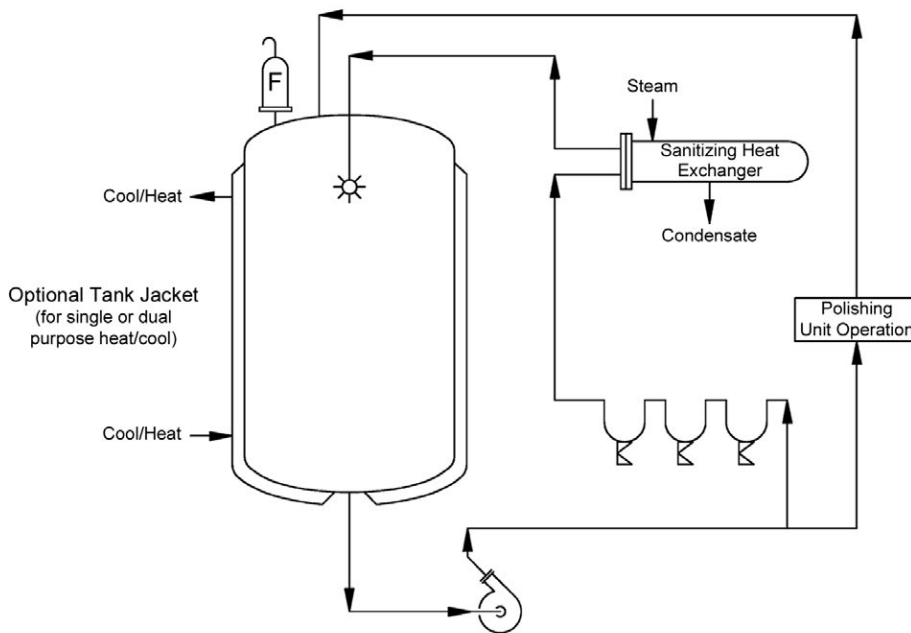
Advantages:

- Water quality continuously maintained
- Counteracts CO_2 absorption that leads to increased water conductivity
- Can maintain the quality of water stored over extended periods of low or no use

Disadvantages:

- Polishing equipment may not be compatible with periodic sanitization
- Operational issues with polishing equipment may compromise the system
- Flow balancing of polishing equipment may be required
- Post polishing filtration also may be necessary depending upon the polishing method
- Additional capital and operating cost with added polishing equipment
- May require additional tube/fittings and equipment space
- Most common for PW systems; not recommended for WFI

Ozonated Storage and Distribution

An ambient temperature storage and distribution system can be operated effectively with an ozonated storage and a periodically ozonated loop for microbial control. See Figure 8.5. Typical levels of 0.02–0.2 ppm of continuous ozone protect the water from microbial contamination.

Normally, two methods of generating ozone are employed: electrolytic and corona discharge. The corona discharge method generates ozone from oxygen or air, while the electrolytic method uses the oxygen that results from separating water molecules. Ozone should be completely removed from high purity water prior to usage by using UV irradiation, per USP PW and WFI requirements [4]. Ozone monitors also should be included to verify that ozone has been eliminated prior to the POU, to maintain consistent ozone levels, and to confirm loop sanitization. In addition, atmospheric ozone monitoring should be installed to address safety concerns (See Occupational Safety and Health Administration (OSHA) Standards (US) [60]).

Additional atmospheric monitoring of oxygen or hydrogen should be evaluated depending upon the technology and specific installation. Ozone should be periodically circulated through the distribution loop by de-energizing the UV light, as required for sanitization and controlling biofilm development. Typically, the level of ozone concentration during sanitization is increased. Refer to the *ISPE Good Practice Guide: Ozone Sanitization of Pharmaceutical Water Systems* [34].

Figure 8.5: Ozonated Storage and Distribution
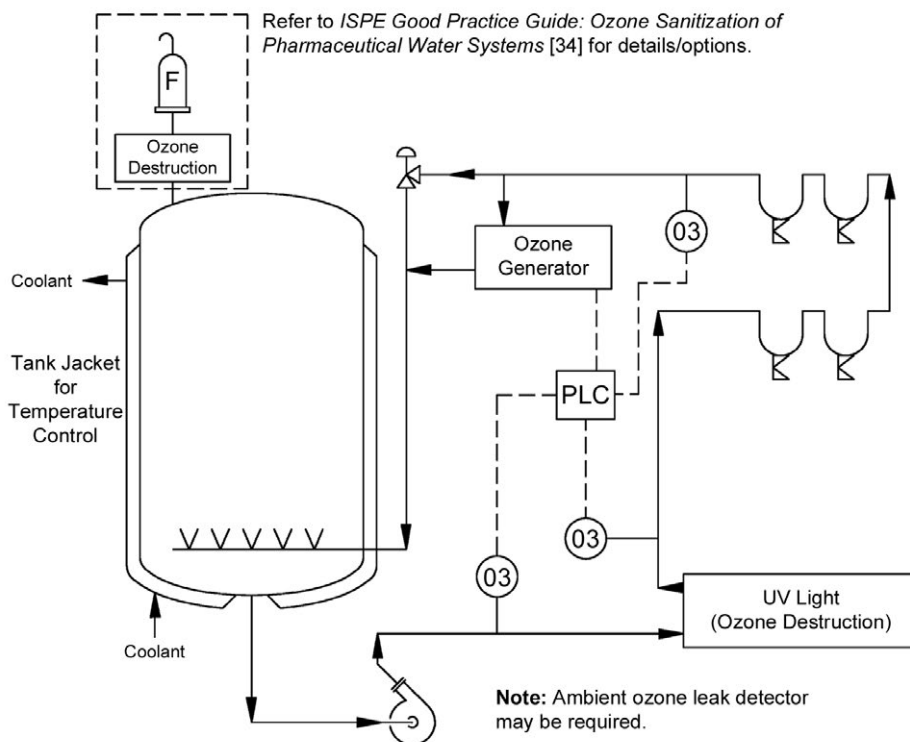
Advantages:

- Short sanitization time
- Excellent microbial control through biofilm prevention
- Tank and pump continuously sanitized
- Return water sanitized in tank
- Compatible non-metallic materials of construction may be considered

- No heat-related hazards during sanitization
- Low cost of operation

Disadvantages:

- Monitoring ozone removal is critical
- Ozone must be in contact with the microbe for effective kill
- Limited effectiveness in remediation of existing biofilm
- Safety concerns during operation and maintenance
- Water must be maintained at a cool temperature to allow the proper dissolution of ozone
- Additional capital and operational cost for monitoring equipment
- POU may require flushing for sanitization
- Safety concerns when flushing with ozone
- Possible concerns with drug product compatibility
- Ozone compatibility with many materials may be a significant concern
- Potential for conductivity increase during periods of low usage

Continuous Hot Storage and Distribution

This system consists of a hot storage tank and one or more hot distribution loops (see Figure 8.6). Temperature is maintained in the storage tank by heat supplied to the tank jacket or alternatively by a heat exchanger in the circulating loop. A sprayball is typically included in this design.

Figure 8.6: Continuous Hot Storage and Distribution
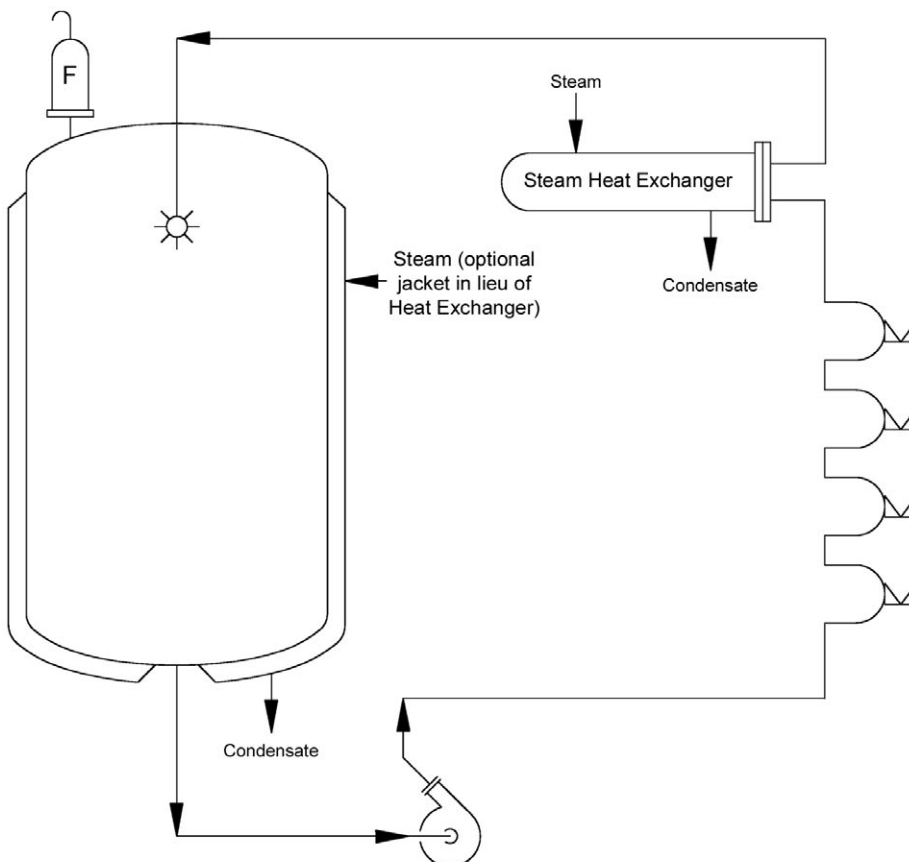
Advantages:

- Excellent microbial control
- Tank and loop sanitization is continuous if operated at a hot temperature (> 65°C (149°F))
- Extremely beneficial if water can be delivered hot to users
- Low capital cost based on minimum equipment required

Disadvantages:

- Heat-related hazards
- Design concerns with avoiding circulation pump cavitation
- Design concerns with condensation inside the vent filter
- Increased rouge potential versus ambient temperature system
- Insulation typically required
- Increased capital and operating cost if POU cooling is required

Hot Storage, Cooled, and Reheated Distribution

This design concept consists of a heated storage tank supplying a distribution loop that includes a cooling heat exchanger prior to the use points, followed by a heating heat exchanger prior to the tank return. See Figure 8.7. Hot water from the storage tank is cooled through the first heat exchanger, circulated to the POU, and then reheated in a second heat exchanger before returning to the storage tank. The purpose of this system is to maximize the time the water is at sanitization temperature and to only cool the water just prior to the POU. This design concept also allows the water to be used at hot temperatures. Sanitation of the use points is achieved by turning off the cooling medium on a periodic basis. To decrease energy and cooling media consumption, an economizing heat exchanger can be used that exchanges heat between the two high purity water streams (discharge and return).

Figure 8.7: Hot Storage, Cooled, and Reheated Distribution
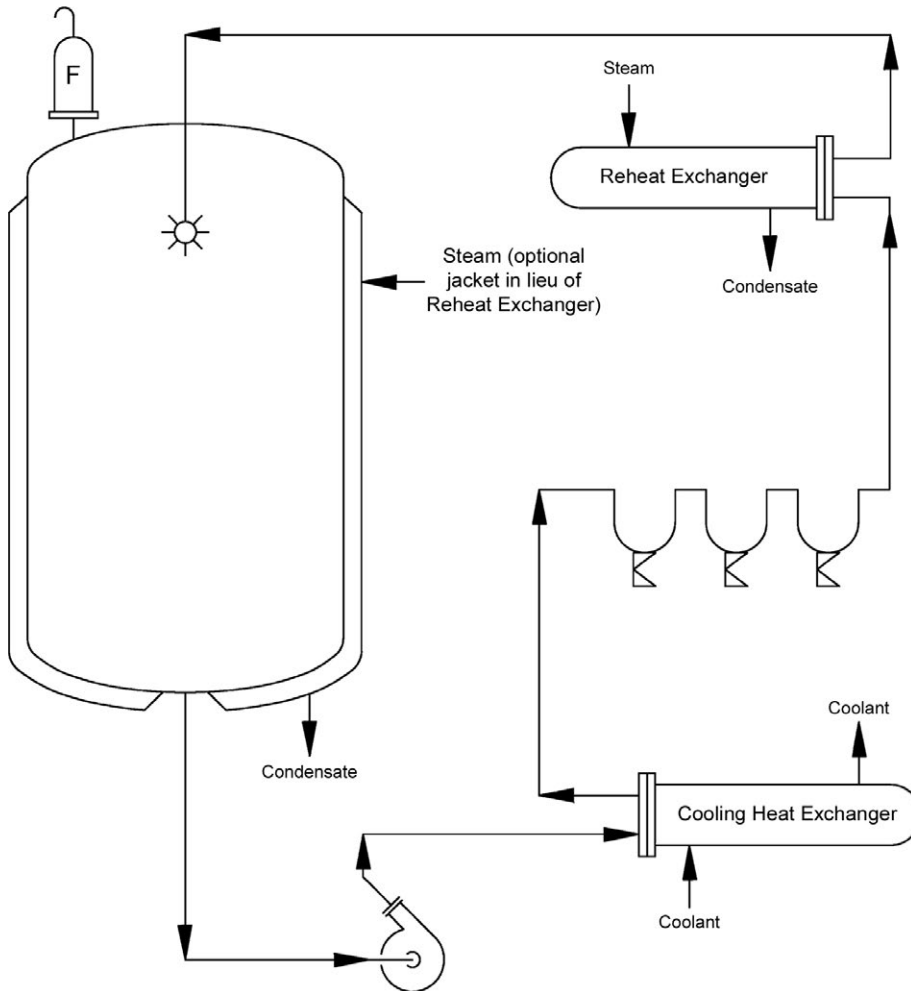
Advantages:

- Most suitable when water is generated hot
- Excellent microbial control
- Easily sanitized in a short period
- May be less costly than multiple POU coolers
- Tank and pump continuously sanitized

Disadvantages:

- Higher utility costs when heated and cooled
- All POU cooled simultaneously
- Heat-related hazards

<u>**Parallel Distribution Loops from a Single Tank**</u>

This system is a combination of multiple distribution loop schemes supplied by one storage tank. Figure 8.8 depicts a hot storage tank with two loops using a single pump, one hot and one cooled and reheated. The loops can be supplied by one pump or by separate pumps if greater reliability and separation is desired.

Figure 8.8: Parallel Distribution Loops from a Single Tank and Pump
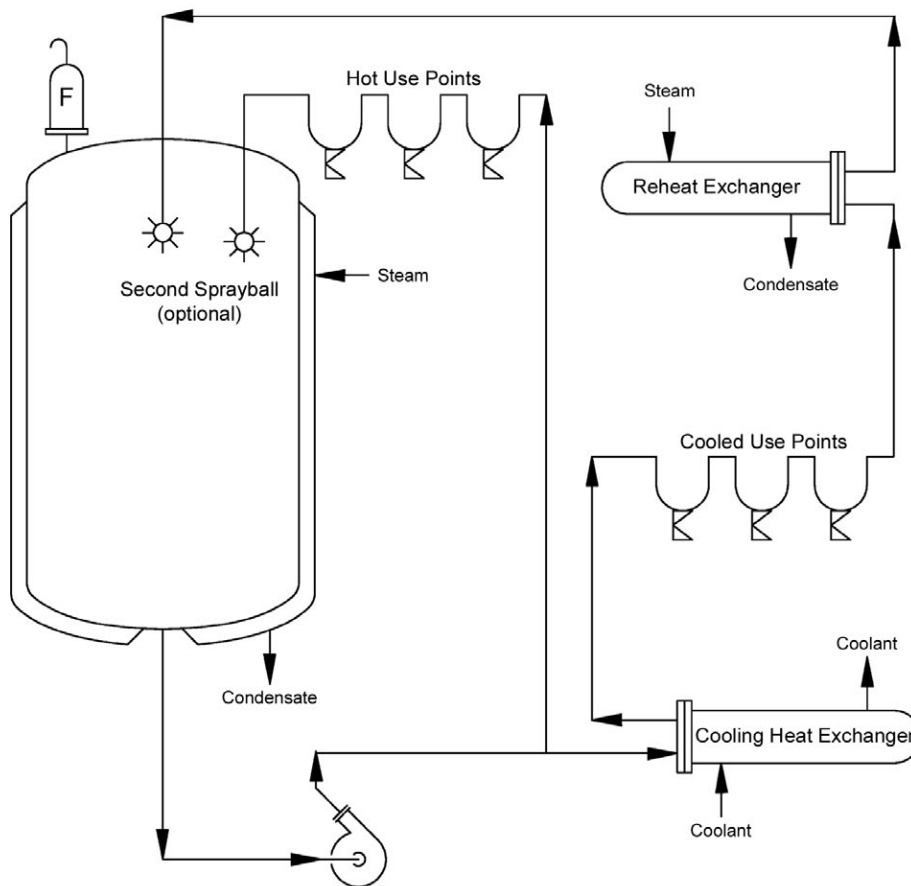
Advantages:

- Lower capital cost versus multiple tanks (and pumps)
- Capable of meeting multiple water temperature requirements
- Capable of serving multiple areas or a large area served by a centralized tank
- A heat recovery exchanger (economizer) may be added to reduce utility costs

Disadvantages:

- May be difficult to balance flow in multiple loops supplied by one pump
- Water returning from each loop must be reheated
- Contamination of one distribution loop results in contamination throughout the system
- Requires flow verification for each loop
- Maintenance or upgrades may require flow rebalance
- Higher utility costs when heating and cooling

Hot Storage, Cooled Bypass Circulating Distribution

This design concept includes hot storage with a cooled distribution system that bypasses a return to the storage tank and includes a cooling heat exchanger prior to the use points, as shown in Figure 8.9. Hot water from the storage tank is cooled through the heat exchanger, circulated to the POU, and then returned to the pump section. When water is drawn from a POU valve, hot water from the storage tank flows into the loop and is cooled by the heat exchanger.

The loop can be sanitized on a periodic basis by turning off the coolant and opening up the return valve to the storage tank, allowing hot water to flow through the loop. The returning of cooled water to the tank can be avoided by optionally flushing the lower temperature water to drain until the loop becomes hot and then return the flow to the storage tank. An alternative is to add a heat exchanger for periodic sanitization of the distribution loop independent of the storage tank. An additional alternative is to continuously return a small portion of the circulating water back to the tank.

Figure 8.9: Hot Storage, Cooled Bypass Circulating Distribution
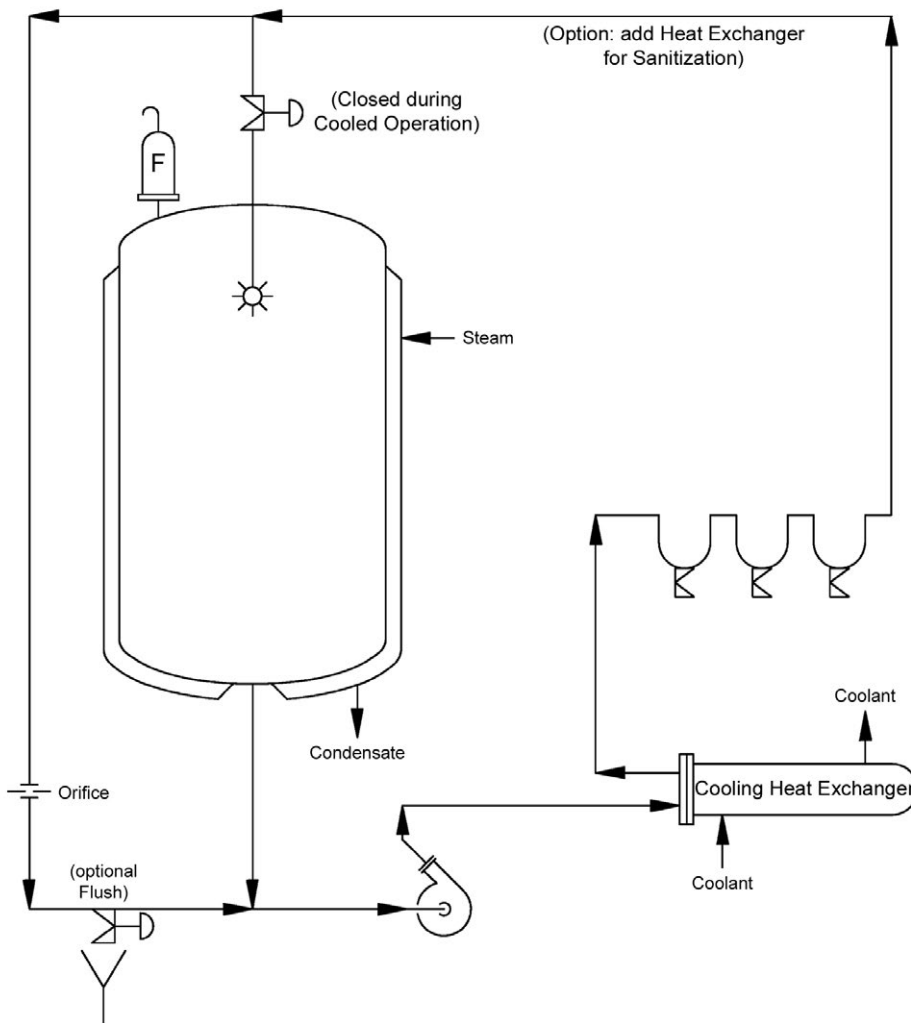
Advantages:

- Beneficial when the water is generated hot and cooled for use
- Excellent microbial control
- Easily sanitized in a short period
- Beneficial for multiple use points
- Lower energy consumption than reheating return water
- May be less costly than multiple POU coolers
- Possible to include multiple loops at different temperatures

Disadvantages:

- No circulation to tank without a separate loop (validate the time without circulation)
- All POU cooled simultaneously
- No mixed use
- Requires a properly designed hygienic orifice or control valve

<u>**Hot Distribution with Point of Use Cooling**</u>

This system consists of a hot tank and hot distribution loop, but has one or more POU requiring water at lower temperature that are equipped with POU cooling heat exchangers. See Figure 8.10. Hot water is flushed to drain through the POU heat exchanger for sanitization, and then cooled before opening up the POU valve. As an option, the use of Pure Steam can allow for sanitizing the exchanger and downstream distribution on demand. Alternatively, multiple POU valves can be included in the distribution from the cooling exchanger; however, multiple POU valves can pose a higher risk of microbial contamination.

POU cooling applications may require additional features to ensure they remain as clean as possible. Blow down with appropriately clean air may be required to eliminate standing water. Automation may also be desirable to reduce the risk of improper operation.

POU exchangers are most advantageous when there are both hot and lower temperature water use points off the same loop, and the number of low temperature users is small. Since they maintain the water hot until it is drawn from the loop, they provide excellent microbial control, provided there is active use and consideration given to flushing/sanitizing if infrequently used. As the number of low temperature users increases, the capital costs and space requirements become prohibitive, and one of the other configuration examples should be considered. Water consumption is high because of flushing, although this is minimized by the scheme shown. Energy consumption is moderate because only water drawn out of the loop is cooled. Maintenance requirements are high because of the added exchangers and valves. Complexity is high as each exchanger should be properly flushed and sanitized. Each drop is limited in capacity by the sizing of the exchanger.

Figure 8.10: Hot Distribution with Point of Use Cooling
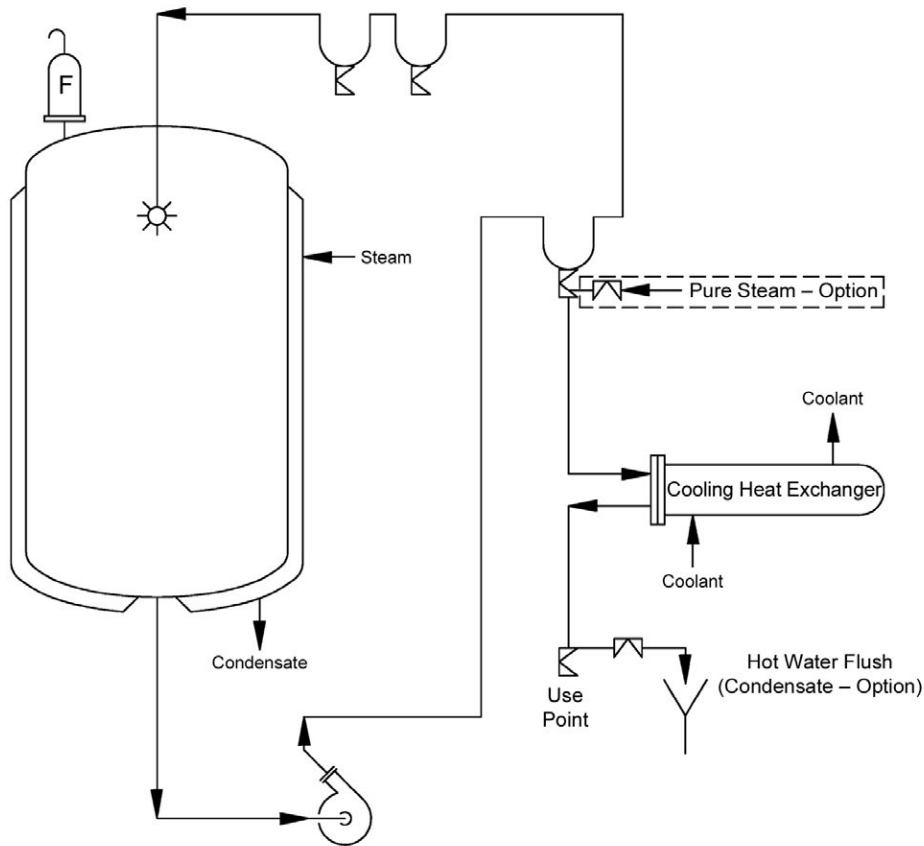
Advantages:

- Beneficial when only needed at minimum quantity of POU
- Cools only the water used with moderate energy consumption

Disadvantages:

- Higher cost for multiple reduced temperature use points
- Wastes water due to flushing to achieve temperature
- Drain quenching (cooling) may be required prior to discharge
- Heat-related hazards

Hot Distribution with Cooled Sub-Loop

This system, shown in Figure 8.11, includes a pumped, cooled sub-loop off the main hot distribution loop to provide the reduced temperature water to one or more POU. The secondary pump provides the circulation through the cooling heat exchanger, to the use points, through the sanitization heat exchanger, returning to the pump. The water in the sub-loop circulates, but does not return to the main loop. The cooled sub-loop is a tankless design and requires a method to avoid backflow into the main loop (i.e., block-and-bleed)

Figure 8.11: Hot Distribution with Cooled Sub-Loop
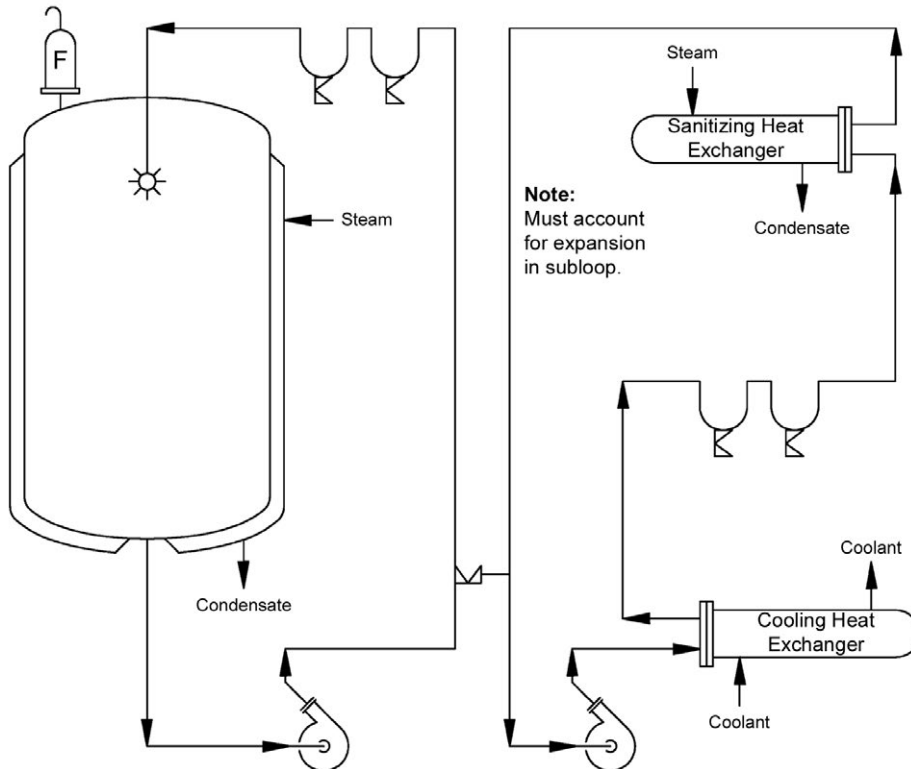
Advantages:

• Can be used for multiple cooled use points
• Continuous flow through sub-loop
• POU can be heated or cooled
• Eliminates the cost and space required for additional tankage
• Minimizes the contamination of the entire system by sub-loop

Disadvantages:

• Water expansion during sanitization of the sub-loop must be addressed
• May require a hot loop to operate at higher pressure
• Periodic sanitization required of the sub-loop
• May require periodic purging of the cooled sub-loop

<u>**Primary/Secondary Distribution**</u>

Primary/secondary distribution consists of a primary storage and distribution system that then supplies one or more remote secondary storage and distribution systems POU. See Figure 8.12.

Figure 8.12: Primary/Secondary Distribution
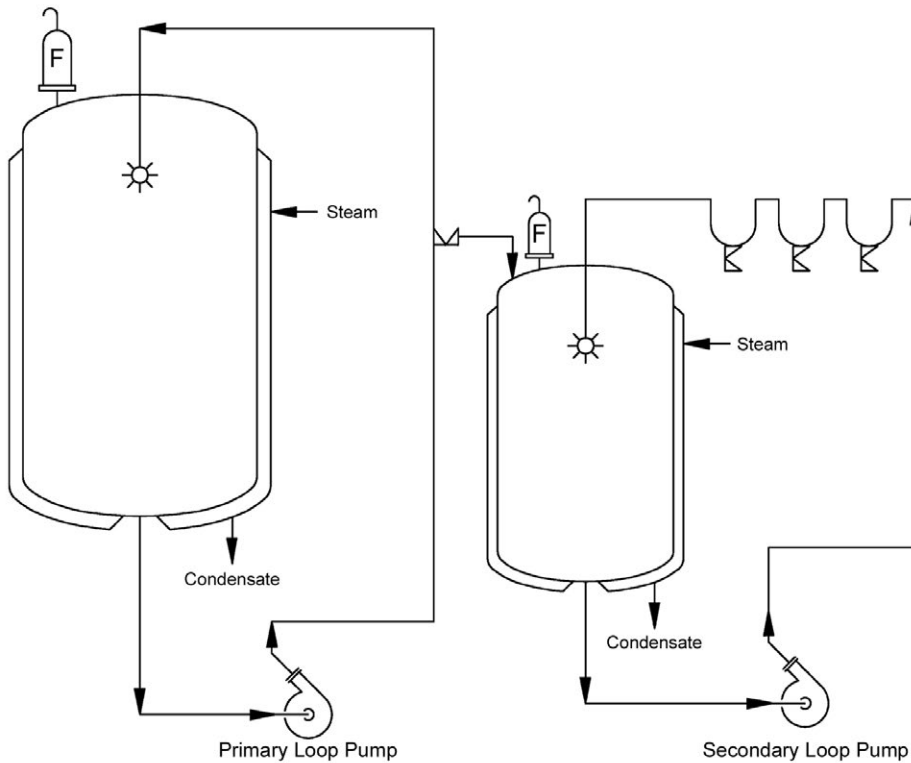
Advantages:

- Allows the installation of smaller diameter tubing to service a localized area in lieu of extending a large diameter loop
- Avoids routing multiple distribution loops from a storage tank to the manufacturing areas
- Well suited for multiple areas served by centralized storage
- Allows flexibility and diversity in delivery
- May allow for servicing a secondary area without additional treatment equipment

Disadvantages:

- Additional capital cost and possible higher operating cost

8.7   Sampling at Point of Use and Dedicated Sample Valves

The location and installed orientation of POU valves and sample valves often pose significant sampling issues. A simple manual or automated POU valve that is easily accessible can be sampled representative of the way the high purity water is used, provided it is of suitable size; however, the addition of a hose to the POU, sampling a remote location, or the direct connection to a tank or other equipment can significantly complicate sampling methodology.

Refer to the *ISPE Good Practice Guide: Sampling for Pharmaceutical Water, Steam, and Process Gases* [33] for additional information regarding sample valve, methods, and installation practices.

9 Laboratory Water

9.1 Introduction

Laboratory water requirements may differ from those for manufacturing. This chapter provides an overview of the available approaches for laboratory water purification and distribution, as well as a step-by-step method to help determine what type of system design best meets a user's needs.

9.2 System Design Considerations

Water quality requirements for laboratory purposes vary widely depending upon the type of analysis to be performed, requirements for testing with compendial water, and the governing organization. Non-pharmacopeial related agencies that cover water quality for laboratory purposes, such as ISO, ASTM, and Clinical and Laboratory Standards Institute (CLSI) [20, 18, 61], typically are used as a source of information.

The wide range of user needs leads to a variety of possible approaches, so specific laboratory user information is necessary to design a cost effective and efficient solution. The design team should understand related design information such as:

Defining User Needs

- What laboratory tasks require water?

- What quality of water is needed for each task?

- What are the regulations that must be complied with?

- Where is the location of each task?

- Is there a work pattern for each task?

- Can these tasks be clustered in various laboratory locations (e.g., by water quality needed, analytes of concern)?

- Can one group of tasks be served by a single POU outlet?

- How much water is needed at each POU and by task or task group?

Solution Design Based on User Needs

- How many POU are needed?

- What water characteristics (quality, etc.) are needed at each POU?

- What purification technologies could be used to produce the water qualities required?

- Does water need to be distributed to more than one location?

- Other parameters to be considered, such as:

  - Building characteristics

  - Laboratory architecture

- Criticality of water in the process

- Water source options

- Ergonomics of use points and drains

- Economics

9.3 Determining User Needs

9.3.1 Quality Needs

Laboratories often require a selection of waters with distinct purity specifications, dependent upon analytical applications and regulatory requirements. Compendial procedures need to use water meeting appropriate compendial water quality attributes.

Potential impurities in PW may be grouped into:

- Inorganic ions (typically monitored by conductivity or resistivity, or by specific chemical tests)

- Organic compounds (typically monitored by TOC or by specific tests)

- Bacteria (monitored by total microbial plate counts or other methods)

- Endotoxins (monitored by LAL test)

- Nucleases (monitored by specific enzyme assays)

- Particulates (typically managed by filtration)

- Gases (typically managed by degasification /purification equipment and monitored by specific tests, if required)

Within any of these groups, particular substances also may have a specific interference in a particular test, such as components that produce overlapping peaks in chromatography or contaminants in the water that are identical to the analytes in the test sample.

Table 9.1 provides guidance regarding the types of impurities that may be important for an application when selecting a water purification system. Quantified impurity levels are not provided because of the wide variations in water purity needed within any one type of application. Table 9.1 is intended primarily for the design engineer without an analytical laboratory background, and can serve as a basis of discussion with laboratory personnel regarding water grade/purity needs.

Table 9.2 lists the purity specifications for commonly used laboratory water grades. These should be thought of as minimum specifications. Additional considerations may be listed in source documentation for these water grades. A laboratory's water purity needs for particular applications may exceed minimum requirements for a specific attribute of a given water grade. More stringent requirements and additional purification technologies may be applied to maintain several attributes at lower levels. Conversely, the most suitable water grade for a particular application may exceed the purity needs of specific attributes for the application. Unless otherwise mandated by regulatory requirements, the water purity provided may be optimized with the water purity needed. Maintenance of a higher water purity than needed by applications can be costly and usually is unnecessary, unless it is a regulatory requirement or expectation.

Table 9.1: Importance Level (widely observed) for Parameters/Contaminants in Different Techniques[1]

Technique	Application Sensitivity[2]	Importance Level of the Water Contaminants					
		Inorganic Ions	Organic Compounds	Particulates	Bacteria	Endotoxin	Nuclease
Bacterial Culture	Low – High	Low	Medium	Medium	Medium	Low	Low
Clinical Biochemistry	High	Medium	Low	High	Medium	Low	Low
Electrochemistry	Low – High	Medium – High	Medium – High	Medium	Low – High	Very Low	Very Low
Electrophoresis (Polyacrylamide Gels)	High	High	High	Medium	High	Low	Low (High for Protease)
Electrophoresis (Agarose Gels)	High	High	Medium	Medium	High	Low	High
Electrophysiology	Low – High	High	High	Medium	High	High	High
ELISA	Low – High	Low	Medium	Medium	High	Low	Low
Endotoxin Determination	Medium – High	Low – High	Medium – High	Medium – High	High	High – Very High	Low
Flame-AAS	Low – High	High	Low	Medium	Medium	Very Low	Very Low
GF-AAS	High	Very High	High	High	High	Low	Low
GC	Low – High	Low – High	Medium – High	Medium	Low – High	Very Low	Very Low
GC-MS	High	High	High	Medium	High	Very Low	Very Low
General Wet Chemistry	Low – High	Low	Low	Medium	Low	Very Low	Very Low
Glassware Washing	Low – High	Low – High	Medium – High	Medium	Low – High	Low	Very Low – Low
Histology	Low – High	Low	Medium	Medium	Medium	Medium	Very Low
HPLC	Low – High	Low – High	Medium – High	High	Low – High	Low	Very Low – Low
LC-MS	High	High	High	High	High	Low	Low
Hydroponics	Low – High	Low	Medium	Medium	Low	Very Low	Very Low
ICP-AES	High	High	Medium	Medium	High	Very Low	Very Low
ICP-MS	High	Very High	High	High	High	Very Low	Very Low
Immunocytochemistry	High	High	High	High	High	High	Medium
Ion Chromatography	Low – High	Medium – Very High	Medium – High	High	Medium – High	Very Low	Very Low
Mammalian Cell and Tissue Culture	High	High	High	High	High	Very High	High
Microbiological Media Preparation	Low – High	Low	Medium	Medium	High	Low	Very Low
Microbiological Analysis	Low – High	Low	Medium	Medium	High	Medium	Low
Molecular Biology	High	High	High	High	High	Low – Medium	Very High
Monoclonal Antibody Research	High	High	High	High	High	Very High	Low
Plant Cell and Tissue Culture	High	High	High	High	High	Medium	Medium
Radioimmunoassay	Low – High	Low	Medium	Medium	High	Very Low	Very Low
Solid Phase Extraction	High	Medium	High	Medium	Medium	Low	Low
Spectrophotometry	Low – High	Low	Medium	High	Low	Very Low	Very Low
Steam Generation	Low – High	Low	Medium	Medium	Low	Low	Very Low

Table 9.1: Importance Level (widely observed) for Parameters/Contaminants in Different Techniques[1] (continued)

Technique	Application Sensitivity[2]	Importance Level of the Water Contaminants					
		Inorganic Ions	Organic Compounds	Particulates	Bacteria	Endotoxin	Nuclease
TOC Determination	High	High	High	Medium	High	Medium	Low
Trace Metal Detection	High	Very High	High	Medium	High	Low	Low

Notes:

1. Table 9.1 is provided as an example of the widely observed importance level of a selection of water quality parameters/contaminants in different laboratory techniques. The level of importance depends on the sensitivity expected for the application, the material used, the method applied, and the regulatory constraints. A range of levels is listed for a number of attributes because of the wide variety in water purities needed for the many forms of the technique and types and levels of analytes involved.

2. Application sensitivity refers to the level of analyte detection, quantitation, or contaminant impact expected with that application. Typically: High = ppb or higher sensitivity levels, Medium = ppm to ppb sensitivity levels, and Low = ppm or lower sensitivity levels

AAS = Atomic Absorption Spectroscopy	ICP-AES = Inductively Coupled Plasma Atomic Emission Spectroscopy
ELISA = Enzyme-Linked Immunosorbent Assay	
GC = Gas Chromatography	ICP-MS = Inductively Coupled Plasma Mass Spectrometry
GF-AAS = Graphite Furnace Atomic Absorption Spectroscopy	LC-MS = Liquid Chromatography Mass Spectrometry
HPLC = High Performance Liquid Chromatography	TOC = Total Organic Carbon

Table 9.2: Specification Summary for Various Non-Pharmacopeial Water Grades that may be used in Pharmaceutical Laboratories

Organization/ Reference	ISO3696 (1995) [62] Water for Analytical Laboratory Use			ASTM D1193 (2018)[1] [63] Standard Specification for Reagent Water				ASTM D5196 (2013) [64]	CLSI 4th Ed (2006) [61]
Water Grade or Type	Grade 1	Grade 2	Grade 3	Type I	Type II	Type III	Type IV	Standard Guide for Bio-Applications Grade Water	CLRW (Specified Quantitative Attributes Only)
Specified Source and Purification Approaches	Grade 2 Source; RO + 0.2 μm Filtration or DI + 0.2 μm Filtration or Re-Distillation in glass)	Multiple-Distillation or DI or RO+DI	Single-Distillation or DI or RO	Distillation or equivalent + Mixed Bed DI + 0.2 μm Filtration	Distillation	Distillation, DI, EDI, and/ or RO + 0.45 μm Filtration	Distillation, DI, EDI, and/ or RO	Drinking Water Source; Suitable process(es)	*
pH value at 25°C (77°F) (inclusive range)	*	*	5.0 to 7.5	*	*	*	5.0 to 8.0	*	*
Conductivity μS/ cm at 25°C, max	0.1	1.0	5.0	0.0555	1.0	0.25	5.0	*	0.1
Resistivity MΩ-cm at 25°C, min	*	*	*	18	1.0	4.0	0.2	18.2 ± 1 [2]	10
Temperature Compensated Conductivity Measurement?	YES	YES	YES	YES	YES	YES	YES	YES	YES
TOC (as C), maximum	*	*	*	50 μg/l (50 ppb)	50 μg/l (50 ppb)	200 μg/l (200 ppb)	*	20 μg/l (20 ppb)	500 ppb
Oxidizable matter O₂ content mg/l, maximum	*	0.08	0.4	*	*	*	*	*	*
Absorbance at 254 nm and 1 cm optical path length, absorbance units, maximum	0.001	0.01	*	*	*	*	*	*	*

Table 9.2: Specification Summary for Various Non-Pharmacopeial Water Grades that may be used in Pharmaceutical Laboratories (continued)

Organization/ Reference	ISO3696 (1995) [62] Water for Analytical Laboratory Use			ASTM D1193 (2018)[1] [63] Standard Specification for Reagent Water				ASTM D5196 (2013) [64]	CLSI 4th Ed (2006) [61]
Water Grade or Type	Grade 1	Grade 2	Grade 3	Type I	Type II	Type III	Type IV	Standard Guide for Bio-Applications Grade Water	CLRW (Specified Quantitative Attributes Only)
Specified Source and Purification Approaches	Grade 2 Source; RO + 0.2 µm Filtration or DI + 0.2 µm Filtration or Re-Distillation in glass)	Multiple-Distillation or DI or RO+DI	Single-Distillation or DI or RO	Distillation or equivalent + Mixed Bed DI + 0.2 µm Filtration	Distillation	Distillation, DI, EDI, and/ or RO + 0.45 µm Filtration	Distillation, DI, EDI, and/ or RO	Drinking Water Source; Suitable process(es)	*
Residue after evaporation on heating at 110°C (230°F), mg/Kg, maximum	*	1	2	*	*	*	*	*	*
Silica (as SiO₂) mg/l, maximum	0.01	0.02	*	*	*	*	*	*	*
Total Silica µg/l, maximum	*	*	*	3	3	500	*	*	*
Sodium µg/l, maximum	*	*	*	1	5	10	50	*	*
Chloride µg/l, maximum	*	*	*	1	5	10	50	*	*
Heterotrophic Bacteria Count cfu/ml, maximum	*	*	*	Type A: 0.01 (10 cfu/ 1000 ml)	Type A: 0.01 (10 cfu/ 1000 ml)	Type A: 0.01 (10 cfu/ 1000 ml)	Type A: 0.01 (10 cfu/ 1000 ml)	1 (100 cfu/ 100 ml)	10
	*	*	*	Type B: 0.1 (10 cfu/ 100 ml)	Type B: 0.1 (10 cfu/ 100 ml)	Type B: 0.1 (10 cfu/ 100 ml)	Type B: 0.1 (10 cfu/ 100 ml)		
	*	*	*	Type C: 10 (100 cfu/ 10 ml)	Type C: 10 (100 cfu/ 10 ml)	Type C: 10 (100 cfu/ 10 ml)	Type C: 10 (100 cfu/ 10 ml)		
Bacterial Endotoxins EU/ ml or IU/ml	*	*	*	Type A: 0.03	Type A: 0.03	Type A: 0.03	Type A: 0.03	0.01	*
	*	*	*	Type B: 0.25	Type B: 0.25	Type B: 0.25	Type B: 0.25		
	*	*	*	Type C: *	Type C: *	Type C: *	Type C: *		
Particulate and Colloids	Implied limitation by 0.2 µm filter	*	*	Implied limitation by 0.2 µm filter	*	Implied limitation by 0.45 µm filter	*	*	Implied limitation by 0.22 µm filter
Nucleases, Proteases	*	*	*	*	*	*	*	Limited as needed for certain applications	*

Notes:

*Not Specified, Not Required, Not Applicable, or No Limit

1. Water may be produced with alternate technologies if specifications are met and water is appropriate for the application.
2. If in-line resistivity testing is not possible, then the total concentration of inorganic ions must not exceed 2 µg/L for cations such as Aluminum, Ammonium, Arsenic, Cadmium, Chromium, Cobalt, Copper, Iron, Lead, Magnesium, Nickel, Potassium, Sodium, Titanium, Zinc, and anions such as Chloride, Nitrate, Phosphate, Sulfate, and Fluoride [64].

Table 9.3 lists the pharmacopeial specifications for GMP water used for manufacturing. These should be considered when there is a need to replicate manufacturing conditions.

Table 9.3: Specification Summary for Various Pharmacopeial Water Grades That May Be Used in Pharmaceutical Laboratories – Part 1: European, Japanese, US, and Indian Pharmacopoeias

Organization/ Reference	European Pharmacopoeia 9.8 (2019)			Japanese Pharmacopoeia XVII (2016)			US Pharmacopeia 42 (2018)		Indian Pharmacopoeia (2018)	
Water Grade or Type	Purified Water	Water for Injection	Highly Purified Water[5]	Water	Purified Water	Water for Injection	Purified Water	Water for Injection	Purified Water	Water for Injections
Specified Source and Purification Approaches	Drinking Water Source; Dist or DI or RO or other suitable methods	Drinking Water Source; Distillation or purification process equivalent	European Pharmacopoeia (Ph. Eur.) Commission Suppressed Highly Purified Water (HPW) from the Ph. Eur. effective 01APR2019	Japanese Drinking Water (Water Supply Law, Ordinance No.101, Article 4, 2003)	"Water" Source; RO, UF, Deionization, Distillation, or a combination thereof	Water or Purified Water Source; Distillation or RO-UF	Drinking Water Source; Suitable process	Drinking Water Source (US, EU, Japan, WHO); Distillation or equivalent/ superior process	Drinking Water Source; Dist or DI or RO or other suitable methods	Purified Water Source; Distillation or equivalent/ superior process
Description	Clear and colorless liquid	Clear and colorless liquid		*	Clear and colorless liquid having no odor	Clear and colorless liquid having no odor	*	*	Clear, colorless, odorless liquid	Clear, colorless, odorless liquid
pH value at 25°C (inclusive range)	*	*		*	*	*	*	*	*	*
Acidity or Alkalinity	*	*		*	*	*	*	*	MRed – not red, BTBlue – not blue	MRed – not red, BTBlue – not blue
Conductivity µS/cm @25°C, maximum	5.1[1]	1.3[1]		*	2.1[2] [1.3[1] in JP Info Ch 21]	2.1[2] [1.3[1] in JP Info Ch 21]	1.3[1]	1.3[1]	5.1[1]	1.3[1]
TOC (as C), maximum	0.5 mg/l (500 ppb)[3] [Alt to Ox Sub]	0.5 mg/l (500 ppb)[3]		*	0.50 mg/l (500 ppb)[3]	0.50 mg/l (500 ppb)[3]	Instrument response to 0.50 mg/l standard (500 ppb)[3]	Instrument response to 0.50 mg/l standard (500 ppb)[3]	0.5 mg/l (500 ppb)[3] [Alt to Ox Sub]	0.5 mg/l (500 ppb)[3]
Oxidizable Substances (Permanganate Red. Subst.)	Negative to test of 0.1 ml of 0.02M KMnO$_4$ [Alt to TOC]	*		*	*	*	*	*	Negative to test of 0.1 ml of 0.02M KMnO$_4$ [Alt to TOC]	*
Residue after evaporation on heating at 105°C, mg/100 ml, maximum	*	*		*	*	*	*	*	*	*

Notes:

*Not Specified, Not Required, Not Applicable, or No Limit

1. In-line/Stage 1 Conductivity specification at 25°C with other values at other temperatures. Ph. Eur.'s WFI and USP's PW and WFI additionally have off-line Stage 2 and 3 specifications which may alternatively be met.
2. Performed as an atmosphere and temperature equilibrated test. Alternatively, per JP Chapter 21, the test may be performed in-line with the specified limit at 25°C and other values at other temperatures. There is no USP <645> Stage 3-like option in JP.
3. Due to significant figures, Ph. Eur.'s, MP's, and IP's TOC specifications are not greater than 549 ppb, whereas JP's, ChP's, BrP's and USP's are not greater than 504 ppb.
4. Not required if Conductivity meets WFI specifications.
5. Deleted in 2019.
6. If private sourced water is used, must comply with Japanese Drinking Water, plus this Ammonia limit.
7. Used where high biological quality required.

Table 9.3: Specification Summary for Various Pharmacopeial Water Grades That May Be Used in Pharmaceutical Laboratories – Part 2: Chinese, Brazilian, Mexican, and International Pharmacopoeias

Organization/ Reference	Chinese Pharmacopoeia (2015)		Brazilian Pharmacopoeia 5 (2010)			Pharmacopoeia of the United Mexican States 12 (2018)			International Pharmacopoeia 8th Edition (2018)	
Water Grade or Type	Purified Water	Water for Injection	Purified Water	Water for Injection	Ultrapure Water	Purified Water Level 1	Purified Water Level 2[7]	Water for Injection	Purified Water	Water for Injections
Specified Source and Purification Approaches	Drinking Water Source; Dist or DI or RO or other suitable methods	Purified Water Source; Distillation	Drinking Water Source; Dist or DI or RO or other suitable methods	Properly Treated Water Source; Distillation	Purified Water Source; supplemental purification with Dist, DI, RO, other	Drinking Water Source; Dist or RO or DI or Other	Drinking Water Source; e.g., 1P/2P RO; UF, DI, EDI	Potable Water Source; Dist or equivalent	Suitable Water Source; Dist, DI, RO, or other suitable methods	Potable or Purified Water Source; Distillation
Description	Clear, colorless liquid, odorless	Clear, colorless liquid, odorless	Clear, colorless, tasteless, odorless liquid	Clear, colorless, tasteless, odorless liquid	Clear, colorless, tasteless, odorless liquid	Transparent and colorless liquid	Transparent and colorless liquid	Transparent and colorless liquid	Clear, colorless liquid; odorless	Clear, colorless liquid; odorless
pH value at 25°C (inclusive range)	*	5.0–7.0	*	*	*	5.0–7.0	*	*	*	*
Acidity or Alkalinity	MRed – not red, BTBlue – not blue	*	MRed – not red, BTBlue – not blue	MRed – not red, BTBlue – not blue	*	*	*	*	MRed – not red, BTBlue – not blue	MRed – not red, BTBlue – not blue
Conductivity µS/cm @25°C, maximum	5.1[1]	1.3[1]	1.3 (Alt to NH_3, Ca/Mg, Cl, NO_3, SO_4)	1.3 (Alt to NH_3, Ca/Mg, Cl, NO_3, SO_4)	0.1	5.1[1]	1.3[1]	1.3[1]	*	*
TOC (as C), maximum	0.50 mg/l (500 ppb)[3] [Alt to Ox Sub]	0.50 mg/l (500 ppb)[3]	0.50 mg/l (500 ppb)[3] [Alt to Ox Sub]	0.50 mg/l (500 ppb)[3] [Alt to Ox Sub]	0.05 mg/l (50 ppb) [Optional, application-specific]	0.5 mg/l (500 ppb)[3] [Alt to Ox Sub]	0.5 mg/l (500 ppb)[3]	0.5 mg/l (500 ppb)[3]	*	*
Oxidizable Substances (Permanganate Red. Subst.)	Negative to test of 0.10 ml of 0.02M $KMnO_4$ [Alt to TOC]	*	Negative to test of 0.2 ml of 0.02M $KMnO_4$ [Alt to TOC]	Negative to test of 0.2 ml of 0.02M $KMnO_4$ [Alt to TOC]		Negative to test of 0.1 ml of 0.02M $KMnO_4$ [Alt to TOC]	*	*	Negative to test of 0.5 ml of 1% $KMnO_4$	Negative to test of 0.2 ml of 0.02M $KMnO_4$
Residue after evaporation on heating at 105°C, mg/100 ml, maximum	1	1	*	*	*	*	*	*	1 (5 mg from 500 ml)	1 (5 mg from 500 ml)

Notes:

*Not Specified, Not Required, Not Applicable, or No Limit

1. In-line/Stage 1 Conductivity specification at 25°C with other values at other temperatures. Ph. Eur.'s WFI and USP's PW and WFI additionally have off-line Stage 2 and 3 specifications which may alternatively be met.
2. Performed as an atmosphere and temperature equilibrated test. Alternatively, per JP Chapter 21, the test may be performed in-line with the specified limit at 25°C and other values at other temperatures. There is no USP <645> Stage 3-like option in JP.
3. Due to significant figures, Ph. Eur.'s, MP's, and IP's TOC specifications are not greater than 549 ppb, whereas JP's, ChP's, BrP's and USP's are not greater than 504 ppb.
4. Not required if Conductivity meets WFI specifications.
5. Deleted in 2019.
6. If private sourced water is used, must comply with Japanese Drinking Water, plus this Ammonia limit.
7. Used where high biological quality required.

Table 9.3: Specification Summary for Various Pharmacopeial Water Grades That May Be Used in Pharmaceutical Laboratories – Part 1: European, Japanese, US, and Indian Pharmacopoeias (continued)

Organization/Reference	European Pharmacopoeia 9.8 (2019)			Japanese Pharmacopoeia XVII (2016)			US Pharmacopeia 42 (2018)		Indian Pharmacopoeia (2018)	
Water Grade or Type	Purified Water	Water for Injection	Highly Purified Water(5)	Water	Purified Water	Water for Injection	Purified Water	Water for Injection	Purified Water	Water for Injections
Specified Source and Purification Approaches	Drinking Water Source; Dist or DI or RO or other suitable methods	Drinking Water Source; Distillation or purification process equivalent	*(HPW column: European Pharmacopoeia (Ph. Eur.) Commission Suppressed Highly Purified Water (HPW) from the Ph. Eur. effective 01APR2019)*	Japanese Drinking Water (Water Supply Law, Ordinance No.101, Article 4, 2003)	"Water" Source; RO, UF, Deionization, Distillation, or a combination thereof	Water or Purified Water Source; Distillation or RO-UF	Drinking Water Source; Suitable process	Drinking Water Source (US, EU, Japan, WHO); Distillation or equivalent/ superior process	Drinking Water Source; Dist or DI or RO or other suitable methods	Purified Water Source; Distillation or equivalent/ superior process
Heterotrophic Bacteria Count cfu/ml, maximum	Action Level 100 [in monograph, mandatory]	Action Level 0.1 (10 cfu/100 ml, 200 ml test) [in monograph, mandatory]		*	Action Level 100 (R2A) [in Info Ch 21,non-mandatory]	Action Level 0.1 (10 cfu/100 ml) (R2A) [in Info Ch 21, non-mandatory]	100 (optimal medium) [in Info Ch 1231, non-mandatory]	0.1 (optimal medium) (10 cfu/100 ml, 200 ml test) [in Info Ch 1231, non-mandatory]	100 (R2A) Absence specified pathogens [in monograph, mandatory]	0.1 (10 cfu/100 ml, 200 ml test) [in monograph, mandatory]
Bacterial Endotoxins EU/ml or IU/ml (note ≤ or <)	< 0.25 (dialysis solutions only)	< 0.25		*	*	< 0.25	*	< 0.25	≤ 0.25 (dialysis solutions only)	≤ 0.25
Chloride µg/l, maximum	*	*		*	*	*	*	*	*	*
Sulfate, ppm, maximum	*	*		*	*	*	*	*	*	*
Calcium and Magnesium ppm, maximum	*	*		*	*	*	*	*	*	*
Carbon Dioxide ppm, maximum	*	*		*	*	*	*	*	*	*
Ammonia ppm, maximum	*	*		0.05(6)	*	*	*	*	*	*
Nitrates ppm, maximum	0.2	0.2		*	*	*	*	*	0.2	0.2
Nitrites ppm, maximum	*	*		*	*	*	*	*	*	*
Aluminium ppb, maximum	10 (dialysis solutions only)	10 (dialysis solutions only)		*	*	*	*	*	10 (dialysis solutions only)	10 (dialysis solutions only)
Heavy Metals ppm, maximum	0.1(4)	*		*	*	*	*	*	0.1(4)	*

Notes:

*Not Specified, Not Required, Not Applicable, or No Limit

1. In-line/Stage 1 Conductivity specification at 25°C with other values at other temperatures. Ph. Eur.'s WFI and USP's PW and WFI additionally have off-line Stage 2 and 3 specifications which may alternatively be met.

2. Performed as an atmosphere and temperature equilibrated test. Alternatively, per JP Chapter 21, the test may be performed in-line with the specified limit at 25°C and other values at other temperatures. There is no USP <645> Stage 3-like option in JP.

3. Due to significant figures, Ph. Eur.'s, MP's, and IP's TOC specifications are not greater than 549 ppb, whereas JP's, ChP's, BrP's and USP's are not greater than 504 ppb.

4. Not required if Conductivity meets WFI specifications.

5. Deleted in 2019.

6. If private sourced water is used, must comply with Japanese Drinking Water, plus this Ammonia limit.

7. Used where high biological quality required.

Table 9.3: Specification Summary for Various Pharmacopeial Water Grades That May Be Used in Pharmaceutical Laboratories – Part 2: Chinese, Brazilian, Mexican, and International Pharmacopoeias (continued)

Organization/ Reference	Chinese Pharmacopoeia (2015)		Brazilian Pharmacopoeia 5 (2010)			Pharmacopoeia of the United Mexican States 12 (2018)			International Pharmacopoeia 8th Edition (2018)	
Water Grade or Type	Purified Water	Water for Injection	Purified Water	Water for Injection	Ultrapure Water	Purified Water Level 1	Purified Water Level 2[7]	Water for Injection	Purified Water	Water for Injections
Specified Source and Purification Approaches	Drinking Water Source; Dist or DI or RO or other suitable methods	Purified Water Source; Distillation	Drinking Water Source; Dist or DI or RO or other suitable methods	Properly Treated Water Source; Distillation	Purified Water Source; supplemental purification with Dist, DI, RO, other	Drinking Water Source; Dist or RO or DI or Other	Drinking Water Source; e.g., 1P/2P RO; UF, DI, EDI	Potable Water Source; Dist or equivalent	Suitable Water Source; Dist, DI, RO, or other suitable methods	Potable or Purified Water Source; Distillation
Heterotrophic Bacteria Count cfu/ml, maximum	100 (R2A) [in monograph, mandatory]	0.1 (R2A) (10 cfu/ 100 ml, 200 ml test) [in monograph, mandatory]	1 (100 cfu/ 100 ml) using any valid method; also absence of *E. coli* and *P. aeruginosa* [in monograph, mandatory]	0.1 (10 cfu/ 100 ml) 200 ml, using any valid method) [in monograph, mandatory]	0.01 (1 cfu/ 100 ml, 200 ml test) [in monograph, mandatory]	*	*	*	*	*
Bacterial Endotoxins EU/ ml or IU/ml (note ≤ or <)	*	<0.25	*	≤ 0.25	*	*	*	< 0.25	*	≤ 0.25
Chloride µg/l, maximum	*	*	pass	pass	*	*	*	*	pass	pass
Sulfate, ppm, maximum	*	*	pass	pass	*	*	*	*	pass	pass
Calcium and Magnesium ppm, maximum	*	*	1	1	*	*	*	*	pass	pass
Carbon Dioxide ppm, maximum	*	*	*	*	*	*	*	*	pass	pass
Ammonia ppm, maximum	0.3	0.2	0.2	0.2	*	*	*	*	pass	pass
Nitrates ppm, maximum	0.06	0.06	0.2	0.2	*	0.2	0.2	0.2	pass	pass
Nitrites ppm, maximum	0.02	0.02	*	*	*	*	*	*	*	*
Aluminium ppb, maximum	*	*	*	*	*	*	*	*	*	*
Heavy Metals ppm, maximum	0.1	0.1	*	*	*	0.1	*	*	pass	pass

Notes:

*Not Specified, Not Required, Not Applicable, or No Limit

1. In-line/Stage 1 Conductivity specification at 25°C with other values at other temperatures. Ph. Eur.'s WFI and USP's PW and WFI additionally have off-line Stage 2 and 3 specifications which may alternatively be met.

2. Performed as an atmosphere and temperature equilibrated test. Alternatively, per JP Chapter 21, the test may be performed in-line with the specified limit at 25°C and other values at other temperatures. There is no USP <645> Stage 3-like option in JP.

3. Due to significant figures, Ph. Eur.'s, MP's, and IP's TOC specifications are not greater than 549 ppb, whereas JP's, ChP's, BrP's and USP's are not greater than 504 ppb.

4. Not required if Conductivity meets WFI specifications.

5. Deleted in 2019.

6. If private sourced water is used, must comply with Japanese Drinking Water, plus this Ammonia limit.

7. Used where high biological quality required.

The water grades denoted in Tables 9.2 and Table 9.3 frequently do not specify limits for all the groups of impurities. This is particularly marked for the USP, Ph. Eur., and JP specifications for grades of pharmaceutical water [4, 5, 6]; such grades may not be appropriate for all laboratory-related uses. For water to be appropriate for a particular application, its suitability for the intended purpose should be verified and the consistent, reliable production of water of suitable purity should be ensured.

In addition to their purity specifications, waters that need to meet regulatory requirements may have additional requirements, including:

- Which feed water source is to be used

- Limitations on how the water is to be purified

- How and where the purity attributes are to be monitored

- How the monitoring equipment is to be calibrated

- How the purification system performance is to be trended and maintained

Where a particular type of water is specified, for example, when using an ASTM method, these requirements must be met by the purification system selected.

Where laboratory water quality needs differ from those of manufacturing (e.g., microbiological limits), it may be necessary to establish laboratory water specifications or process control parameters to avoid requiring the laboratory to use water attributes and limits replicating manufacturing water standards that may not be required.

9.3.2   Quantity Needs

The water demand profile at each POU location is needed to size the water generation system(s) and determine if any distribution loops are needed. The water demand/diversity information should include:

- Volume delivery information, including maximum demand

- Batch or continuous delivery needs as well as maximum and average flow rates

- Time required to deliver the specified quantity of water

- Frequency of use or operation

- Pressure

- Temperature

These values should be obtained or estimated in real time, as well as over an operating shift or day. Normal and worst-case water usage profiles should be prepared for 8 hour, 24 hour and 7 day periods. This information, along with diversity of use, dictates the design specification for the system(s).

9.3.3   Data Collection

Table 9.4 provides an example table for data collection.

Table 9.4: Example User and Water Data Collection Worksheet

User		Water Quality Need		Water Quantity Need							
Location[1]	Laboratory Analysis or Equipment	Regulatory Requirement if Applicable (e.g., GMP, GLP, ISO, CLSI) [65, 20, 61]	Purity of Water Needed as Required by Equipment or Procedure	Use Rate of Equipment or Task[2]	Duration	Estimated Volume Per Use	Number of Uses Per Day[3]	Volume Used Per Day	Water Temperature Needed	Water Pressure Needed	Comments[3]

Notes:
1. Floor, room, and area (e.g., tech support or QA).
2. For example: glassware washer, pipette washer, autoclave, or task/analysis.
3. Often several uses will always be sequenced together. For example, glass washer and autoclave. This should be noted in the comment section to ensure that Step 1 (glass wash cycle) is not considered without Step 2 (autoclave wash cycle) in a demand profile.

Water use information should be compiled and grouped according to the layout and common test requirements. For example, one POU may be used to supply water for several laboratory analyses.

9.3.4 Monitoring Needs

Monitoring requirements for water purification systems should be assessed. It should be established that a water purification system produces water of suitable purity fit for its intended purpose. Process control testing should be considered to ensure effective component operation and to minimize operational cost and quality risks with the knowledge that it may not be practical or cost effective to monitor all, or even many, potential impurities after each stage of purification in laboratory equipment. Tests to ensure that the water purification and distribution systems are working adequately usually are performed in addition to the measurement of specific control checks (e.g., baseline blanks) as part of test procedures. A general approach is shown in Table 9.5.

Table 9.5: Monitoring Requirements for Types of Impurities

Impurity Type	Monitoring	Type	Location	Frequency
Ions	Conductivity or Resistivity	In-line	Pre/Post RO, post IX, post EDI, product	During operation
Organics	TOC	Online or off-line	Product	During operation or occasionally
Particles	Particle count*	Online	Product	Very rarely used
Bacteria	TVC, epifluorescence	Off-line	Product	Typically weekly (use dependent)
Endotoxins	LAL	Off-line	Product	Occasionally (use dependent)
Large Bio-active Molecules	Specific tests	Off-line	Product	Occasionally (use dependent)
Gases	Specific tests	Online	Product	As required
*Normally managed by filtration				

Key parameters that should be measured or used include:

- Resistivity for ionic contamination

- TOC for organic impurities

- Total viable counts as a measure of bioburden

Where biological contamination is critical, measurements of endotoxin and nuclease levels also can be valuable. Concentrations of weakly-ionized silicon and boron species may be controlled by suitable system design, and if required, specific monitoring.

Generally, parameters are measured in the product water or as close to the dispense point as practical. This gives values for the water actually used and avoids breaking into the water purification circuit. The exception is resistivity, which is measured in-line at several points. It provides an indication of RO, EDI, and IX performance and can be measured after, and on occasion, before (calculation of percent rejection) these technologies.

The frequency of off-line measurements varies considerably. It should be based on an assessment of the effects of loss of water purity and the likelihood of a water quality excursion. Confidence obtained by regular, relatively frequent logging, initially coupled with the utilization of statistical tools, may enable the period between analyses to be decreased with time. Particular care should be taken after activities that may introduce impurities, such as routine maintenance, changing components, and sanitization.

Based on system design, scale differences, or regulatory requirements, the same design concepts normally are not applied for similar functionality exactly or systematically to both large (production) systems and small (laboratory) water systems. Parameters monitored in large water systems may not be systematically measured in small systems. Comparing the rationale of monitoring to the constraints involved, for example, the importance of making a microbiological measurement between two purification stages that are located close to one another, compared to the risks/constraints of installing a sampling port between the two purification elements, may be used as justification for the difference in approach.

This difference in approach also could be linked to the water system design selected. A laboratory water system should not be considered a "black box." The control of intermediate water purification operations in the system allows for improved process control and the anticipation of problems, thereby improving compliance with good practices. Depending on regulatory or other requirements, an analysis of the equipment design/content may be required to ensure compliance.

The extent of monitoring required depends on the size and complexity of the system(s); see Section 9.5.

9.3.5 Compliance

Laboratory equipment may require compliance with various regulations including:

* Quality management systems (e.g., Good Laboratory Practices, GMPs [64])

* Pharmacopeia (e.g., USP, Ph. Eur., JP [4, 5, 6]

* CFR [65, 66] or local regulations

* Other water standards (e.g., ISO, ASTM, CLSI [20, 18, 61])

Additional regulations also may be requested (e.g., CE, UL marks [67, 68] as a general organizational policy requirement or for local legal compliance; therefore, it is important to list the compliance needs prior to selecting the final laboratory water solution.

9.3.6 Laboratory Environmental Needs

A comprehensive review of all the laboratory work spaces requiring access to laboratory water should be performed to select suitable systems that meet user requirements, including:

* Quantity of POU needed

* Location of the different areas needing water and the possibility to group them

* Physical location of each POU (e.g., rooms, elevation, at sinks)

* Use constraints defined by some procedures including:

  - Maximum distance to the use location

  - Filling large containers

  - Large flow rates

* Site-location constraints including:

  - Limited access (e.g., clean room, off hours use)

  - Contaminating atmospheric conditions (e.g., volatile organics, corrosive vapors)

  - Noise considerations

  - Utilities available (e.g., electricity, source water, drain)

  - Space available

9.3.7 Costs

A comprehensive cost analysis that includes the direct and indirect lifecycle costs of the proposed laboratory water options should be developed and reviewed by QA/QC, manufacturing, engineering, facilities, and regulatory stakeholders.

Some of the direct lifecycle costs for the system are:

- Capital costs

    - Engineering

    - Equipment and material procurement

    - Construction/installation

    - Commissioning/qualification

- Operating costs

    - Consumables (e.g., filters)

    - Utilities (e.g., water, energy)

    - Calibration

    - Maintenance

    - Training

Note: More automated systems may be more expensive to purchase but less expensive to operate.

Indirect costs are an estimate of the potential costs in case of problems. Such an analysis should minimally cover the cost associated with water quality or quantity problems (e.g., when facing a lack of suitable water over several hours or days).

9.4   Water Purification Technologies

There are various combinations of purification technologies with which it is possible to produce the waters used in laboratories. The technologies are similar in type to those used for production purposes, although usually on a smaller scale and different in detail. For further information, see Chapters 4 and 5.

Central water purification plants have scope for the full range of technologies described in Chapters 4, 5 and 6, however, smaller systems with single or multiple POU have restricted options due to limitations in space, cost, and the availability of dedicated personnel to maintain them. These restrictions do not have to reduce the quality of the water produced but potential users need to be aware of these factors when choosing and operating such systems.

Laboratory systems are usually fed with municipal water or partially treated municipal water. They often include the following stages:

1. Pretreatment, to avoid overloading later purification stages and to protect the RO membrane

2. RO filtration to remove most impurities

3. Optional IX or EDI to reduce the level of inorganic impurities

4. Storage in a reservoir for partially PW

5. The stored water can be further purified in various ways:

    a. The stored water is used as a feed to a polishing loop, which can include exposure to UV light, IX, carbon absorption, filtration and monitoring for resistivity and possibly, TOC.

    b. The stored water is recirculated through some or all of these purification and monitoring technologies and returned to the reservoir. The RO permeate may also be fed directly into this loop to purify it before it enters the reservoir.

    c. The stored water can be pumped directly to the POU through some or all of these technologies.

    d. One or more dispense points are normally included in these systems and POU filtration can be fitted to the dispense points.

Pretreatment is included to remove chlorine and excessive levels of particulates that could damage or block the RO membrane. Very low-usage systems may need minimal or no pretreatment.

RO systems allow the passage of a percentage of the feed water as a PW permeate and reject to drain the remaining water containing increased levels of impurities. As much as 90% of the feed water can be rejected. Various approaches are used to minimize this.

The rate of production of RO permeate from small RO units is typically too low for direct use and a water reservoir is commonly included. This reservoir can also be used as a source of intermediate grade PW. To increase the purity of the water stored in the reservoir, it is possible to pass the RO permeate directly through an ion exchange pack or an EDI module before entering the reservoir. Recirculation through purification technologies and returning this water to the storage tank will also purify the reservoir water effectively. The RO permeate is not sterile and it is important that the size of the reservoir used and the design of the system minimizes the time that water remains static with technologies in place to remove bacteria and their by-products, when appropriate, from the water. Systems should also be kept operational on an ongoing basis to minimize static water.

UV exposure will control bacterial growth and, if a suitable UV source is used, convert residual organics into ionized compounds, which can be removed by subsequent IX. To achieve the lowest TOC levels, exposure to short wavelength UV is strongly recommended (see Chapters 4 and 5 for additional details).

IX resins are invariably contained in a variety of plastic (usually polypropylene or polyethylene) packs. Various mixtures and types of anion and cation resins are used and virtually ionic impurity-free water can be produced by these mixed-bed resin packs. Packs may contain high purity activated carbon to help remove organics. EDI may also be used in polishing loops. Electronic sensors can be used to detect, identify, and monitor packs and their status.

IX packs need to be replaced periodically when their IX capacity is diminished. Various approaches are used to detect when to change packs. The simplest is to set an alarm on the resistivity sensor to identify when the product water resistivity has fallen. However, this leaves the possibility of weakly bound ions, including boron and silicon species, and organics being released from the pack and contaminating the product water. This can be avoided by changing the packs early while they still have sufficient capacity left. An alternative is to split the IX capacity in two and monitor the resistivity between them. When the capacity of the first pack is used up the second pack has most of its capacity remaining, eliminating the risk of ionic-impurity release. Both packs can be changed at this point or the second pack can be moved to the first position, making more effective use of the IX capacity.

UF can be fitted within a polishing circuit to remove any particles and large organic molecules including endotoxins, RNase and DNase. They can also be installed at POU.

Dispense points can take various forms and often several use points can be fitted to a purification system. Useful features include flexible outlets and a means to easily dispense preset volumes. 0.2 µm filters are often fitted to dispense outlets to remove bacteria and minimize back contamination of the system. Alternatively, positively charged filters and UF can be used to remove endotoxins or other materials. For dedicated outlets for specific applications, other media may be fitted as POU devices.

Recirculation is generally beneficial to maintain water purity by minimizing bacterial buildup and repeatedly passing the water through purification technologies. Periodic recirculation is used to accomplish the same bacterial benefit while minimizing any rise in temperature.

9.5   Laboratory Water Supply Options

There are a range of means to provide pure water for laboratory applications. For applications of low volume or that are localized to one area, the choice usually is between a single dedicated water purification system, typically fed from municipal water, and packaged water.

For larger scale installations, a water purification solution can be based on the combination of one or more approaches, including:

- A purification system with a permanent extensive distribution system to the entire building

- One or more local purification systems with a local distribution loop to a floor or laboratory

- Small purification system with local storage and loop

- Individual POU units supplied with municipal water or partially PW

- An extension of a distribution system used for pharmaceutical production

- Water polishers or dispensers fed from any of these distribution systems

9.5.1   Water Generation System and Distribution Options

When water is required at multiple locations or when large volumes of water are necessary, several different design possibilities exist:

Large – Central System for the Entire Building

A large makeup system for which the generation and storage is in one location, with pure water distributed to several laboratories or floors, can provide water throughout an entire building. These systems typically are custom designed. POU can be connected directly from the distribution loop or the loop water can be treated by local polishers (units designed to further purify the water) to give enhanced purity to meet specific application requirements.

Use of redundant makeup water purification systems providing pure water to the same storage reservoir and distribution loop, and located in the same location provides redundancy at the primary makeup level, reducing the risk of completely shutting down a facility. See Figure 9.1. When one system is down for routine maintenance or service, the other system can continue to provide pure water. On the other hand, the redundant equipment must not be allowed to remain stagnant for extended periods of time or other risks to water quality will occur.

Figure 9.1: Example of a Central System

◊	Pretreatment	X	First Purification Process	∇	Tank	+	Further Purification		
O	Distribution Pump	P	Polisher	W	Washer	C	Central System		
		A	Analyzer		Point of Use				
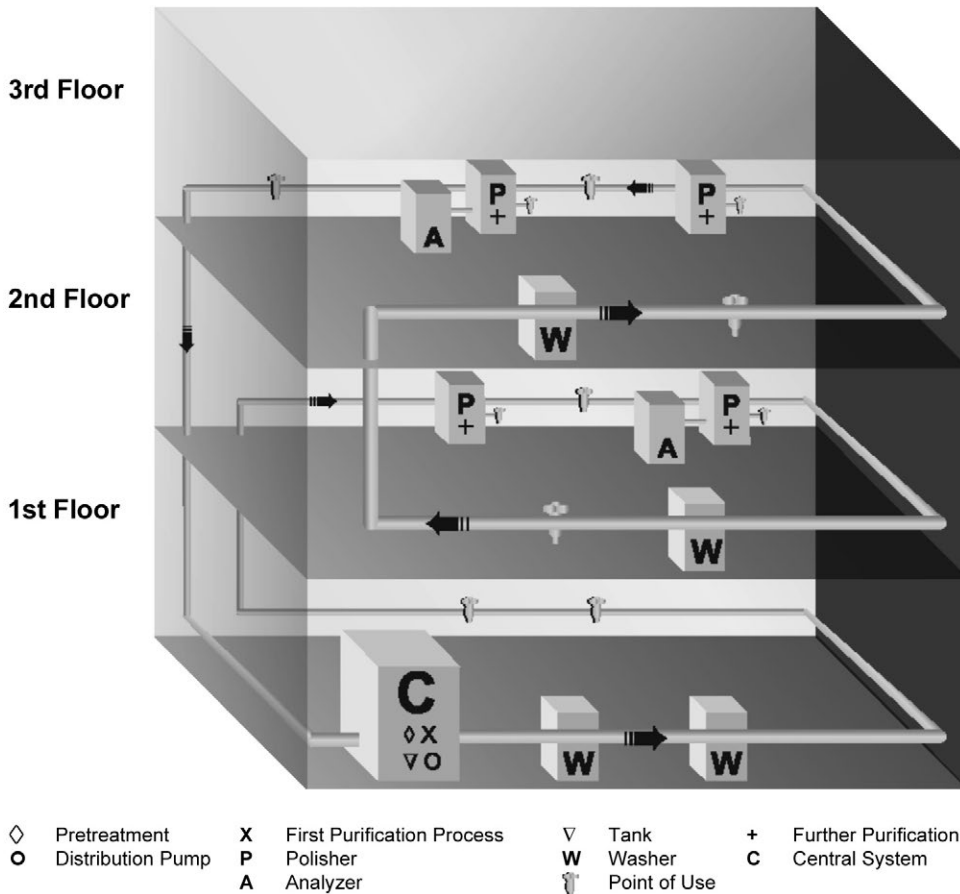
Localized – Central System for a Floor/Laboratory

Several local loops (with each loop providing water floor by floor or department by department) enable each smaller system to be designed to meet local requirements. See Figure 9.2. For example, when a high volume of water is required at one location (e.g., dishwashers and washing) and demand is much less in other locations, a better approach may be to dedicate a system to this high-demand location rather than trying to provide for this in the complete distribution network. Medium-sized generation systems typically are standard prepackaged units with a custom-designed distribution system.

Figure 9.2: Example of Localized Systems

◊	Pretreatment	**X**	First Purification Process	▽	Tank	**+**	Further Purification
O	Distribution Pump	**P**	Polisher	**W**	Washer	**L**	Localized Central
		A	Analyzer		Point of Use		System
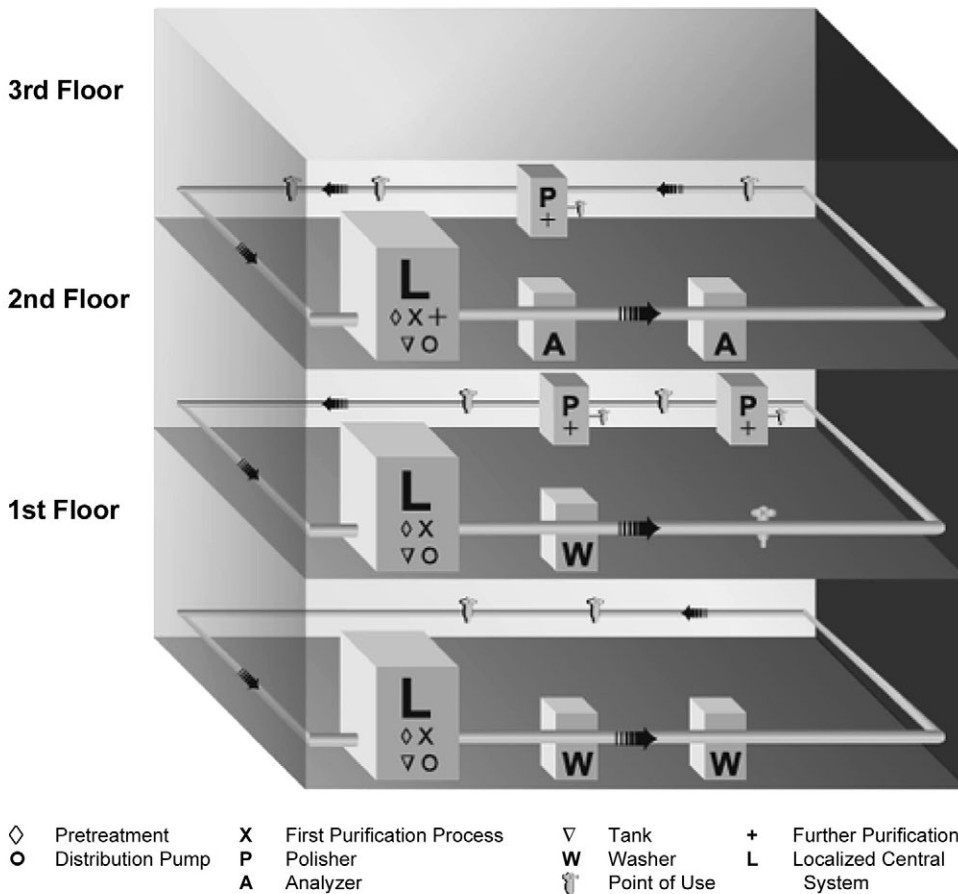
Small – One or More Individual Units per Building, Floor, or Laboratory

POU systems (often referred to as bench-top units), can provide a variety of different water qualities and quantities at a much smaller scale than the large production or centralized systems. In practice, they can be situated in a wide variety of locations, for example, on the wall or under the bench, and can include storage and local distribution. See Figure 9.3. They also can have various monitoring and dispensing options. They typically are predesigned, prepackaged, and compact units.

Distribution loops and any potential contamination introduced by the distribution loop may be avoided using this approach while serving each location with its own POU unit, each of which may include the makeup purification system, storage, and additional polishing, as needed. It is important to understand that each POU system needs routine maintenance and has its own operating costs. Depending on the number of POU systems installed, there may be economic justification for providing a bulk grade of feed water to each POU system, and the water purification system design becomes to the central system design described earlier.

When compared with packaged waters, the advantages of POU systems include purification and ongoing water monitoring available on demand. For instruments or analyzers used for manufacturing purposes, calibration and maintenance are vital to increase the probability of ongoing good operation and performance conditions. System designs that facilitate such operations can be advantageous.

Figure 9.3: Example of Small Stand-Alone Units

◊	Pretreatment	**X**	First Purification Process	∇	Tank	**+**	Further Purification
A	Analyzer	**P**	Polisher	**W**	Washer		Point of Use
		SA1	Stand-alone Unit	**SA2**	Stand-alone Unit with Polishing		
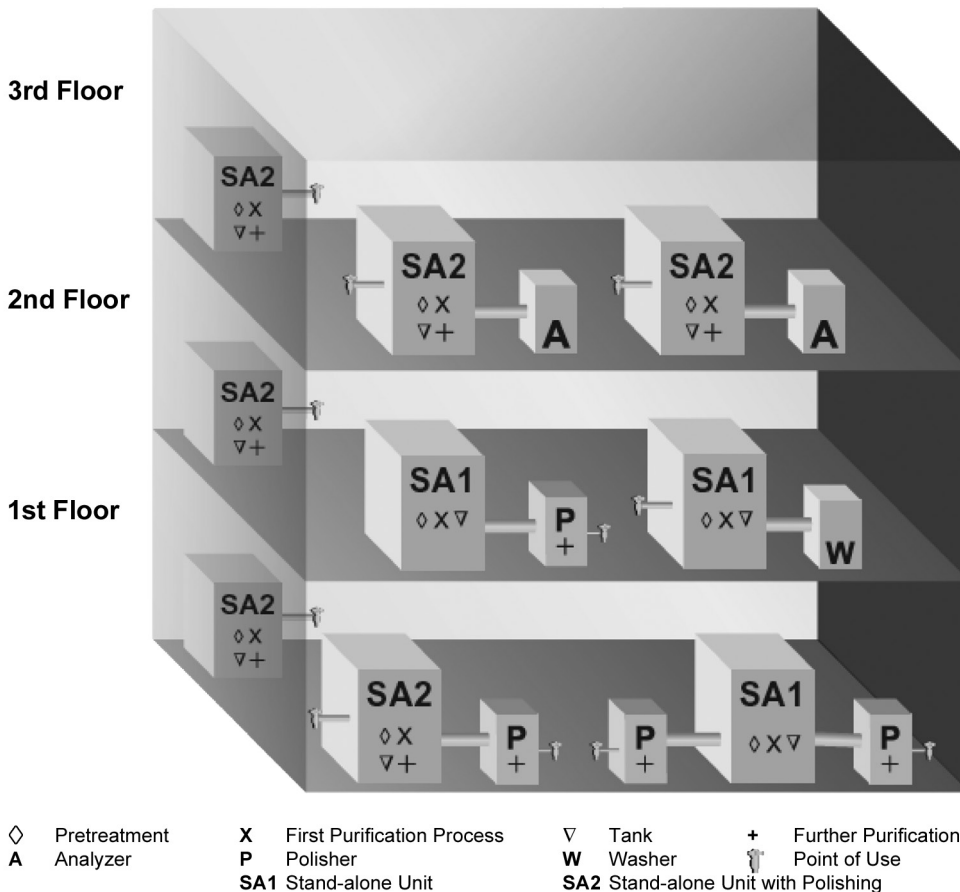
Note: In addition to the approaches shown in Figures 9.1, 9.2, and 9.3, another option is to use large or medium loop systems for most applications, and address specific needs using individual POU systems or local loops that include the makeup purification system, storage, and additional polishing at a much smaller scale and as required. This approach avoids the need to extend piping to all departments, potentially simplifying the design of the main water purification system.

Supply from a Manufacturing Plant

When pure water is available from an adjacent production area, it could be distributed through a loop to the laboratory block, or locally as an extension of the loop. The water could be treated to meet local requirements. Note that the distribution piping, if extended to the laboratory, may have more design, quality, and maintenance requirements (e.g., microbiological) than a dedicated laboratory system. Contamination risks from a multipurpose system (e.g., manufacturing and laboratory) should be considered.

9.5.2   *Packaged Water*

Packaged water is an alternative source of laboratory grade water. There are two general applications and associated purity levels typically used:

•   Very high purity waters for specific analytical purposes where small volumes are needed

•   Less pure waters considered to be equivalent to compendial PW for general laboratory use where larger volumes typically are used. The latter types of packaged waters may be used in small scale manufacturing and process development applications that may be considered as laboratories.

9.5.2.1 Simplicity and Cost Advantages of Packaged Laboratory Waters

The simplicity of using a packaged form of water may be a more cost effective and suitable option to satisfy a relatively small volume and perhaps a high purity requirement, when considering the capital and operating costs, as well as the complexity of designing, installing, qualifying, maintaining, and monitoring a water purification system, regardless of size.

Packaged waters may be purchased in containers of manageable size and packaging configurations that allow their integration into laboratory operations in a similar way to other laboratory reagents, complete with expiration dating, lot numbers, and documentation certifying purity or compliance with standards. Allowed contaminants leaching from the packaging into the water may not be consistent with the implications of the name of the water and should be considered. A risk assessment may be performed to determine the potential impact of the contaminants on the uses of these waters; therefore, the potential cost and complexity of such risk-based assessments should be part of the decision process to ensure that the packaged water approach will be acceptable.

9.5.2.2 Purity

USP sterile packaged water purity requirements have less stringent inorganic specifications and less sensitive organic contaminant tests than in-house produced water [4]. The Ph. Eur. and JP also use less sensitive wet chemical tests for these packaged waters [5, 6]. These less stringent specifications allow the presence of organic or inorganic packaging leachables that could exceed the specifications for bulk PW, the minimal purity required by most compendia for pharmacopeial testing. A review and investigation of the purity documentation (Certificate of Analysis or Certificate of Compliance) should be performed to determine if the stated purity (or compliance with compendial specifications) relates to the source water placed into the container, or whether it relates to the guaranteed purity of the water within the container throughout its shelf life.

PW packaging often is plastic or may have elastomeric closures or container entry ports, all of which may leach organic plasticizers, molding releasing agents, or glues and associated solvents and monomers into the water. The organic extractables may become evident with escalating TOC levels over the water's shelf life. Some elastomers, as well as glass packaging materials, may be prone to leach inorganic ions into the water, degrading its conductivity and pH. Inert packaging materials, which usually are used only for special purposes or more costly waters intended for specific analyses such as HPLC, may be an exception.

Packaging leachables are partially controlled by the specifications for the waters (because of selective and broad inorganic limits and a selective organics test insensitive to many extractables). There is potential for variability in the levels of packaging leachables:

* Over the shelf life of different container types

* From supplier to supplier

* Potentially from batch to batch of a given supplier

This potential variability in purity may require risk-based assessments for containers to assure suitability.

If the water's microbial content is a concern for laboratory applications, any claimed bioburden level by the packaged water's quality documentation is likely to be a transient attribute, and compromised as soon as the package is opened.

9.5.2.3 Verification of Suitability of Packaged Waters

If a packaged form of PW is being considered for use in place of bulk pure water produced by an on-site water purification system and the purity specifications are not identical, the laboratory should verify fitness for use in each of its applications (e.g., per USP Chapter <1231> [4]). In-house specifications (e.g., TOC and conductivity) should be established for these packaged waters, tested on samples taken from representative containers, rather than basing acceptance upon the certificate of analysis, to help ensure that unsuitable packaged waters are not used in susceptible applications.

Suitability verification may not be required if the packaged water is used for its labeled and intended purpose, such as water for HPLC analyses; despite this, such waters may not be suitable for all HPLC analyses. A risk-based approach to assessing overall application suitability is considered appropriate.

As soon as the package is opened and air is allowed to enter the container, the purity starts to degrade. For packaged waters, it is recommended that water from these containers is used for only a short period of time after opening unless the water's purity degradation has been shown to be inconsequential to its laboratory applications.

If the water required for a given laboratory's operations is not a compendial grade, but rather a grade specified, for example, by ASTM, ISO, CLSI [18, 20, 61], or similar organizations, the suitability of packaged forms of these waters for the user application should be verified, unless certified for a specific purpose by the manufacturer of the packaged water. In addition, because some of these water grades have microbial and endotoxin specifications in addition to their chemical specifications, consideration should be given to the potential negative impact on these attributes from how water is removed from the package and for how long the opened package is kept in use.

9.5.2.4 Balance of Cost and Suitability

Packaged waters may be appropriate in laboratories, particularly where there is a need for a minimal amount for compatible applications. Where water is more generally needed for analytical applications, the risks and cost of assuring suitability for each application, potentially for each new batch or shipment received, should be balanced against the cost of installing and maintaining a purification system to produce pure water, the application suitability for which may be related directly to ongoing quality monitoring.

9.5.3 Related Considerations

9.5.3.1 Quantity Needs

Large distribution configurations usually are considered when PW is required at different locations or in large volumes. It may be practical to meet high local flow or pressure requirements by additional local pumps and reservoirs, even with a large distribution system.

The distribution design should maintain water quality provided by a centralized system. The general advantages and disadvantages, described in Chapter 8, for the different distribution configurations (loop, etc.) could be directly applied to the selection of the distribution configuration used in a laboratory.

9.5.3.2 Quality Needs

In general, a large system should be considered when an equivalent water quality is required in a variety of locations. Specific higher water purity requirements can be accounted for by individual polishing equipment. As the number of different water qualities required in an area increases, so does the importance of individual POU systems to account for specific needs. Several local distribution systems may be more effective in meeting diverse water purity requirements, if they can be localized.

Designing a large system to produce water based on the most stringent water purity application requirements is an alternative approach; however, this solution is considered unlikely to balance the advantages and limitations (costs, complexity of maintaining high water quality in a distribution system). As the length of distribution increases, the greater the difficulty in maintaining the equivalent levels of quality at all points, and the greater the risk of contamination (particularly bacteriological). The distribution design, materials in contact with the water and components installed, etc., can affect differences in quality significantly.

9.5.3.3 Monitoring and Compliance Needs

The greater the degree of equipment centralization, the greater the need for more localized monitoring controls. Time spent checking/controlling satisfactory equipment operation (when compared with individual POU systems) may be optimized by localization; however, providing monitoring information to users (quality parameters, etc.) may be important. In a centralized configuration, the installation and associated costs of remote control/alert or individual monitoring equipment at the points where such information is important should be considered.

A system that distributes water to different locations with different regulatory requirements should align the main part of the installation requirements (design, equipment selection, maintenance program, etc.) to the most stringent regulatory requirements.

9.5.3.4 Environmental Constraints

The overall laboratory architecture and that of the various departments and floors in a building should be analyzed. If a single large system is chosen, its distribution should comply with typical design practices (see Chapter 8) and be verified that successful installation is possible (wall supports, etc.). The total length and height between the lower and upper distribution points has a significant impact on the final distribution design, and on whether the water quantity and quality desired can be delivered consistently.

If large-scale storage and distribution are considered for an existing building, the available architecture (for example, door openings) should be able to accommodate integration of the solution (for example, storage, etc.). Exposed distribution system pipework can provide flexibility for distribution system modifications. The noise level should be considered when choosing the location where a water system will be installed, as equipment delivering large volumes of PW is in general noisier than standard laboratory equipment. These factors should be studied when new construction is planned.

Space available within the laboratory may be restricted. Distribution equipment and local units use bench/wall space, or storage space if located under the bench. Placement of these alternatives should be considered.

9.5.3.5 Maintenance Needs

In a single main installation, the advantage of having less systems to maintain may be offset by the complexity of the installation and the distribution system. A trained technician may need to be available to deal with issues in a timely fashion. The risks of problems usually increase with the complexity and length of the distribution; therefore, more frequent maintenance may be required, and depending on the configuration selected, may affect laboratory operations.

9.5.3.6 Risk Management

The consequences of a lack of water caused by preventive or corrective maintenance should be analyzed and compared to the user requirements at the laboratory, departmental, and floor levels. Sanitization or repair of the distribution system does not have the same consequences for a centralized system with distribution for the entire building, rather than for a department or a laboratory. A duplex (multiple) approach minimizes the risk of interruption of water supply; however, it adds cost and is limited to cover the problems linked to the makeup system.

Distribution complexity, length, and operating conditions (e.g., pressure, temperature, equipment, etc.) are directly related to risk management and should be considered before making the final configuration decision. For example, horizontal distribution (one floor) compared to vertical distribution (over several floors) minimizes pressure-drop related issues and optimizes the linear velocity of water in the pipes.

9.5.3.7 Users' Convenience

The location and quantity of the PW POU may depend upon user requirements such as:

- Time spent to get water

- Frequency water is required

- Risks associated with a decrease in water quality during transportation

The final solution proposed should take into consideration the potential water purities required and provide an optimized way of providing users with water of the appropriate quality.

9.5.3.8 Future Laboratory Expansion or Modifications

Information on future modifications of the installation should be considered when making final design/configuration selections. As distribution complexity increases, so does the level of risk, difficulty, and expense associated with changes to the laboratory's distribution to serve future needs. The possible need to perform a revalidation could add complexity and cost. Smaller size production units allow an easier renewal program, as the investment can be planned over several years, renewing one smaller installation at a time.

9.5.3.9 Cost

The total cost equals the combination of the capital investment, operating, lifecycle, and risk management costs.

In addition to these costs, the financial investment strategy of the organization (high capital – low operating costs) has an impact on the final decision.

Initial investment depends on site-specific factors; in general, local systems are likely to be less expensive if there are few users widely distributed and with disparate water requirements. A large or medium-distributed system is likely to be more cost effective for large volume usage of a similar water quality within one building.

9.5.3.10 Comparison

The final choice should be the result of an analysis based on the advantages and disadvantages of the various configurations in regard to the quantities and qualities of water required, geographic distribution of these requirements, budget, etc.

Establishing these needs is critical. The advantages and disadvantages of the various configurations and system designs are summarized in Table 9.6, providing an overview of factors to consider in the selection process. These comments are for guidance only as other aspects may drive the final choice.

Table 9.6: Comparison of Laboratory Water Delivery Schemes

Scheme Design Attribute	Large – Central System for Entire Building	Localized – Central System for a Floor or Laboratory	Small – One or More Individual Units per Floor or Laboratory	Supply from Manufacturing Plant	Packaged Water
Availability	Custom-designed purification and distribution system	Prefabricated purification unit plus custom distribution system	Prefabricated purification unit with local POU(s) or very limited distribution	Distribution system connected to or part of manufacturing system	Commercially available from scientific supply houses/catalogs
Capital Cost per System	Large	Moderate	Low	Low – High (loop design dependent)	N/A
Capital Cost per Unit Volume	Low – Moderate	Low – Moderate	Moderate – High	Low – Moderate	N/A
System Owner/ Financial Responsibility	Site Dependent	Department	Department/ Project	Manufacturing	Department/ Project
Operating Costs • Consumables • Calibration Requirements • Monitoring • Utilities • Maintenance Revalidation	Site Dependent	Site Dependent	Moderate per unit volume	Site Dependent	High per unit volume
Failure Impact (quality or supply)	System Dependent – typically large to moderate	System Dependent – typically moderate	System Dependent – typically limited	System Dependent – potentially large	Typically limited
Maintenance	Specialized Maintenance Personnel	Experienced/ Trained Personnel	Trained Users	Manufacturing Responsibility	None
Design and Construction	Complex	Moderate	Low	Complex	None
Location – Space	Large, but only one area	Medium in support area	Small, but could be multiple	Distribution piping only	Transfer/storage area and quantity dependent
Location – Noise	Very noisy, but only one area	Medium in support area	Low	Low	None
Water Wastage	Technology Dependent	Technology Dependent	Technology Dependent	Low	None
Poor Feed Water Quality Management	Treatment at central unit (single point)	Treatment at each unit	Treatment at each unit	Manufacturing responsibility	N/A

Table 9.6: Comparison of Laboratory Water Delivery Schemes (continued)

Scheme Design Attribute	Large – Central System for Entire Building	Localized – Central System for a Floor or Laboratory	Small – One or More Individual Units per Floor or Laboratory	Supply from Manufacturing Plant	Packaged Water
Upgradability (e.g., changed usage or quality requirement)	Replace/upgrade or add – significant engineering needed	Replace/upgrade/add – some engineering needed	Replace/upgrade or add unit	Supply dependent	Buy more
Relocation	Difficult	Medium	Easy	N/A	N/A
Revalidation	Complex	Moderate	Easy – Moderate	Easy – Moderate	N/A
Importance of Supplier Certification Program	Variable	Variable	Variable	Manufacturing Responsibility	Critical
Quality Variability at different use points on a loop	Design Dependent	Design Dependent	N/A	Low	N/A
Management of Water System by User	Access Limited/Remote	Generally Accessible	Local	Access Limited/Remote	N/A
Need for Water Usage Suitability Verification	Low – during qualification then by meeting specifications in routine sampling	Low – during qualification then by meeting specifications in routine sampling	Low – during qualification then by meeting specifications in routine sampling	Low – during qualification then by meeting specifications in routine sampling	High (potentially with every batch or shipment or even every container)
Assurance of Quality at Time of Use	Validation, periodic sampling, and centralized monitoring	Validation, periodic sampling, and centralized monitoring	Localized monitoring and sampling	Manufacturing group responsible for validation, periodic sampling, and centralized monitoring	Refer to in-house testing and quality control process
Sanitization	Whole system shutdown	Local system shutdown	Individual unit	Whole system shutdown	N/A
Regulatory Requirements for System Management	Defined by the most stringent requirement in the whole system	Defined by the most stringent requirement in the localized system	Defined by specific local requirements	Defined by the most stringent requirement in the whole system	Defined by specific local requirements
Meeting Users Water Quality Needs	Distributed water quality established for the building, polish at POU as necessary	Distributed water quality established for the local needs, polish at POU as necessary	Water quality established for each POU	Water quality established by manufacturing, polish at POU as necessary	Water quality established by suitability verification
N/A = Not Applicable					

9.6   Maintenance

Preventive maintenance on a laboratory water purification system usually helps to anticipate problems and to ensure the long-term performance and reliability of the water purification system. The maintenance program should be defined based on the manufacturer's maintenance recommendations and on a risk impact analysis.

A maintenance program may include the replacement schedules for consumables and spare parts caused by wear and tear, preventive verification/tests on critical components, and the definition of the monitoring program. Definition of the monitoring program could reiterate the operating range, the alert and actions levels defined for the different parameters, as well as maintenance actions to be conducted when values are out of range.

When equipment is not used in a regulated environment, the actions performed on water systems used in a pharmaceutical laboratory should be documented. This traceability allows greater efficiency during troubleshooting actions. When the equipment is used in a regulated environment, or depending on its classification in terms of criticality, the level of regulatory practices and the preventive maintenance frequency will be different.

9.7   Instruments and Calibration

Calibration is required by quality management systems (pharmaceutical GMP, ISO 9001, etc. [65, 69]) on equipment used to measure, control, or monitor. The reliability and confidence obtained from a value provided is linked to the calibration method, calibration frequency, and results obtained.

The measurement of quality parameters, for example, conductivity, TOC, and bacteria, after each purification step, may not be relevant in a laboratory water system when the distances between two purification stages are minimized and the risks of contamination through insertion of hygienic sampling instruments may be higher than the anticipated benefits. The measurement of water quality and operating parameters after major water purification steps in a laboratory water system may help to anticipate operation and performance problems.

Frequency of calibration should be based on the type of measurement performed (e.g., temperature, conductivity, TOC, pressure), the type of instruments used (e.g., method, model, etc.), and the importance of the measurement for the application, in addition to the importance of the application in the entire process. The frequency should be defined following a risk impact analysis approach.

9.8   Commissioning and Qualification

C&Q of water systems are discussed in Chapter 12. The same qualification approach should be followed for laboratory water systems.

If the laboratory water system is an extension of a manufacturing distribution loop into the laboratory area, the issues and testing that apply to the validation of the water system for manufacturing also apply to the POU in the laboratory area.

Where the water system is exclusively for laboratory use, the specific purity attributes required in the laboratory may differ from those required for water used for manufacturing. These laboratory purity differences (or impurity allowances) may be reflected in the use of different or considerably scaled-down purification unit operations, and different system materials, distribution system designs, and POU valve types than those typically present in manufacturing water systems.

Small, tightly packaged bench-top or wall-mounted water purification units may be designed to operate to the point of reduced quality (e.g., exhaustion) from one or more purification modules; the point of reduced quality usually is signaled by a built-in sensor. There is a risk of producing and using unacceptable water associated with these types of laboratory water system designs; maintenance approaches should be evaluated prior to system selection and purchase, and challenged or verified during qualification. The high number of purity attributes, operational,

maintenance, and design differences between manufacturing and laboratory water systems usually indicates a different qualification strategy for laboratory water systems than that typically used for manufacturing water systems.

9.8.1 Importance of Internal Laboratory Water Specification Standards

The minimum chemical purity of water normally required for analytical purposes is compendial PW. A pharmaceutical laboratory PW system may not require a microbial specification, because only the water's chemical purity is of consequence to a number of laboratory uses.

Where the water purity attributes required from a laboratory water system differ from the purity attributes needed by and described by an organization's raw material standards or monographs for manufacturing PW or WFI systems, separate specifications to define laboratory water quality should be developed. These specifications may be the basis for the acceptance criteria for water system qualification processes; documented standards for the quality of waters needed in the laboratory should be defined. Where these standards are not defined, the laboratory may be required to apply water attributes and limits from manufacturing water standards. The manufacturing water attributes and limits may be unnecessary or not sufficiently stringent and for which the laboratory water systems may not have been designed to control appropriately.

9.8.2 Tailoring Laboratory Water System Qualification to Intended System Capability

Large laboratory water systems may be entirely custom designed and built. These systems can be planned to include special monitoring and sampling capability between unit operations.

For medium to smaller-sized laboratory water systems, smaller purification units with preconfigured unit operations usually are obtained as a single unit. These preconfigured units may provide less opportunity for sampling between modules for monitoring individual unit operations.

Requirements to verify the performance of individual unit operations should be determined based on the overall system design and quality needs. Retrofitting sampling capabilities for qualification purposes to prefabricated systems may not be feasible, as they often are compact, well-tuned systems.

Smaller bench-top or wall-mounted single POU systems also may have limited user access to on-board gauges and instruments for calibration and standardization purposes.

Where gauges and instruments are for informational purposes only (e.g., to signal performance changes in the system), and definitive QC testing is performed either off-line (with occasional grab samples) or by portable in/at/online instruments that can be calibrated/standardized, then lack of access may not be a problem. Where the on-board gauges and instruments are intended for QC purposes, then user accessibility, the ability to calibrate, and pharmacopeial compliance of instrument features are more significant. Therefore, such capability should be investigated during the water system selection process in order to ensure compliance with user and regulatory needs.

A systematic duplication of the qualification approach used for manufacturing water system designs may not be appropriate for laboratory water systems. The duration of the qualification process, which includes the Performance Qualification (PQ), should be customized for the evaluation of the laboratory water quality attributes and the nature of the water system's operation. For example, if there are no microbial attributes of concern for the laboratory water, the only impact of biofilm development would be to reduce the longevity or efficiency of chemical purification unit operations. This would be apparent in the chemical quality of the effluent water. Without microbial attributes of concern in the final water, the period of qualification and frequency of sampling may be tailored to evaluate the consistency of the chemical purification processes. However, if the unit operations are not intended to be periodically replaced because of exhaustion, such as RO modules, periodic microbial monitoring may be of operational value, rather than being a quality requirement per se.

The qualification of a laboratory water system may be more limited (or more stringent) than that for a manufacturing water system, and protocols should be developed to accommodate those differences, as long as the total qualification

process reveals the operational consistency of the water system for controlling the quality attributes of concern. If a specific water system monitoring feature or a particular quality attribute is an absolute requirement for an organization's water system validation program, a laboratory water system that contains those features and is able to control the mandated purity attributes should be purchased and installed.

9.8.3 Special Validation Considerations for Small Laboratory Systems

9.8.3.1 Conductivity Compliance and Consistency

Most small water purification units, especially the compact, prefabricated, single POU systems, contain an on-board conductivity/resistivity instrument with its sensor positioned within the finished water stream. If the purification unit has been in a standby mode, system manuals often instruct the user to initially recirculate the water through the unit or flush water to drain until the conductivity/resistivity reading gives acceptable values. If that instrument can be calibrated and complies with the compendial requirements, the readings can be evaluated against those compendial specifications. If, however, the instrument cannot be calibrated or otherwise does not meet compendial requirements, it can still be used as an informational instrument whose performance should be periodically compared or correlated to an instrument that does meet compendial requirements through the in-line testing of the same water.

The relationship of those data correlations can then impart a level of confidence to the informational instrument readings for day-to-day operations. Since the on-board instrument is only an informational instrument, periodic testing on water from the system using a compliant instrument is needed to ensure ongoing compendial compliance.

Whenever the product water does not meet those conductivity specifications after appropriate recirculation or flushing to drain, it is usually a sign that a purification module within the unit should be replaced. After such a replacement has been executed, the water generally resumes conformance with the conductivity specifications. Having procedures in place to assure proper use of the water system with appropriate precautions to preclude using unacceptable water is very important. Verifying that this exhaustion/module replacement/use resumption phenomenon reproducibly occurs also can be an element of the system's qualification.

9.8.3.2 TOC Compliance and Consistency

It is not universal for such compact, prefabricated purification units to contain on/at-line TOC monitoring. For those that do not have built-in TOC monitoring capability, the TOC test for such systems should be performed either on grab samples from the system or by connection, often at a POU, to a TOC instrument.

The TOC purification capability of such a system is an attribute that could, like conductivity, change dramatically in a short period of time when using ionic exhaustion as the signal for reactive maintenance. Without on/at-line TOC monitoring, it is impractical to determine TOC with every use, unlike what is usually possible with in-line conductivity.

The consistency of TOC concentrations is important to validate, not only during routine use up to the point of potential TOC removal exhaustion, but also immediately after any purification module replacement when TOC spikes are common. Therefore, the duration of frequent grab sample or on/at-line TOC monitoring during qualification needs to at least encompass a period long enough to verify the predictability of TOC removal exhaustion, which may occur either before or after ionic exhaustion. In addition, after a specified long idle period between system uses, the point in time after pre-use flushing or polishing recirculation when the monitored conductivity signals that the water is ionically acceptable for use, should be verified as attaining acceptable TOC quality.

9.8.3.3 Consistency of Other Attributes

This same approach used for TOC should be applied to any quality attribute defined as important and not monitored with every use. This attribute performance characterization could then be incorporated into usage and maintenance SOPs for the system (which may be different from those recommended by the purification unit manufacturer) that would preclude unwittingly making and using unacceptable quality laboratory water. The qualification process could then verify that these other attributes, though infrequently tested, are consistently met when the system is operated appropriately.

10 Rouge and Stainless Steel

10.1 Introduction

The basic corrosion resistance of SS (Stainless Steel) originates in its ability to form a protective or "passive" layer on its surface. The formation of this layer (not a film) is instantaneous in an oxidizing atmosphere such as air, water, or other fluids that contain oxygen. Once the layer has formed, the metal becomes "passivated" and the oxidation rate will slow down to inconsequential limits. The passive layer can be explained as the chromium-enriched oxide layer that improves the corrosion resistance of the base metal (see Section 10.3.4).

There is no specific definition for rouging, and rouge may be confused with localized corrosion (e.g., pitting corrosion) as similarly colored products are generated. Rouge in SS systems utilized in the biopharmaceutical/life science industry is a general term used to describe a variety of discolorations on the product-contact surfaces caused by variations in hydration agents and the formation of metallic (primarily iron) oxides and/or hydroxides from either external sources, or from alteration of the chromium rich passive layer.

Rouge is an anomaly generally perceived in the industry as a nuisance or source of harm to SS product/process contact surfaces, rather than a contaminant that may or may not be deleterious to WFI (Water for Injection), PW (Purified Water), Pure Steam, raw materials, or final products. Rouge is not aesthetically pleasing; it is a result of the use of a material that is never chemically identical in all its forms, contains a very high proportion of iron (approximately 65%–70%), and is exposed to a highly complex set of processes and chemical, mechanical, and electromechanical influences.

The presence of rouge normally is more apparent in systems operated continuously or intermittently at elevated temperatures, or exposed to the presence of halogen salts (usually not present in biopharmaceutical water systems), particularly chlorides, which are one of the most common elements in nature. Soluble chlorides, forming the basis for good electrolytes, can easily compromise the integrity of the passive layer and allow corrosive attack to occur.

To avoid the problem of rouge presence, the use of SS higher alloys such as AL-6XN® and Hastelloy®, or in some cases non-metallic materials such as PVDF, become attractive alternatives, except for the potential increased capital costs that may arise with the application of these choices. The best alternative to evaluating the true impact of rouge is to provide science-based results determined from investigative endeavors and/or risk assessments.

Note: Concern should be focused on whether the presence of rouge is detrimental to drug products, and the serious risk it may pose to patients without providing a benefit, rather than its repercussions on capital equipment protection. Although rouge is not recognized as an elemental impurity in brand and generic drug products, FDA guidelines regarding elemental impurities, for example, arsenic and lead, were implemented on 1 January 2018 [70]:

> *"FDA, together with other organizations, such as the International Council for Harmonization (ICH) and the U.S. Pharmacopeial Convention (USPC), have engaged in long-standing efforts to best protect patients from the risks posed by elemental impurities by developing limits for their amounts in drug products, and standardized approaches to use in determining the amount of elemental impurities in these products."*

This chapter considers:

- Rouge and rouge formation

- Rouge analysis

- Risk of rouge and the risk of remediation (de-rouging) processes

- The risk analysis/risk control on remediation (de-rouging) processes

There is no absolute answer to the question of how to deal with rouge. Rouge may be a risk, but the alternatives offer risks too. This chapter presents basic information on rouge and an estimation of several risks, but cannot provide the risk estimation for every process or product. Information is presented on what rouge is and what the consequences of rouge may be for the water/steam system and production equipment. De-rouging processes and their consequences are also discussed. Decisions should be made based on alternatives structured around owner/user's specific systems and production situations.

Figure 10.1: Structure and Approach of Chapter 10
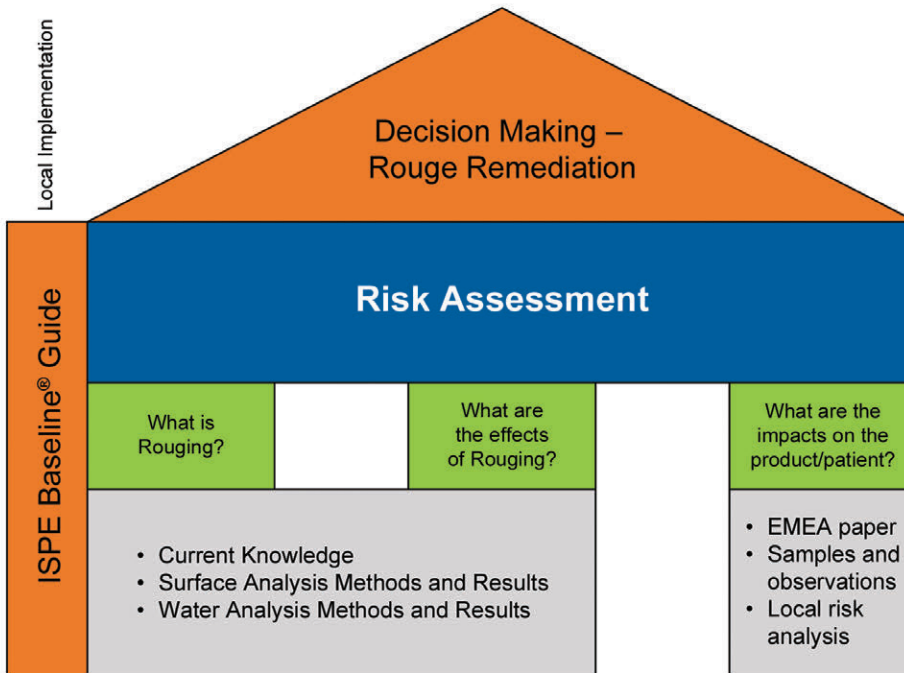
10.2 Regulatory Stance

10.2.1 Food and Drug Administration

The FDA has no written position addressing rouging, its existence, or presence in high purity water, steam, and product/process systems. Their criterion is to meet established standards of quality for those systems.

21 CFR (Code of Federal Regulations) Chapter I, Part 211, Subpart D – Equipment, Section 211.65(a) – Equipment construction [53]:

> "Equipment shall be constructed so that surfaces that contact components, in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements."

21 CFR Chapter I, Part 211, Subpart D – Equipment, Section 211.67(a) – Equipment cleaning and maintenance [71]:

> "Equipment and utensils shall be cleaned, maintained, and, as appropriate for the nature of the drug, sanitized and/or sterilized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements."

Federal Food, Drug, and Cosmetic Act (US) – § 351 (a)(2)(B) [72]:

> *"A drug or device shall be deemed to be adulterated if it is a drug and the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this chapter as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess."*

10.2.2 USP

The USP neither identifies rouge as a contaminant nor proposes alert and action limits or methods for detecting rouge product streams; the USP usually does not address design or material criteria directly, but rather indirectly by defining limits for the components that ultimately will enter the human body.

The scope of the USP covers the quality of the water used, not the system that delivers it, and rouging is a matter that relates to material selection for the system; conversely, design criteria are intended to minimize the risk to the water. The USP requires representative sampling; therefore, inferring the sample represents the water quality for the entire system and the water quality between sampling periods; the USP gives only specifications to that quality. Additionally, design criteria are intended to ensure this quality, and to keep the process under control for a longer time (even if the water is not compendial water). The owner/user should decide if the water quality obtained from a system that shows rouge is still compliant with the USP as well as internal requirements for the process.

Note: At time of publication of this *ISPE Baseline® Guide: Water and Steam Systems (Third Edition)*, it appears that there are no documented cases showing that the presence of rouge in high purity water or Pure Steam systems has resulted in the systems being out of compliance with current pharmacopeial requirements. However, because the subject of rouge appears to be omnipresent at regulatory audits, owners/users should be prepared to address and explain management of rouge in their systems, including the means for detection and monitoring, and most importantly, remediation, when and if needed.

10.2.3 European Pharmacopoeia

The Ph. Eur. monographs do not address rouge or give guidance in this matter. The EMA's Guideline on the Specification Limits for Residues of Metal Catalysts or Metal Reagents [73] described the maximum acceptable metal residues arising from the use of catalysts in the synthesis of pharmaceutical substances. This was superseded on 1 June 2016 by ICH Q3D, Guideline for Elemental Impurities [74], but it does not address the presence of iron (Fe), the main culprit for the rouge presence. In their list of 24 elements and their established Permitted Daily Exposures for Elemental Impurities, iron (Fe) is not included, while chromium (Cr), copper (Cu), molybdenum (Mo), and nickel (Ni) are present [74].

ICH guideline Q3D:

> *"…applies to new finished drug products (as defined in ICH Q6A and Q6B) and new drug products containing existing drug substances."*

While it applies to all dosage forms, different limits are specified for oral and parenteral routes of administration [74]. Q3D can be employed as guidance for conducting a risk assessment on heavy metals in products and/or water systems.

10.3   Surface Conditions and Treatments

10.3.1   Oxidation

Oxidation is a common form of electrochemical reaction where one element yields an electron, while at the same time, another substance absorbs an electron; the complete process constitutes a redox reaction, which, in this case, is the combining of oxygen with various elements and compounds in metals or alloys in interaction with their environment, such as exposure or use. It can occur regularly and slowly, as in rusting, or rapidly, as in metal pickling. It can be beneficial if it is involved in forming the passive layer, or detrimental if it plays a part in the formation of corrosion.

10.3.2   Corrosion

Corrosion is the chemical or electrochemical interaction between a metal and its environment that results in undesirable changes in the properties of the metal. This interaction may lead to impairment of the function of the metal, the environment, and/or the technical system involved. Corrosion resistance is one of the main reasons why SS is used in biopharmaceutical/life science systems. Each form of corrosion can be identified by visual observation, but sometimes magnification is helpful or required. Valuable information toward the solution to a corrosion problem can often be obtained through careful observation of corroded test specimens (sacrificial spools) or studying equipment failure due to corrosion.

10.3.3   Corrosion and its Variables

It is convenient to classify corrosion by the forms in which it manifests itself; the basis for this classification being the appearance of the corroded metal and the specific cause for its appearance, which can be either a chemical dissolution of the metal or an electrically- (galvanic) driven process. Additionally, whether the corrosion is derived from an active oxide layer metal such as iron, zinc, aluminum, and copper (anodic or least noble end in the galvanic series of metals and alloys), or a passive oxide layer metal such as SS, titanium, gold, and silver (cathodic or noble end in the galvanic series of metals and alloys) should be considered.

Classification of corrosion based on the forms in which it manifests includes [75]:

- *General or Uniform Corrosion* refers to the relatively uniform reduction of thickness across the entire surface of a corroding material.

- *Galvanic Corrosion* *sometimes called dissimilar metal corrosion,* is an electrically driven process by which the materials in contact with each other oxidize or corrode.

- *Crevice Corrosion,* *considered a form of galvanic corrosion,* is a localized corrosion of a metal surface at, or immediately adjacent to, an area that is shielded from full exposure to the environment because of close proximity between the metal and the surface of another material.

- *Pitting Corrosion* *is another form of galvanic corrosion* and is an extremely localized type leading to the creation of small pits or holes at the surface of the metal.

- *Stress Corrosion Cracking* is a type of corrosion that occurs because of sudden failure of normally ductile metals subjected to a constant tensile stress in a corrosive environment, particularly at elevated temperatures.

- *Intergranular Corrosion* is a form of relatively rapid and localized corrosion associated with a defective microstructure known as carbide precipitation.

10.3.4 Passivation

Formation of a passive or inert layer (not a film) on the clean surface of SS alloys is a naturally occurring phenomenon when the surface is exposed to air, aerated water, or any other oxidizing atmosphere. Airborne impurities, high temperatures, lack of oxygen, and other direct contact materials can compromise the integrity of this layer, causing the metal to lose its ability to ward off corrosive processes.

The passive layer normally is just a few nanometers (< 10 nm) thick and consists primarily of chromium oxide, a mixture of iron oxides and iron hydroxides, and small quantities of nickel hydroxides. The layer displays relatively good electron conductivity, and is formed by a reaction between metal ions on the surface with an oxidant (or redox system) such as oxygen; therefore, the oxide layer is at a lower energy level and represents a stable state.

The passive layer may be augmented by a chemical treatment (passivation) that removes exogenous iron or iron compounds from the surface of SS by means of a chemical dissolution, most typically by a treatment with an acid solution that will remove the surface contamination (and enhance the formation of the passive layer), but does not significantly affect the SS itself.

The purpose of the passivation process is to restore and/or enhance the spontaneous formation of the chemically inert surface or protective passive layer after welding and fabrication of a new system or welding of new components in an existing system. The passive layer is a product of the interaction between the SS basic material and the corresponding flowing solutions. The thickness and constitution often depend on the solution utilized and generally cannot be predicted or calculated.

See ASTM A380 Standard Practice for Cleaning, Descaling, and Passivation of Stainless Steel Parts, Equipment, and Systems [76] and BS EN 2516 Passivation of corrosion resisting steel and decontamination of nickel based alloys [77].

For more information related to passivation methods and procedures such as, when is passivation necessary, its qualification, QC and processes, evaluation of cleaned and/or passivated surfaces, refer to the most current edition of the ASME BPE [37].

10.3.5 Electropolishing

Rouging is assembled-system specific. Irrespective of the specific rate of corrosion, rouge typically will occur in SS piping systems regardless of whether the materials used are unpolished, mechanically polished, or electropolished; however, the rate at which rouge occurs may differ depending upon the process/product-contact surface finish.

Electropolishing can be utilized **only** to treat parts or components (see ASTM A967 [56]) not entire assembled systems; in these cases, the minimization of surface area and its resulting reduction of surface anomalies may show a beneficial effect only in providing less surface for CFU to develop.

Surface passivation occurs simultaneously with electropolishing under proper conditions. The quality of passivation depends on the type of SS, the formulation of the electropolishing solution, and the conditions of operation. Surface smoothing obtained by electropolishing also improves corrosion resistance. In addition, electropolishing removes heat tint and oxide scale. (See ASTM B912 [78].)

Mechanical or chemical cleaning, or de-rouging procedures, may damage electropolished surfaces, greatly reducing the effective service life of the component(s). (See Section 10.7.2 of this Guide.)

For more information related to electropolishing purpose, methods, procedures, essential variables, and minimum surface requirements for process qualification samples, refer to ASME BPE Bioprocessing Equipment an International Standard, Non-mandatory Appendix H, Electropolishing Procedure Qualification [37].

10.4   Rouge Formation

10.4.1 Rouge Composition and Classification

To help identify rouge deposits, the various observed types are characterized following a classification based on their source [79]:

- **Class I** – *Migratory Rouge* – consists of various oxides and hydroxides derived from the source metals (iron(II) oxide (also called ferrous oxide) (FeO) being the most prevalent). It predominantly is orange to red-orange, particulate in nature, non-adherent, and tends to migrate from its originating point on the original metal surface. These deposited particles can be removed from the surface leaving the composition of the SS unchanged.

- **Class II** – *In Situ Oxidation of Non-Passive Surfaces* – localized evident observation of rouge (iron(III) oxide (also called ferric oxide or hematite) (Fe_2O_3) being the most prevalent). It occurs in a spectrum of colors (orange, red, blue, purple, grey, and black). It can, most commonly, be the result of a chloride or other halide attack on the surface of the SS. Integral with the surface, it appears more frequently on mechanically polished surfaces or where the interaction of metal and flowing product may have compromised the passive layer.

   Note: This rouge cannot be removed by wipes; only acid etching will remove it.

- **Class III** – *Black Oxide Produced by Hot Oxidation* – surface oxidation condition occurring in high-temperature environments, such as Pure Steam systems. As the rouge layer thickens, the system's color transitions from gold to blue and to various shades of black. This surface oxidation initiates as a stable film and is rarely particulate in nature. It is an extremely stable form of magnetite (iron(II)(III) (Fe_3O_4) (or sesquioxide, an oxide containing two atoms or radicals of some other substance). This rouge will reformulate immediately after acid removal. Often magnetite forms an annealing-like layer protecting the metal underneath. Its removal is subject to local interpretation.

For further details on these classifications, methods to remediate the presence of rouge (de-rouging), and considerations that affect the amount of rouge formation during fabrication and operation of a system, refer to ASME BPE [37].

Note: Guidelines or regulations specifying the need/requirements to de-rouge (eliminating rouge) or the frequency of de-rouging processes do not exist.

10.4.2 Rouge and its Potential Contributors

To advance the understanding of rouge formation, after performing an analysis of its potential contributors, the following parameters may be identified as possible rouge formation initiators:

- Material composition

- Fabrication and installation methods

- Process environment

- Maintenance and repairs

10.4.3 Material Composition

10.4.3.1 Material Chemistry

The preferred material for the fabrication of system components in the manufacturing of biopharmaceutical/life science products is 316L SS (UNS S31603), which typically has a content of approximately 65%–70% iron (Fe). This should conform to applicable fabrication specifications and standards. When this type of SS is specified for automatic welding of tubing and fittings, the composition of the material may vary. Table 10.1 demonstrates that variability.

Table 10.1: 316L Stainless Steel Tubing Chemical Composition – Comparison

	A240		A270		DIN1.4404		DIN1.4435		AL-6XN®		DIN1.4565		Hastelloy® C4	
C	0.03	0.03	0.035	0.035	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.00	0.02
Cr	16.0	18.0	16.0	20.0	16.5	18.5	17.0	19.0	20.0	22.0	23.0	25.0	14.00	18.00
Mn	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	5.0	7.0	0.00	1.00
Mo	2.0	3.0	2.0	3.0	2.0	2.5	2.5	3.0	6.0	7.0	4.0	5.0	14.00	17.00
Ni	10.0	14.0	10.0	14.0	10.0	13.0	12.5	15.0	23.5	25.5	16.0	18.0	72.00	60.14
P	0.045	0.045	0.045	0.045	0.045	0.045	0.045	0.045	0.04	0.04	0.03	0.03	0.00	0.04
Si	0.75	0.75	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	0.00	0.08
S	0.03	0.03	0.005	0.017	0.015	0.015	0.015	0.015	0.03	0.03	0.1	0.1	0.00	0.03
N	0.1	0.1	--	--	0.11	0.11	0.11	0.11	0.18	0.25	0.4	0.6	--	--
Cu	--	--	--	--	--	--	--	--	0.75	0.75	--	--	--	--
Co	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Ti	--	--	--	--	--	--	--	--	--	--	--	--	0.00	0.70
Fe	69.05	62.05	68.92	59.9	68.3	62.8	64.8	59.8	46.47	41.4	50.44	43.24	0.00	3.00
Average % Fe	65.545		64.409		65.55		62.3		43.935		46.84		--	

10.4.3.2 Ferrite Content

In industrial practice, austenitic SS usually are formulated with a composition that results in a microstructure predominantly of austenite with a small percentage of retained ferrite. This type of microstructure can reduce significantly the tendency of castings to crack. The retained ferrite can be minimized or eliminated with appropriate thermal-mechanical processing. The amount of residual ferrite after thermal-mechanical processing (such as hot and/or cold work plus annealing) can be altered considerably by the specific processing methods employed. The effect of residual (delta) δ-ferrite on the corrosion resistance of austenitic SS varies depending on testing medium, material conditions, and processing history.

For more general information on ferrite, its influence in biopharmaceutical service, and the control of ferrite content in welds of austenitic SS, refer to ASME BPE [37].

10.4.4 Fabrication and Installation Methods

10.4.4.1 System Design/Installation

Rouge in a piping system operating under a single set of fluid service conditions is an anomaly, the cause of which can be attributed to multiple factors rather than resulting from a single originating source.

The propagation of rouge is generally believed to be dependent upon three major factors:

•   Material of Construction (MOC)

•   System dynamics

•   Process environment

The MOC for this discussion is 316L SS. While this material may be the source in some situations, it may not necessarily be the entire cause. The origin of rouge can better be attributed to the influence of the other two aspects: system design and process environment. Additional factors to consider include water quality and oxygen concentration.

The system design characterizes the dynamics of the piping system and determines velocity, as well as high impingement regions. The process environment (temperature, pressure, etc.) affects the electrochemical properties within the tubing and components.

10.4.4.2 System Dynamics

System components, configuration, and flow velocities (see Section 10.4.5.5) contribute to the dynamics imposed on a piping system. These dynamics play a large part in the initiation and propagation of rouge in a system that may be predisposed to rouge formation. For a system to be predisposed to develop rouge, it has to be constructed of a material not entirely compatible with the fluid service. A well-passivated system will show rouge after a time, as the passive layer will change to the appropriate level resulting from the equilibrium between the flowing product and the process/product-contact surfaces. Oxidation of the ferritic component of SS is the root cause of rouge, but the mechanics that instigate the onset of rouge are the system dynamics coupled with a possible diminished thickness in the passive layer.

A flaw or imperfection in the passive layer may constitute a breach, permitting an aggressive fluid to attack the chemistry of the SS. This attack initiates an electrochemical reaction in which ferrous oxides are produced. At the source location, this can be structurally damaging. As downstream deposits, the ferrous oxides may be unacceptable from a cosmetic or hygienic standpoint without detriment to the structural integrity of the pipe/tube or component in that downstream region.

10.4.5 Process Environment

10.4.5.1 Water Systems

Water system rouges, generally part of Class I or Class II, are attached weakly to the product-contact surface and are relatively easily removed or dissolved. Data from testing has shown that the levels in the water are relatively stable – de-rouging and repassivation increase the levels.

10.4.5.2 Steam Systems

Steam systems usually generate Class III high-temperature rouge. Class III rouge is much more difficult to remove (although not usually done) compared to Class I and Class II rouges, because of structural and chemical composition differences. The high temperature originated deposits form magnetite, iron oxide with some substitution of chromium, nickel, or silica in the compound structure. Significant amounts of carbon generally are present in these deposits, because of the reduction of organics present in the water, which sometimes produces the "smut" or black layer that may form during de-rouging. Remediation processes for this class of rouge will etch the process/product-contact surfaces to a greater or lesser degree, based on the remediation (de-rouging) solutions used.

It is important to note that the black oxide layer produced by hot oxidation as in Class III rouge is not instantaneous but may take weeks or months to form, and in many cases, acts as a protectant for the SS passivated surfaces.

10.4.5.3 Process Equipment

Water and steam systems, process equipment (e.g., vessels, autoclaves, and parts washers) also are likely to show rouge. This can be caused by buffers, CIP cleaning solutions, and sterilization cycles, etc.

Production equipment contacting product, particularly at the end of a line, offers a particular risk for the product; therefore, risk assessments also should include production equipment.

10.4.5.4 Gases

The influence of gases on rouge formation remains questionable. One of the many theories subscribes to the influence of CO_2 as a promoter for rouge formation, although there is little scientific evidence. Another theory points to the beneficial influence of oxygen, as this gas contributes to the formation of a passive layer; this is consistent with the observation that rouge formation is more likely in hot storage systems with low O_2 solubility. Systems at lower temperatures have improved O_2 solubility, and therefore, may be less prone to rouge formation, although this effect also remains unproven.

Water systems may be operated using nitrogen for tank blanketing. This practice may be instigated as a measure for rouge prevention; however, it has not been proven that nitrogen inhibits or prevents rouge, and may not be cost effective. The decision to use nitrogen as an inert gas for tank-ventilation in a blanketing system should be carefully considered, and be recommended only when there is significant improvement in water quality. It has been suggested that nitrogen may not improve water quality *per se*, but it will prevent CO_2 absorption.

10.4.5.5 Flow Velocities/Force

There are several ways in which the thickness of the passive layer that protects SS surfaces can be compromised, such as high fluid velocities and effects from high turbulence and fluid impingement. Flow velocities, particularly in pump housings, tend to create microcavitation effects, which may lead to the release of particles from the process/product-contact surface that can migrate throughout the system.

Traditionally, flow velocities > 5 ft/s have been considered the design standard for compendial water system tubing/piping systems. The theory was that higher velocity water flow reduces the likelihood of bacterial adhesion to surfaces, and as a result, minimizes biofilm formation. It is understood that biofilm formation is unlikely to be significantly affected by velocity; therefore, system design may be evaluated more appropriately in the context of proper system dynamics and equipment/material suitability (see Chapter 13).

In addition, there may be unique areas in a system design requiring specific evaluation based on their physical and mechanical configurations. These include the effects of flow through reducers, flow orifices, valves, pump impellers, sprayballs, fittings and instruments, as well as from their placement and configuration within the system. The effects of reducers and elbows close to a pump discharge, along with convoluted piping configurations, can complicate design issues resulting in velocity effects that may weaken or breach the passive layer, exposing the base metal to oxidation and corrosive attack.

Note: Application of the 5 ft/s philosophy may be replaced by a judicious analysis of turbulent flow, and a balance between cost of installation and cost of operation with the aim of total cost of ownership.

10.4.5.6 Temperature

Temperature is a major component in defining the type of rouge that may develop within a system. The effect of temperature on the structural integrity of a piping system, if considered in isolation, may not be problematic when the system has been appropriately designed. Coupled with factors affecting product-contact surfaces such as compromised passive layers, however, high flow velocities, fluid impingement, and elevated temperatures can promote the onset of corrosion/erosion and change the chemical characteristics of rouge.

There is no clear identification of temperatures that mark a boundary in which a system can be predicted to develop rouge. Rouge is the result of multiple factors acting in harmony. While temperature is a relative factor in the onset and propagation of rouge, it cannot be quantified in advance. Historical data and analytical evidence pertaining to specific piping systems with a specific set of criteria should be developed.

Rouge may not be found abundantly in cold (4°C–10°C; 39.2°F–50°F) to ambient water systems, and when discovered in these types of systems, it typically is Class I. Conversely, rouge often is found in hot water (65°C to > 80°C; 149°F to > 176°F) and Pure Steam systems. This anomaly is system specific and efforts to address rouge remediation require a well-planned analytical approach for detection and evaluation on a per system basis. There is no empirical evidence providing a causal relationship between temperature ranges and the presence of rouge, although it is considered that systems operating at higher temperatures are more prone to develop rouge. (Although some have speculated on the motility of the ionic species in the water.) Compliance and quality demands may require high temperatures to suppress threats to water quality and microbiological growth.

Ambient temperature water systems seem to exhibit less rouging than WFI or Pure Steam systems operating continuously at elevated temperatures. Temperature fluctuations experienced during sanitization of ambient temperature water systems do not appear to exacerbate the formation of rouge.

10.4.5.7 Sprayballs

Sprayballs are used frequently in the design of both ambient temperature and heated storage vessels for compendial water, except when ozone is used for sanitization, as sprayballs increase off-gassing [34].

Sprayballs, typically made of 316L SS, are commonly static spherical devices with holes drilled to create a spray pattern that ensures cleaning solution contact with designated components or portions of the equipment. These devices rely on water velocity and impingement to provide the desired cleaning patterns. They also wet the interior surface of the dome (tank top) and prevent uncontrolled microbiological growth in this area. Spray devices include rotating mechanisms that offer similar advantages at lower flows and pressures.

Although these devices are moderately successful in eliminating visible rouge within tanks, they have little impact on rouge within the remainder of the system. It also has been observed that in some sprayball arrangements, particularly at the points of stream impact on the walls, increased rouge develops. There is one hypothesis that fluid impingement compromises the surface integrity of the wall and creates a source of rouge that may be distributed throughout the system.

10.4.5.8 Pumps

The detection of rouge within a pharmaceutical water system is often first seen at system pump casings and/or impellers, because they are routinely and easily accessed for service. Visible rouge appears to develop at these pieces of equipment and rapidly increase, particularly in heated systems. There are many theories supporting these observations, ranging from metallurgical flaws (i.e., high ferrite concentrations) to cavitation (including microcavitation), impellers fabricated from cast alloys, fluid velocities that may quickly erode the passive layer, and temperature-related issues. There are no clear explanations for the occurrence of this phenomenon, and the specification and use of low ferrite pump materials may not significantly deter the formation of rouge.

Hygienic centrifugal pump designs have provided multiple improvements recently, particularly when using exotic alloys such as Hastelloy® or AL-6XN®; in these cases, a notable absence of rouge may indicate also a significant reduction of its presence throughout these systems.

10.4.6 Maintenance and Repairs – Basic Approaches

The maintenance and repair of an existing hygienic process, compendial water, or Pure Steam system is an opportunity to either minimize the onset of rouge or conversely, to set the stage for its formation. During installation and repair functions, the various process/product-contact surfaces may be compromised by scratched markings, welding residues, etc., making the base material susceptible to corrosive attack and possibly prompting the onset of rouge.

Maintenance and repair functions should be conducted based on logical and well-planned dismantling and erection protocols, applied by appropriately trained personnel, followed by stringent inspection techniques. Passivation of only the newly installed portions of an existing system should be considered, because modification involves disturbing (e.g., cutting, welding, etc.) established circuits or loops. Design techniques and protocols for this kind of modification may consider the installation of header circuit block valves to avoid flowing passivation solutions throughout existing circuit or loops. The existing portions of the system may not substantially benefit from the flow of passivation solutions and it may have a significant cost. In addition, if rouge monitoring is used, the installation of sacrificial sampling spools, at least at the beginning and end of the newly installed section, should be considered.

10.5   Rouge Detection (Methodology)

The type of analytical method used to detect rouge should be evaluated based on its ability to provide useful information. High-end surface analysis or sophisticated water analysis may not be beneficial without knowing how to use the information.

The first step should be an evaluation of the question: *What information is needed to make a decision (supporting a risk-based approach)?*

Each analysis method provides specific information. The analysis should support the effort to estimate the risk for the specific system/process/product. Conducting the analysis and estimating the results requires advanced knowledge and experience in the field of material science and should be performed only by a trained expert.

The presence of rouge in high purity waters and Pure Steam systems fabricated with 316L SS materials that are exposed to continuous or intermittent high temperatures, cannot be detected using methods involving temperature, flow, pressure, and TOC measurements. The presence of rouging can be identified either through process fluid analyses of mobile constituents or solid surface analyses of surface layers composition; the latter requires undesirable shutdowns to conduct examinations of:

- Dismantled pump heads (casings and impellers)

- Valve diaphragms

- Tank interiors

- Pump discharge tubes

- Loop return tubing and sprayballs at tanks

- Sacrificial or sampling spools

In order to establish the barrier properties of the passive layer, various invasive and non-invasive analytical techniques can be employed to assess the SS process/product-contact surfaces of utility fluids, as well as the fluids themselves. These analyses can help to detect, determine its chemistry, and quantify the rouge.

Analytical methods can be segregated into fluid (non-invasive), and surface (invasive) analytical techniques. Fluid analyses require the periodic collection of representative samples from one or more POU throughout a given system. These analyses also may require the periodic removal of a representative fixed surface medium, such as a sacrificial spool or a test coupon, for visual and destructive analysis of the surface. Timing of sampling required should be considered; samples may be taken during a variety of system conditions, for example, after the weekend, after longer times without consumption, and in times of full production.

The methods described may help to detect and analyze rouge; however, they provide information only about it, and cannot help in the remediation decisions. For example, an electron microscope picture may show a very detailed surface with rouge on it, but does not answer questions about water quality. Surface analysis may provide a better understanding of what is happening, but a liquid analysis provides more valuable information about water quality.

Methods described in Sections 10.5.1 and 10.5.2 (especially 10.5.2) are suitable for basic research on rouge and the mechanism that triggers its formation. They also may be used to properly identify rouge (to ensure that it is not a different form of corrosion). They are not applicable in day-to-day operations.

10.5.1 *Process Fluid Analyses for the Identification of Mobile Constituents*

Fluid analyses provide a means of identifying the mobile constituents within a subject water or steam system. They represent the current quality status of the media and the result of rouging.

For general information on analytical methods for the identification of mobile constituents of rouge, refer to ASME BPE [37].

10.5.2 *Solid Surface Analyses for the Identification of Surface Layer Composition*

Surface analyses provide information on the nature, microstructure, and composition of surface layers. They may represent the future status of the media, and the possible threat of rouging to the water quality.

For general information on analytical methods for the identification of mobile constituents of rouge, refer to ASME BPE [37].

10.6   Risk Analysis – Rouge and Its Remediation

A baseline level of acceptance for particulates and metal oxides should be established, based on risk assessment analyses that include potential damage to the process/product. A rouge remediation process of these systems (see Section 10.7.2) should then be considered, based on an observed and quantified escalating level of particulates and surface accumulation of those oxides.

Table 10.2 provides an example risk-based approach to rouge and its remediation measures.

Table 10.2: Risk Analysis/Risk Control

Risk Analysis		Risk Control
Event (e.g., possible fault, potential error)	**Effect of Failure**	**Actions: Risk Reduction Strategies**
Particles of rouge may end up in the final product.	Negative effects of rouge particles on patients are to be expected.	1. Calculate the amount of rouge from process media (e.g., WFI, Pure Steam, cleaning media, CIP solutions) that can contaminate the final product and determine if the quantity of heavy metals, for example, Cr, Ni, Mo, expected in the final product meets the Permitted Daily Exposure (PDE) stated in ICH guideline Q3D [74] (see Section 10.2.3 of this Guide). 2. Should the results indicate that the theoretical levels of heavy metals in the end product or water/steam are likely to exceed the PDE limits, test the water/steam for heavy metals (Cr, Ni, Mo). 3. If test results exceed the PDE limits and an increased heavy metal concentration cannot be explained by, e.g., substrates in use, conduct a remediation (de-rouging) procedure. Thereafter, introduce regular inspections of the system. To protect the final product from rouge, installation of filters in the system may be necessary.

Interaction between rouge and final product, i.e., ingredients/media.	Negative effects of rouge particles on final product, i.e., ingredients are to be expected.	1. Calculate the amount of rouge from process media (e.g., WFI, Pure Steam, cleaning media, CIP solutions) that can contaminate the final product and determine if the quantity of heavy metals, for example, Cr, Ni, Mo, expected in the final product meets the PDE stated in ICH guideline Q3D [74] (see Section 10.2.3 of this Guide).
		2. Consider whether chemical reactions between rouge components and the end products or ingredients are possible at the determined concentration.
		3. If end products or ingredients react with rouge components, consider conducting one of the following measures:
		  a. Install filters in appropriate locations in the system.
		  b. Carryout a remediation procedure (de-rouging).

The system contains parts (e.g., sprayballs, pumps, measuring ports, valves, heat exchangers) that may be affected by rouge.	Some parts of the system do not work properly.	Visual inspection, function tests, i.e., calibrations of the parts concerned should be carried out as part of regular maintenance procedure. This will ensure that these parts are in proper working order.
Filters may be affected by rouge particles.	Filters are blocked by rouging particles.	1. Visually inspect filters during maintenance. 2. If filters are blocked by rouge, shorten maintenance intervals. 3. If filters are damaged by rouge, add differential pressure monitors for improved filter monitoring.

Table 10.2: Risk Analysis/Risk Control (continued)

Risk Analysis		Risk Control
Event (e.g., possible fault, potential error)	**Effect of Failure**	**Actions: Risk Reduction Strategies**
Detection of rouge during normal operation triggers unscheduled remediation (de-rouging) measures.	Shut downs interfere with production.	1. Calculate the amount of rouge that can contaminate the final product from process media (e.g., WFI, steam, cleaning media, CIP) and determine if the quantity of heavy metals, for example, Cr, Ni, Mo, expected in the final product meets the PDE stated in ICH guideline Q3D [74] (see Section 10.2.3 of this Guide). 2. If the result indicates that the theoretical levels of heavy metals in the end product or water/steam are likely to exceed the PDE limits, introduce a routine visual inspection to allow scheduling of de-rouging measures.
Remediation (de-rouging) procedures alter/corrode the surface of the materials.	Changes to the roughness of the product-contact surfaces, the resistance and cleanability of the materials, leakages are to be expected.	1. Check the resistance of materials to cleaning chemicals (see Section 10.7.2 of this Guide). 2. Check the condition of the system after a de-rouging measure (e.g., random roughness measurements, visual inspections, wipe tests).
Remediation (de-rouging) is not carried out or documented properly (e.g., use of wrong chemicals, inadequate documentation, incorrect switching of valves).	Remediation (de-rouging)/cleaning agents may contaminate the product.	1. Before proceeding with remediation (de-rouging) measures, determine whether any cross reaction between the system and the de-rouging agents is likely to occur regarding leachables and/or extractables. 2. After each remediation (de-rouging) measure, clean and rinse the system (see Section 10.7.2 of this Guide). 3. After each rinse, check the system (following remediation) for chemical residues (e.g., using pH indicator strips, conductivity measurements). 4. Verify and document the success of the remediation (de-rouging) measures (e.g., roughness measurements, visual inspections, wipe tests, heavy metal concentrations). 5. Based on the success of remediation (de-rouging) measures, reconsider future measures to prevent automatic reaction without improvement. 6. Develop remediation (de-rouging) SOPs.

10.7   Rouge Remediation (Methodology)

10.7.1   Rouge Observation

Rouge has not been documented to alter the water quality beyond compliance demands; therefore, water and steam systems can remain in use and in compliance with output quality requirements. When there is a notable increase in levels of rouge in a system, it becomes necessary to perform a risk analysis for its possible remediation (i.e., de-rouging).

The risk analysis/risk control on rouge will help to define the appropriate measures to prevent the compromise of the product or process quality. Regular analysis of water and product samples for heavy metals/particles and trend development can be a supportive action to keep track of rouge and rouge development.

This may be achieved by:

- Regular heavy metal analysis during routine monitoring of the water system

- Visual inspection and documentation during maintenance

- Specific analysis of the product and comparison with compliance and internal standards

- Choosing analytical methods that identify:

    - Changes in rouge propagation

    - Changes in rouge structure

    - Changes in heavy metal concentrations

10.7.2   De-Rouging

De-rouging is a remediation procedure commonly conducted on high purity water and Pure Steam systems; however, as rouge typically reoccurs, current practice is to exercise different approaches, including leaving systems as they are, establishing remediation (de-rouging) practices at intervals of 1–3 years, or as determined by the findings of a rouge monitoring program. De-rouging does not provide a permanent solution to the presence of rouge in a high purity water or Pure Steam system; however, this procedure can minimize rouge in a system.

Once a de-rouging process has been conducted, there is no methodology to show that surfaces exposed to the available solutions have been thoroughly freed of all traces of rouge. Only representative system samples, for example, sacrificial spools, can be analyzed for de-rouging effectiveness. De-rouging processes potentially may be detrimental to exposed base metal surfaces when applied with the most aggressive chemicals and in the presence of variations in rouge deposits, which increase the chances of surface etching and erosion.

It should be noted that specific systems and their components often may be found to contain more than one of the three classified types of rouge, making the process of de-rouging more challenging. A formulated solution may work on one type of rouge, but not on another, increasing the possible chemical intrusion in the process/utility systems. When de-rouging, one rouge type may be removed and replaced by a different type, adding to the complexity of the process and its expected results. Aggressive chemical removal of rouge often requires re-passivation procedures, which will restore the chromium oxide layer, but may benefit only compromised (de-rouged) surfaces.

For information on chemicals for rouge remediation/de-rouging methods and procedures, consult the most current edition of ASME BPE [37].

10.7.3 Routine Cleaning of Equipment

After the remediation (de-rouging) process is completed, the system should undergo a routine cleaning process (e.g., CIP) or a standard sanitization process.

10.8 Conclusions

Rouge is an electrochemical phenomenon. While its chemistry is understood; there are diverse theories regarding its formation, although the conditions under which it is more likely to appear and progress are generally agreed. Where it originates and the specific causes for its appearance are less well understood.

Rouging occurs in any pharmaceutical water or steam system, independent of how the system was designed and built. As a cost-effective preference, the industry utilizes an alloy (316L SS) that offers all the best observed advantages for use in biotechnology and pharmaceutical processes. This alloy it is not supposed to corrode and it is naturally protected by a passive layer that can be enriched with chemical treatments, but unfortunately can be compromised by welding, mechanical stresses, airborne impurities, chlorides, elevated temperatures, and contact with solutions that contain aggressive acids. Processes to counteract those threats include both preventive and reactive means to minimize and stabilize its presence, and in some cases, remove rouge from product-contact surfaces, despite knowing that it will soon reappear if exposed to similar conditions.

The basic consideration for a decision for system remediation should not be the status of the water or steam systems, but the quality of the water and steam in the systems. It is necessary to estimate if the changes in the systems may pose a threat to the water and/or steam quality and the associated product(s). On the other hand, it is necessary to discuss the available alternatives; remediation processes may remove a possible threat in the form of rouging, but can create another risk.

Remediation processes are invasive processes; the risk that arises with their application should be estimated with thorough analyses. The process should be designed in a way that there is no additional risk for other water systems, the environment, or the staff executing the process. To satisfactorily achieve these requirements, detailed information about the utilization of chemicals in the remediation processes is absolutely necessary; like any other invasive process in the qualified water and/or steam systems, the remediation processes also should be evaluated.

This chapter has endeavored to establish a firm foundation of knowledge based on what is currently understood about rouge. From this point forward, and with the cooperation of a broad spectrum of experienced professionals, a strong structure consisting of science-based concepts, science-based risk analyses, research results, and practical experiences should be constructed. Once this structure is completed, rouge may be considered an everyday occurrence worthy of attention, but not of unwanted or questionable reactions. The risk of rouging should be estimated; the risk of remediation also should be estimated. The comparison of these risks should form the basis of how an owner/user manages this phenomenon.

11   Control and Instrumentation

11.1   Introduction

Controls and instrumentation often are used within pharmaceutical water and steam systems to:

*   Control the operation of equipment and components

*   Monitor and record data on the performance of equipment

*   Monitor and record data on pharmaceutical water quality

The concepts and regulatory philosophy of defining critical versus non-critical parameters are discussed as it relates to controls and instrumentation.

Although there is no regulatory requirement for the use of online instrumentation, its use is encouraged by regulatory agencies and pharmacopeia [4, 25, 8]. A monitoring program may include a combination of online (both in-line and at-line) and off-line instruments. At the time of publication, the authors are aware of a draft release of EU GMP Annex 1 [80] that may require at least some online instrumentation in pharmaceutical water systems.

*   **Online** denotes an instrument installed as part of the water system that displays and/or collects information in real time. In-line and at-line instruments are both online instruments and indicate how the instrument is installed in the water system.

*   **In-line** indicates that the instrument is in the main flow of the process water within the component or piping; typical in-line sensors include temperature, pressure, flow, and conductivity.

*   **At-line** (also known as side stream) means that the instrument is located on a side stream or take–off point from the main flow of the process water, component, or piping; typical at-line sensors include pH, ORP, TOC, and ozone. The water delivered to the side stream is typically sent to drain after the instrument.

*   **Off-line** denotes the instrument is unconnected to the water system, for example, a laboratory instrument.

Some instruments, such as ultrasonic flow meters and pipe clamp temperature sensors, do not technically fit the definitions of in-line or at-line but are still considered online instruments.

Note that some references define the term online differently, including FDA's guidance on Process Analytical Technology (PAT) [25] and the PAT section (Chapter 5.25) of the Ph. Eur. [5] (in draft at time of publication).

An online measurement system may consist of several components. The sensor is the device attached to the process piping, either directly into the process stream (in-line) or into tubing that diverts a small portion of the process fluid (at-line). The electrical output of the sensor is then converted to a measurement (e.g., μS/cm, ppb, pH, etc.), and the result is transmitted via analog output or digital signal to an external monitoring device such as a Programmable Logic Controller (PLC), chart recorder, or printer. The output may also be displayed locally or on an HMI.

Proper installation and calibration of instruments are critical to making accurate measurements. Manufacturer literature should be consulted when establishing installation and calibration procedures.

There are a multitude of measurements that can be made online in a pharmaceutical water system. These include physical parameters such as pressure, temperature, and flow, and chemical attributes such as conductivity, TOC, and hardness. Historically microbial attributes have been determined off-line. However, Rapid Microbial Monitoring is emerging as a technology to determine microbial levels online in real time.

Chemical impurities tend to be homogeneously dispersed throughout the distribution system, unlike microbial impurities, which can be localized at specific points including dead legs, valves, and hoses.

If instrumentation (online or off-line) or automated equipment are used to measure or record a critical parameter, action and alert limits should be established. A method of addressing spikes or anomalies should also be instituted.

Systems often consist of a combination of manual, semiautomatic, and automatic features. Automation can have a significant impact on the cost and performance of a pharmaceutical water system. There is no single optimum level of control and instrumentation for all pharmaceutical water systems. The optimum level of control and instrumentation for a system balances the benefits of improved process control, improved documentation, and lower labor costs against the cost of procuring, installing, validating, and maintaining the control systems and instruments. The reliability aspects of controls and instruments should be evaluated to ensure product quality. The level of automation for a pharmaceutical water system often is consistent or exceeds the automation used for the manufacturing process it supports; however, this is not a requirement.

Error and uncertainty can have a significant effect on the selection, operation, and calibration of instruments. See the Guide to the Expression of Uncertainty in Measurement [81] or the Guidelines for Evaluating and Expressing the Uncertainty of NIST Measurement Results [82] for more information.

11.2   Principles and Purpose of Measurements and Instrumentation

To achieve GMP compliance, the user must demonstrate through documented evidence that the pharmaceutical water system is in control to consistently produce and deliver water of acceptable quality [65].

Although many quality attributes can be continuously monitored using online instrumentation, there is no compendial or regulatory requirement for online monitoring of pharmaceutical water quality. It is, however, strongly recommended in USP <1231> [4]. Implementing the FDA's guidelines for Pharmaceutical cGMPs for the 21st Century – A Risk-Based Approach [1], FDA's guidelines for PAT [25], and the PAT section (Chapter 5.25) of the Ph. Eur. [5] can enhance the usage of online instrumentation. A monitoring program typically includes a combination of online instrumentation (both in-line and at-line), manual or automated documentation of operational parameters, and off-line laboratory analysis of water samples.

Control systems and instruments, when used to measure, monitor, control, or record a CPP and/or a CQA, are critical and must be qualified [10, 83]. For example, the temperature of the final water product may be considered critical for microbial control. In this case, the temperature control of the water (e.g., sensors and alarms) is considered critical, but the temperature of the heating media (e.g., steam) is not considered a critical parameter.

Documentation should clearly indicate which instruments are critical and which are non-critical. Since instruments can serve the dual purpose of process control and product release, the measurements obtained should be identified for either, or both, functions.

All instruments and controls identified as critical by a risk assessment or criticality assessment require qualification [9]. See Chapter 12 for more information.

Items that should be recorded in the system documentation pertaining to instrumentation include:

•   Maintenance procedures and record keeping

•   Reporting of results

•   Trend analysis of all data

•   Calibration data and procedures

The monitoring program during start-up typically defines instrument maintenance and calibration frequency as well as alert and action levels for the process variables.

Off-Line Testing

Water sampled for off-line testing (i.e., a grab sample) is not identical to online sample testing. Various conditions change the attributes of the off-line sample, including:

- Atmospheric contamination, such as CO_2 equilibrium and conductivity increases due to atmospheric gases

- pH stability

- Physical handling and human contamination

- Glassware and sample container contamination

These factors may cause off-line testing results to differ significantly from online measurements. In the case of chemical measurements of high purity waters, equal or higher readings (i.e., an equal or higher level of impurities) are typically obtained from off-line testing compared to online measurements.

11.3   General Instrumentation Requirements

11.3.1 Instrument Selection and Installation

Instruments should be chosen for performance over the entire process range and according to compendial or product needs, where applicable, to meet process and product quality requirements.

Instruments should be selected and installed in a way that reduces the potential for contamination, following the manufacturer's recommendations and good practices.

- For sensors, contact surfaces should be constructed of materials that are compatible with the water they contact and **all planned sanitization methods.** Materials of construction, surface finishes, and hygienic design (see Chapter 8) are usually specified for sensors installed in distribution systems.

- Sensors in direct contact with waters with strict microbial limits should be of hygienic design. Non-hygienic sensors are usually used in feed water and pretreatment systems.

- Depending on the type, sensors may be installed in-line or in a side stream (at-line). Side stream water may be reused, depending on chemical and microbial suitability.

- Installation of sensors into dead legs or creation of dead legs should be avoided (see Chapter 8).

Sensor location is dependent on the purpose of the measurement and its criticality. When possible, sensors should be installed in a manner that avoids exposure to harsh process conditions, for example, chemicals and temperature extremes if the sensor is not designed to withstand these conditions. Chemical sanitization can cause irreversible damage to sensors, depending on the materials of construction; therefore, sensors should be selected and protected to minimize damage from the sanitizing agents.

Sensors incompatible with passivation agents, sanitization agents, or sanitization temperatures should be installed so that they are easily removed or bypassed without creating a dead leg. These sensors or devices may need to be identified and physically marked. Water systems should be designed in a way that it is unnecessary to break into a recently sanitized system to re-install sensors that were removed for sanitization.

Sensors and instruments should be installed in accordance with manufacturer's instructions to ensure proper operation. For example, flow sensors should be installed in the correct orientation and with the correct upstream and downstream straight run of tube/pipe. The impact of process and ambient conditions on a sensor's accuracy and reliability should be addressed.

Conductivity sensors are particularly sensitive to air or steam bubbles, which can be present where there is turbulence, cavitation, or interstitial confluence. Orienting sensors according to the manufacturer's requirements helps eliminate gases or particles from collecting between the measurement electrodes.

Membrane-based sensors, such as those used in pH and ozone measurements, can be particularly sensitive to pressure fluctuations. Mitigation actions include using a compatible screen/device to protect the membrane or a dedicated pressure-reducing valve prior to the sensor.

11.3.2 Types of Measurements/Instrumentation

11.3.2.1 Pressure and Differential Pressure

Pressure may be monitored and controlled throughout the purification process to ensure optimum equipment performance. Measuring the difference in pressure before and after an element such as a filter is known as differential pressure (ΔP). The occurrence of a large ΔP (relative to initial/installed ΔP) across a filter can indicate when backwashing or element replacement is necessary. Differential pressure measurement across resin beds is useful in detecting resin fouling and poor flow distribution. Monitoring RO feed, interstage, permeate, and concentrate pressures can provide an early warning of membrane fouling and scaling. Back pressure control in distribution systems may be critical if minimum pressures are required at POU, or if tanks use sprayballs. Distribution loop return pressure also can be used to control pump speed via a VFD.

Outside of RO control, pressure normally may not be considered a critical quality parameter. However, the water system should maintain a minimum positive pressure at all times to limit ingress of air or bacteria.

11.3.2.2 Temperature

When there is a specification to maintain a specific temperature range for water usage, its measurement may be considered critical. Often, the most critical application of temperature measurements is the monitoring of thermally sanitizing conditions. In distribution systems where temperature is controlled or where heat sanitization is used, temperature may be considered critical to ensure correct system operation or effective sanitization. In hot distribution systems or in ambient or cold systems that are periodically sanitized, temperature should be monitored in multiple locations to assure acceptable distribution of heat and to identify the coldest spot. Typically, a heat sanitization process is characterized by a frequency, minimum duration, and minimum temperature. The cold spot identifies the minimum temperature of the loop for a sanitization cycle. In ozone-sanitized systems, temperature is critical to ensure adequate ozone solubility.

Other cases where temperature may be considered critical include those that impact equipment and safety. Temperature measurements before/after a heat exchanger would be used to adjust the exchanger controls or for safety at a use point. Temperature can have an impact on equipment performance, such as RO efficiency. Often temperature is monitored and controlled at various locations to ensure optimum equipment performance and for microbial control. Temperature interlocks may be used for safety purposes or to prevent damage to membranes, resins, or equipment if water temperatures drift outside allowable ranges.

11.3.2.3 Flow Rate and Flow Velocity

Flow measurements are used throughout all parts of a water system. Flow rate is a measure of volume per unit time and is temperature dependent. Flow velocity is determined from the flow rate divided by the tube/pipe inner diameter, and is typically expressed in m/s or ft/s.

Flow rate measurements are used for several purposes, including assurance of:

- Sufficient flow to the next purification step

- Delivery of sufficient water to production

- Positive flow at the end of the distribution loop

Flow velocity could be used to demonstrate that the user's internal flow velocity specifications were met. There are no compendial requirements for a minimum flow rate/velocity in a distribution loop, but there are GEPs that require flow measurements. At the time of publication, the authors are aware of a draft release of EU GMP Annex 1 [80], which may include requirements for minimum flow (expressed as turbulence or Reynolds number) in distribution loops.

There are a wide variety of flow technologies used in water systems, including paddlewheel, magnetic, turbine, vortex, Coriolis mass flow, ultrasonic, etc. Most flow sensor technologies require installation according to specific requirements, normally expressed as upstream and/or downstream straight tube/pipe diameters, to assure proper measurement.

Other key considerations are:

- Criticality of the measurement: The accuracy of the flow measurement depends on the selected sensor. Flow measurements may be critical or non-critical. A flow velocity measurement, particularly on the loop return, could be deemed critical if there is an internal specification.

- Ease of calibration: Because flow sensors are generally installed as a part of the piping system, a key consideration in the installation is the need to calibrate the sensors. If the measurement is non-critical, calibration may not be a factor, or it could go on a multi-year cycle. If the measurement is critical, provision should be made to calibrate the sensor in situ, or easily remove and replace it with a calibrated sensor during off-production times.

- Impact on the controls during operation and sanitization: For example, VFDs may be used to drive pumps to ensure the proper flow rate is maintained or to distribute sanitizing agents, including hot water.

Percent Recovery

Percent Recovery is a measure of unit operation efficiency (e.g., volume of water used versus discarded); typically, it is measured in an RO process, although it could be utilized at other purification steps where there is a waste or discharge component.

Percent Recovery = $100 \times (F_{out}/F_{in})$

Where: F_{out} is the outlet flow rate of the process
F_{in} is the inlet or feed flow rate of the process.

High percent recovery is desired, but in RO it comes as a trade-off to percent rejection (see Section 11.3.2.9).

11.3.2.4 Turbidity and Silt Density Index

The Silt Density Index (SDI) test is used to determine the fouling potential of water feeding a membrane filtration process such as RO system, since suspended solids and colloidal material can inhibit the efficacy of RO membranes. This test is defined by its specific procedure (ASTM D4189 [84]).

The common instrument used to determine turbidity is a nephelometer. Nephelometers use Nephelometer Turbidity Units (NTU) as the parametric readout. 5 NTU is generally considered to be the maximum NTU value for feed water to an RO system, although membrane manufacturers typically specify a maximum NTU value. Turbidity tests are also used to ensure that the turbidity of the water complies with the (US EPA) NPDWR [29], particularly in cases of supply from non-public water sources. Tests may be conducted at-line or off-line.

11.3.2.5 Hardness

Hardness measurements are used to determine the Calcium (Ca^{2+}) and Magnesium (Mg^{2+}) concentrations before and/or after water softening. These bivalent cations are usually the most prevalent cations found in drinking waters. While generally harmless to humans, these ions are harmful to downstream RO and distillation processes, as well as other plant equipment including boilers and heat exchangers. Other multivalent cations, such as iron, aluminum, and manganese are usually present at much lower concentrations, but also may contribute to downstream processing problems.

Hardness can be measured at sampling points using off-line chemical test kits that employ chemical reagents. It is a colorimetric test that provides a semi-quantitative result to show the effectiveness of the softener to achieve zero hardness (usually defined as < 0.2–1 mg/L $CaCO_3$ equivalence). Online hardness measurement systems may be used as an alternative to off-line chemical tests. Hardness sensors are used to gauge the effectiveness of the water softener components and regeneration process. After water softening, conductivity is considered a better gauge for assessing water quality. Tests may be conducted at-line or off-line.

11.3.2.6 pH

Since the USP eliminated the pH test requirement for bulk PW and WFI in 1996 [4], Ph. Eur, and JP have followed suit, even to the point of eliminating related acidity/alkalinity tests [5, 6]. However, some pharmacopeias have a pH test for packaged sterile waters, such as Sterile WFI [4, 5, 7].

For bulk waters, pH measurements are mostly found in the pretreatment part of the water system. For example, it could be part of an acid/caustic injection controller to adjust the pre-RO or interstage pH, to maximize percent rejection, and to convert dissolved gases into an ionic form.

If there is a demand for a pH measurement after the pretreatment system, an accurate pH measurement is difficult because of the low ionic strength of these waters. Low ionic strength (or low conductivity) water is susceptible to pH fluctuations due to contaminants introduced from the air, sample containers, and test equipment, as well as measuring challenges such as streaming potential of the sensor that is associated with pH measurement of low ionic strength solutions.

If pH measurement is necessary on the high purity side, it should be done at-line and not in-line, since conventional pH sensors contain an electrolyte that may diffuse across the glass membrane into the water. pH measurements made in the pretreatment system can be in-line or at-line.

11.3.2.7 Oxidation Reduction Potential

Oxidation Reduction Potential (ORP), also known as redox (reduction-oxidation) potential, is an electrochemical measurement of the chemical potential of ions and neutral molecules to cause oxidation or reduction reactions to occur. The signal, in mV, is related to the concentration of oxidizable/reducible species. The quantitative meaning of the ORP signal is limited because it is not ion/molecule specific. ORP can be used in the pretreatment system as a surrogate to a chlorine (or other halogenated oxidizer) measurement, and it can also be used to control bisulfite addition (see Section 11.3.2.8). Measurements may be conducted at-line or off-line.

11.3.2.8 Free and Total Chlorine

Free chlorine is a measurement of the amount of dissolved chlorine and its related molecules in equilibrium with chlorine (hypochlorous acid and hypochlorite), where the amount of each species is pH dependent. The free chlorine measurement is typically an electrochemical measurement, and the measurement is normally compensated for pH.

For waters treated with organic forms of chlorine, such as chloramines, conventional electrochemical chlorine sensors do not work. Instead, an alternative total chlorine measurement technology is applied. This technology measures all forms of reducible chlorine commonly found in water pretreatment systems.

Neither technology (free or total) measures chloride, which is the fully reduced form of chlorine. Free and total chlorine measurements can be made at-line or off-line.

11.3.2.9 Conductivity/Resistivity

Electrical conductivity (referred to as conductivity) is a measure of ion-facilitated flow through a fluid. Specifically, it is the measurement of ionic species such as H^+, OH^-, Na^+, Cl^-, Mg^{2+}, and HCO^{3-}. In the case of a pharmaceutical water system, conductivity is typically used for two key purposes:

*   To monitor the effectiveness of a purification process

*   To assure the ionic purity of a product such as PW or WFI

Conductivity limits for PW, WFI, Pure Steam condensate, and many types of sterile or packaged waters are specified in the water monographs for USP, Ph. Eur., JP [4, 5, 6], and other pharmacopeias. A general primer on conductivity measurements is found in USP <1644> Theory and Practice for Electrical Conductivity Measurements of Solutions and USP <644> Conductivity of Solutions [4].

Conductivity is the most widely used chemical measurement in water systems because of its broad capability to measure ionic concentrations and/or impurities, its speed of response, and relative low cost. However, it is a temperature-dependent measurement, it is non-ion-specific, and it responds to all ions with different efficiency. Consequently, a change in conductivity needs to be viewed with an understanding of the purification process preceding the measurement.

The basic units of conductivity are siemens per centimeter (S/cm), but the more common output for pharmaceutical waters is μS/cm (microsiemens per centimeter). The conductivity of high purity water with no impurities is 0.0550 μS/cm at 25°C; the small conductivity is due to the natural dissociation of water into H^+ and OH^- ions. In some instances, the impurities are expressed as units of resistivity (the reciprocal of conductivity), and the equivalent is 18.2 MΩ-cm at 25°C.

Conductivity measurements are used throughout the water purification system to assure the different purification steps are properly functioning. Some examples are:

*   **Softening:** Though softening only exchanges one type of ion for another, a change in pre to post-softener conductivity indicates that the softener resin is functioning. A significant change in conductivity immediately after regeneration could also indicate the need for a longer rinse time.

*   **RO:** Conductivity is measured pre and post RO (and also in-between if it is a multi-pass RO system) to monitor the effectiveness of the RO purification process. See Section 11.3.2.9 percent rejection.

*   **Conventional IX:** Whether anion, cation, or mixed-bed deionization, pre and post-step conductivity measurements ensure the effectiveness of the process.

*   **CEDI:** Conductivity is measured pre and post-CEDI to monitor effectiveness.

- **Distillation (any technique):** Conductivity may be measured pre and post-distillation to monitor effectiveness.

- **Ozonation and UV (microbial disinfection or TOC reduction):** While conductivity measurements can be used to measure the secondary effects of these processes, there are better measurements available. However, a small increase in conductivity after these purification steps is possible as these steps can result in the generation of CO_2, which forms conductive species when dissolved in water.

- **Deaeration/degassing:** The removal of CO_2 can reduce conductivity.

Conductivity measurements can also be used to detect seasonal or unanticipated quality changes in source water that could impact pretreatment equipment operation. There are other purification-related applications where conductivity is employed such as control of acids or caustics to regenerate cation and anion-exchange resins, monitoring chemical delivery for chemical cleaning of the water systems, and monitoring the removal of chemicals after chemical cleaning.

Temperature has a profound impact upon conductivity measurements because of the temperature effect of ion mobility. To compensate for the temperature effect, most conductivity measurement systems include a temperature sensor embedded in the conductivity sensor, and incorporate one or more compensation algorithms to correct the actual conductivity measurement to a standard temperature, usually 25°C (77°F).

Differences caused by a change in temperature and those caused by a change in ionic concentration can be distinguished using temperature-compensated measurements. For most waters on the pretreatment side, a typical temperature dependence of conductivity is 2% per degree Celsius. However, in high purity waters (for this purpose, consider water with conductivity < 5 µS/cm), the temperature dependence (%/°C) is very complex to determine; it depends on the temperature, and the type and the concentrations of the impurities. Consequently, the proper temperature compensation can never truly be known unless the purification process and the associated chemistry are fully understood. As a result, manufacturers have provided specific algorithms for temperature compensation for different applications. It is common and proper to select the best temperature compensation algorithm for the intended use.

One application is to use the conductivity measurement as an end test for PW and WFI. A conductivity test (USP <645> Water Conductivity [4] (and equivalent tests in other pharmacopeias [5, 6, 7, 26]) is used as a limit test to ensure compliance of these waters to specific ionic-impurity requirements. In this use, **a non-temperature-compensated measurement is required.**

Because conductivity sensors are usually made of inert materials, and because high purity water samples can be negatively impacted when exposed to air, it is common (but not required) to use online conductivity measurements for release of water. The benefits and challenges of online versus off-line measurements are described in USP <1644> [4].

Conductivity sensors are commonly installed in-line, although at-line measurements are not unusual. The materials of construction vary, but similar requirements to other sensors prevail. Due to the design/construction of sensors, there is usually a recommended orientation to ensure proper measurement. The orientation may be critical to prevent the inclusion of air bubbles or particles between the electrodes.

The fundamentals of a conductivity measurement are the measurement of the AC resistance that is normalized for the fixed volume geometry between two electrodes. Consequently, calibration of a conductivity measuring system consists of two parts: calibration of 1) the AC resistance measurement circuitry and 2) the cell constant, which is a geometric property of the sensor. The methods for calibration of each manufacturer's instrument and sensor vary. However, there are clear accuracy requirements in USP <645> and guidelines in USP <1644> [4]. Installation of the sensor should take into account the calibration needs.

As with other measurements, frequency of calibration is dependent on the criticality of the measurement. These are not electrochemical sensors (like those used in pH measurement that usually require frequent (daily/weekly) adjustment). Rather, conductivity sensors are electromechanical sensors that are typically rigid and mechanically robust. Also, the required chemical resistance is typically limited to the fluids found in a PW/WFI system (ranging from drinking water to PW/WFI), and not other chemicals such as acids/bases that could attack the sensor. A calibration cycle of many months to years is common for non-critical sensors, and a cycle of 1 year or less is typical for critical sensors. Calibration of a conductivity measurement system can be a multistep process and may include calibration of the built-in temperature sensor.

Percent Rejection

Percent Rejection is a measure of the efficiency of the removal of ions in a purification process; typically, it is measured in an RO process, although it could be utilized at other ion-reduction steps such as CEDI.

$$\text{Percent Rejection} = 100 \times (1 - K_{out}/K_{in})$$

Where: K_{out} = outlet conductivity of the process
K_{in} = inlet or feed conductivity of the process

High percent rejection is desired, but it comes as a trade-off to percent recovery (see Section 11.3.2.3).

11.3.2.10 Tank Level

Various types of tank-level measurements are used in the pretreatment and storage and distribution portion of a pharmaceutical water system, including:

- Float switches

- Free-space radar

- Guided radar

- Load cells

- Ultrasonic sensors

- Capacitance sensors

- Pressure sensors

Hygienic tank-level sensor designs are available for storage tanks; appropriate hygienic design is recommended for the final product water storage tank.

Tank level is normally not measured for product quality purposes; rather it is measured for production control purposes. The measurement is used to control upstream valves or pumps to deliver water when the tank level reaches the low set point and to stop upstream water delivery when the tank level reaches the high set point. Tank-level measurement can be interlocked with distribution pumps to shut them off, and to warn users of impending loss of water when the level reaches unsafe low levels.

The level may not be considered a critical parameter for water quality (unless produced by batch), but may be considered a critical parameter for water system operation.

11.3.2.11 Total Organic Carbon

TOC is a measure of the non-specific carbon dissolved in water in the form of organic compounds. It is a valuable tool for measuring the aggregate level of organic impurities in pharmaceutical water systems. A TOC test with a nominal limit of 0.5 mg/L (500 ppb) for USP PW, WFI, or Pure Steam condensate is a required test (USP <643>) [4]. Similar limits are in place for comparable waters in other major pharmacopeia [5, 6].

TOC measuring systems are relatively sophisticated analytical instruments that utilize a variety of technologies, but which share the common approach of oxidation to (a form of) CO_2 and detection of the CO_2. Oxidation approaches include chemical, photochemical, electrochemical, and combustion methods; detection approaches include conductivity and IR (Infrared) absorption. There are no specific requirements as to the type of oxidation and detection approaches in any of the pharmacopeias. Samples can be taken manually and analyzed in the laboratory or performed online (usually at-line). The USP, Ph. Eur., JP [4, 5, 6], and other pharmacopeias provide guidance on how to qualify an instrument and how to interpret the results.

In addition to continuous monitoring of equipment performance and pharmaceutical water quality, online TOC systems may be used for final QA testing, thus eliminating or reducing the need for laboratory TOC analysis. When used for critical QA testing of pharmaceutical waters, specific compendial requirements are mandated for instrument performance, including limit of detection and system suitability [4, 5, 6]. Instruments used strictly for process control and monitoring are not subject to these compendial requirements.

TOC may be monitored at several locations in a pharmaceutical water system. However, high instrument cost typically limits the application to critical parameters based on risk and cost/benefit evaluations. Examples include:

- Feed water monitoring can detect seasonal or unanticipated quality changes that could impact pretreatment equipment operation or the potential for resin or membrane fouling.

- Monitoring TOC downstream of carbon beds, ozone generators, organic scavengers, RO units, and UV lights installed for TOC removal can verify appropriate equipment operation and provide advance warning of required maintenance.

- TOC concentrations in pharmaceutical water may be monitored after the final treatment step to verify acceptable quality prior to delivery.

- The most common usage of a TOC measuring system is in the distribution loop after the last POU, before return to the tank. The logic is: if the water meets the TOC requirements on the return line, it meets the requirements at the POU. This is because chemical impurities tend to be homogeneously distributed throughout the system, unlike microbial impurities, which can be localized at specific points including dead legs, valves, and hoses. Systems may include provision for automatic diversion to drain or recirculation back through purification equipment when water quality is outside the acceptable range.

11.3.2.12 Ozone

Dissolved ozone concentrations should be monitored in storage and distribution systems that use periodic or continuous ozone for microbial control. Ozone concentrations can be determined in the laboratory using several wet chemistry methods, or continuously using online instruments (see Chapter 8). Possible ozone leakage from ozone generation equipment and instrument sample streams is monitored to protect personnel while adhering to OSHA (US) ozone exposure limits [85].

Ozone is typically measured by colorimetric or electrochemical methods. In either case, the risk to any off-line approach is that the ozone concentration changes after a water sample is collected. When dissolved in 25°C (77°F) water, ozone has a half-life of approximately 15 minutes. However, when dissolved in high purity water with very low TOC levels, the half-life of ozone can be ≥ 1 h. Also, for samples of water that are collected for off-line testing, outgassing of the ozone from the water sample occurs. It is thus important to make sure that off-line testing is conducted as quickly as possible to ensure an accurate measurement of the sample.

For effective and safe system operation, dissolved or ambient ozone concentrations should be monitored at the following locations:

- At a suitable location in the water system for control of the ozone generator (dissolved)

- Downstream of a $UV_{254\,nm}$ light to ensure ozone destruction prior to water delivery (dissolved)

- In loop return piping to ensure proper ozone concentrations are maintained during sanitization of the loop (dissolved)

- Mechanical room space where ozone equipment is used, for personnel safety of the breathing air according to local exposure requirements (ambient)

All online ozone measurements in water systems are typically made in a side stream to prevent any contamination from the ozone-sensing technology. Typically, the stream discharge cannot be discharged to the atmosphere and is delivered to waste and/or the ozone is destroyed.

See *ISPE Good Practice Guide: Ozone Sanitization of Pharmaceutical Water Systems* [34] for more information.

11.3.2.13 Particles

Liquid particle counters measure the quantity and size distribution of particles per unit volume. They can be installed at various positions in a water system, including (but not exclusively):

- After filters to measure sloughage, breakthrough, and failure

- At the POU for product quality

- Before or after components used for particle reduction, such as pretreatment and rouging filters, RO membranes, final filters

- As part of storage and distribution

Instrumentation should be installed on a side stream (at-line) from the component or section to be measured and monitored.

Liquid particle counters may be < 0.1–5 µm sizing of particles. Range is user selectable.

Because water systems are typically well filtered, particle measurements are not a pharmacopeial-mandated measurement for bulk pharmaceutical waters. In addition, high instrumentation cost means that particle counters are not widely used for bulk waters. However, particle control is required for several sterile compendial waters, including Sterile WFI [4, 5, 6], and it can be required by the water system's owner or operator.

11.3.2.14 UV Intensity

When $UV_{185\,nm}$ (TOC reduction) or $UV_{254\,nm}$ (microbial control/ozone destruction) lamps are used, they are typically replaced on a time schedule. Sometimes the flow chambers have intensity detectors to display the relative output (normally set to 100% upon installation). This allows the user to monitor the lamp power to get some measure of relative lamp intensity over the lamp life. These detectors are typically not calibrated nor to be used as absolute measurements, although some manufacturers offer sensors that are traceable to national/international standards.

11.3.2.15 Rapid Microbial Monitoring

Rapid microbial monitoring is the real-time or near real-time determination of a microbial presence in a sample without the need for incubation, laboratory services, or intervention. Rapid microbial monitoring is a definition, not a single methodology.

Although various laboratory-based plate count methods may be required by the compendia, there are instrument-based methods that can be used as alternative QC methods, if validated. Additionally, rapid microbial monitoring can be used for process control purposes.

Rapid microbial monitoring is commonly referred to as Rapid Microbial Methods (RMM) in Ph. Eur. 5.1.6 [5]. Both terms describe the rapid microbial detection and measurement discussed in this section. For more information see references: Ph. Eur. 5.1.6, Alternative Methods for Control of Microbiological Quality [5], Parenteral Drug Association "Evaluation, Validation and Implementation of Alternative and Rapid Microbiological Methods" Technical Report No. 33. Revised 2013 [86], USP <1223>, Validation of Alternative Microbial Methods [4].

11.3.2.16 Rouge

Online rouge monitoring instrumentation is typically conductometric. The conductometric methodology uses two electrodes, one anode and one cathode, to understand the corrosion development over time. The electrodes are made of the same material as the piping and vessels (typically 316L SS). As it is the oxidation that takes place over time that causes rouge formation, the electrodes and the piping and vessels corrode at the same rate, giving a measurement of rouge development over time. Sensitivity is at the angstrom level allowing for accurate nanometer measurement [87]. Installation locations include areas of the system particularly susceptible to rouge, such as downstream of distribution pumps. Off-line measurements are also possible (see Chapter 10).

11.3.2.17 New Measurement Technologies

Instrumentation using any new and suitable measurement technology, whether mandated by a regulatory authority or not, can be installed on a pharmaceutical water system, as long as it is commissioned and validated following regulatory and company guidelines. Whether using the process, its attributes, and limits as the validation mechanism (as described in the PAT Guidelines [25]), or traditional validation sequencing, all issues of commissioning and validation must be addressed. The integration of the new technology and its data should follow existing and accepted GMPs, regulatory guidelines, or compendial mandates, where applicable. Examples of new and emerging technologies include online speciation of bacteria and online automated endotoxin testing.

11.3.3   Instrument Calibration

The calibration of sensors and instruments should follow a regular program that is deemed appropriate for the type of measurement and its criticality to provide evidence of consistently acceptable performance. Non-critical sensors and instruments may be calibrated on a frequency deemed appropriate for the service. In some cases, certain sensors and instruments may be calibrated only upon request.

Calibration frequency should be determined by process parameters, criticality, and instrument performance. As-found data can be used as calibration verification.

Calibration should follow approved procedures and the results should be documented. Each measurement system in a control loop should be calibrated individually or the loop may be calibrated in its entirety unless otherwise specified by appropriate compendia (e.g., conductivity). All calibrations should be traceable to recognized local, national, or international standards (e.g., SI [88], NIST [89], ASTM [18], JIS [14]). Calibration certificates should be issued that reference the applicable sensor, instrument ID, and serial numbers.

The impact of shipment and installation on the supplier's calibration should be evaluated in lieu of field calibration. The manufacturer's recommendations for calibration and calibration verification should be confirmed.

11.4   Design Conditions versus Operating Range

The control system usage may distinguish between design conditions and operating ranges, and the impact this distinction has upon validation and facility operation. These criteria are defined in Section 2.6 and illustrated in Figure 2.1.

A system should meet all stated design conditions. The acceptability of the water system for operation depends on operating within the proven acceptable ranges.

Normal operating range cannot exceed the proven acceptable range for product water. Design condition selection should reflect accepted common engineering practices.

11.5   Responses to Measurements

The concept of alert and action levels may be applied along with the normal operating and proven acceptable ranges (see Section 2.6), as proactive measures taken when a water system is trending out of control to prevent exceeding specifications. For further discussion, see USP Chapter <1231> [4].

11.5.1   Signal Filtering

All instrumentation has some form of built-in response time, smoothing, averaging, or filtering. Additional features such as user-selectable options of these parameters may also be available. Statistical process control may also be implemented. If used, these techniques should be carefully employed to minimize the disruption of OOS or alert/ action limit triggers without diluting the value of the response time of the data.

11.5.2   How to Handle Instrumentation Spikes

A spike is when an abnormally high or low value of a parameter is indicated for a brief period of time, and is preceded and proceeded by normal operating values. Spikes may be experienced in the measurement of a number of parameters. These excursions may be the result of an actual process event or they may be the result of measurement technique, sensor installation, electronic noise, or other artifact unrelated to the quality of the water. If a spike of a chemical measurement occurs for a brief period of time such that the physical size of the water system dictates that this is impossible, the excursion can be treated as an instrumentation spike, and not a real process event. A procedure for defining and handling spikes should be developed in conjunction with QA based on the specific water system.

Consider an example in which a water system operates between 20°C–30°C (68°F–86°F) and reports temperatures every 10 s. One temperature sensor in the distribution system reports a single value of 85.7°C (186.3°F), then returns to its normal operating range. Meanwhile, no other temperature sensors in the loop report any substantive excursions. In this case, logic shows this was not a real process event, but an instrument anomaly. Delay timers of a practical duration to ensure correctness of the excursions can be used to avoid inadvertent alarms. In other cases, it may be decided to treat these spikes as alert level deviations based upon their frequency and duration, even though their magnitude may exceed the action level.

11.5.3   Machine Learning and Artificial Intelligence

Significant quantities of data are generated by all of the different online measurement devices described in this chapter; analyzing this data and finding patterns can be difficult, tedious work. One developing technology that can be applied is Artificial Intelligence (AI). Machine learning, a subset of AI, is a method of data analysis that automates analytical model building. Using algorithms that iteratively learn, machine learning allows computers to generate insight into data without being explicitly told where to look. Using machine learning, real-time or historical data from instruments can provide insight to help guide decision making.

11.6   Control Systems

11.6.1   Level of Automation

When selecting a control strategy for a pharmaceutical water system, consideration should be given to:

- Total cost of ownership

- Lifecycle costs

- Feed water quality and reliability

- Size and complexity of the purification and distribution system

- Labor costs

- Personnel skill levels and capabilities

- Documentation and reporting requirements

11.6.1.1   Local Instrumentation with Manual Control

In this option, a combination of instrumentation, periodic samples, and visual examination is used to monitor CPPs. Data is collected and recorded manually, thus analysis and trending capabilities are limited. Excursions of critical parameters outside acceptable ranges typically trigger local alarms to reduce the risk of unacceptable water quality. Satisfactory manual operation requires significant human intervention; this requires detailed operating procedures and conscientious documentation of critical quality parameters. This option has the lowest installed cost, but is very labor intensive and is subject to human error.

11.6.1.2   Semiautomatic Control

Semiautomatic control systems use operator control panels, relay-logic control, local chart recorders and printers, and some manual data collection to monitor and control the water system. These systems are considered less labor intensive than the manual ones, but still are labor intensive, based on the manual data collection and monitoring needed.

11.6.1.3   Automated Control

Automated systems use central controllers or computers (PLC or DCS) to control a pharmaceutical water system. The computer system uses appropriate process monitoring instrumentation (e.g., conductivity meters, flow meters, TOC instrumentation, etc.) to gather data and make appropriate adjustments to the system automatically. As water generation systems become more sophisticated, relying on human intervention to control and monitor the water system becomes more difficult and labor intensive. An automated system entails less operator involvement, but necessitates a more highly trained maintenance and engineering support staff. Automated systems typically have higher initial capital expenditure, but lower operating costs.

11.6.4.1   Integrated Systems

These systems include an automated system and a network connection to other computer systems in the building, site, or organization. These systems allow for central, remote, or local site monitoring, automatic electronic data collection, and centralized, remote, or local alarm monitoring with automatic recording, response, and report generation. These may need to be compliant with 21 CFR Part 11 [51] and/or EU GMP Annex 11 [90].

Additional information on control system design is available in *ISPE GAMP® 5, ISPE GAMP® Good Practice Guide: A Risk-Based Approach to GxP Process Control Systems,* and in various guidelines by the Instrument Society of America (ISA) [91, 92, 93].

Whichever level of automation is selected, the commissioning and validation effort should verify operation of the complete system, including vendor-supplied subsystems.

11.6.2 Control System Software

The software for a control system is used to measure, monitor, control, or record CPPs. Programming and design standards, especially concerning operator interface (including security), control techniques, alarm handling, and interlock processing, should be applied during the development, validation, and maintenance phases of the project. The control system software consists of:

- Firmware, operating system, and application software

- User configurable software

11.6.2.1 Firmware, Operating System, and Application Software

Firmware, operating system, and application software is software permanently loaded into memory. If the software is considered critical, user access should be restricted or monitored. While the functions performed by the control system may be divided between critical and non-critical functions, it is impossible to divide or isolate the firmware, operating system, application software, and associated hardware functions. If any of the functions of a control system are considered critical, all of the software is considered critical and should be validated.

11.6.2.2 User Configurable Software

The functions of the user configurable software may be defined as critical or non-critical. The critical functions or modules require enhanced documentation, including validation. In some cases, it may be impossible to divide or isolate software adequately. In such cases, if some of the functions are critical, it may be necessary to validate all the software.

The type of process control required is often the determining factor in the type of software required, and software requirements often define the type of system selected. Major considerations include:

- Number of Input/Output (I/O) points

- Mathematical or statistical functions required

- Reporting features required (particularly if the control system is to be further integrated into other systems)

- Whether or not advanced control techniques are required (e.g., neural nets, fuzzy logic controllers, adaptive gain, dead-time compensation)

11.6.3 Control Hardware and Operation Interface

Critical software requires enhanced documentation and should be designed and tested in accordance with applicable GMPs.

The water system, field instruments, and control requirements affect control hardware selection. Site standards or a large installed base for a particular system may drive the selection of hardware.

12 Commissioning and Qualification

12.1   Introduction

In 2014, ISPE published the *Good Practice Guide: Approaches to Commissioning and Qualification of Pharmaceutical Water and Steam Systems (Second Edition)* [9]. Recently, ISPE published the Second Edition of the *Baseline® Guide: Volume 5 – Commissioning and Qualification* [10]. The revised *Baseline® Guide Volume 5* fully embraces the QRM rational for integrated C&Q and the principles of the ASTM Standard E2500 [24].

- The Second Edition *Baseline® Guide: Volume 5 – Commissioning and Qualification* no longer supports the "Traditional Approach to Qualification" described as "Track 1" in Section 2.6 of the Good Practice Guide

- The "V" Model is no longer supported

- System Impact Assessment has been revised to a "System Classification" approach for identification of systems as either direct impact or not direct impact. Direct impact systems contain CPPs and/or Critical Aspects (CAs)/ Critical Design Elements (CDEs) as identified during execution of the System Risk Assessment (SRA)

- Component Critically Assessment (CCA) has been replaced by CDE determination [10]

The Second Edition *Baseline® Guide: Volume 5 – Commissioning and Qualification* introduces the concept of CDEs, which are design functions, features, or performance characteristics of an engineering system necessary to consistently manufacture products with desired quality attributes. CDEs are identified and documented based on the technical understanding of the designated product CQAs, process CPPs, and equipment design/automation. CDEs are verified through C&Q [10].

This chapter is intended primarily to reference the *ISPE Good Practice Guide: Approaches to Commissioning and Qualification of Pharmaceutical Water and Steam Systems (Second Edition)* [9] and the *ISPE Baseline® Guide: Volume 5 – Commissioning and Qualification (Second Edition)* [10], and is not intended as a replacement for either Guide. These Guides provide more guidance on the overall application of QRM to the C&Q process. Included in the *Good Practice Guide: Approaches to Commissioning and Qualification of Pharmaceutical Water and Steam Systems* is discussion on risk assessment and other activities normally associated with creating and maintaining quality within pharmaceutical water and steam distribution systems.

There is recognition that critical utilities, such as WFI (Water for Injection), may not have product CQAs but have compendial requirements and CPPs. Section 1.6.2 of the *Baseline® Guide: Volume 5 – Commissioning and Qualification*, Second Edition [10], provides the following guidance on the identification of process user requirements or critical utility CQA and CPP. The principles for classifying critical utility CQA and CPP are the same as for pharmaceutical products.

For the purpose of applying the process user requirements and general user requirements concepts to critical utilities, an organization defines the quality attributes of the specified utility and the supporting CPP that needs to be controlled in order to achieve that defined quality. For a WFI system, CQA would be used to describe the Total Organic Carbon (TOC) and microbiological requirements for WFI. The CPPs are the controls associated with the distillation process and the ability to control temperature and pressure.

The *ISPE Baseline® Guide: Volume 5 – Commissioning and Qualification,* Second Edition, Appendix 4 – Direct Impact System Examples, provides the following as examples of typical CQAs and CPPs for a WFI system [10]:

- Typical CQAs

  - Conductivity Temperature (USP and Ph. Eur. define the acceptable conductivity based on temperature [4, 5])

- TOC

- Microbial levels

- Endotoxin levels

- Nitrate Levels (if a requirement)

• Typical CPPs

- System operating pressure

- Temperatures/flow rates

ASTM E2500-13 defines CAs as:

> *"… functions, features, abilities, and performance or characteristics necessary for the <u>manufacturing process and systems</u> to ensure consistent product quality and patient safety."* (Underline added by Guide authors.) [24]

Process user requirements are not CAs (the design aspects are required to assure that the process user requirements are met).

• Process user requirements are what the utility process requires to produce utilities meeting quality requirements

• CAs are how the utility must control and monitor to deliver those quality requirements

• CDEs are the engineering design and automation elements/features that enable the CAs

Refer to the *Good Practice Guide* and *Baseline® Guide: Volume 5 – Commissioning and Qualification,* Second Edition, for details on how the SRA is applied to identify CAs/CDEs and procedural controls [9, 10].

C&Q are important components of the validation process by which a system is put into service and demonstrates consistent production of water or steam of a specified quality, under variable conditions, while operating under defined procedures. The international regulatory community, through ICH, has issued guidance based on the desired state for manufacturing practices [10]. In addition, the ASTM standard published in 2013 (E2500) [24] describes a set of principles, concepts, terminology, and a process for delivering facilities and items of regulated manufacturing capacity. None of these documents is specific to water systems and critical water systems in general.

It is also not the purpose of this chapter to bridge or contrast the differences in the various approaches for documenting or verifying the qualification of a water or steam system to consistently and reliably deliver the required quality. The reader is referred to the previously mentioned guidances and standard, which are consistent with the guidance provided by the FDA's Guide to Inspections of High Purity Water Systems [40]. It is important to note that there is no single correct way to accomplish this assurance of consistent and reliable water quality; therefore, organizations should qualify all the essential elements for achieving and maintaining that final quality, and accurately document for future reference the configuration of the entire system, including its starting water quality.

12.2   Sampling for Water and Steam Systems

Sampling for pharmaceutical water and steam systems is covered in detail in the *ISPE Good Practice Guide: Sampling for Pharmaceutical Water, Steam, and Process Gases* [33]. Below is a brief summary of some important points from that Guide as they pertain to pharmaceutical water and steam systems.

12.2.1   Sampling for Water Systems

Regardless of the approach used to document the consistency and reliability of a particular water system, there are specific finished water quality attributes that must be verified as being consistently met based on the desired water quality (e.g., PW (Purified Water) or WFI):

- Conductivity

- TOC

- Microbial counts*

- Bacterial endotoxin

***Note:** For additional information see Section 12.3.2 and Chapter 13.

The confirmation of these attributes may be accomplished by grab sample testing from the distribution system's POU or by online instruments (where allowed by compendial requirements and available technology). In instituting the principles of PAT, where online testing is utilized for conformance or release testing, an element of the qualification process is to verify that the online values are representative of use-point quality [25]. A difficulty in this regard is that grab samples may reflect somewhat poorer quality than their online counterparts, especially for conductivity and TOC attributes. Nevertheless, with careful attention to controlling external influences, the impact can be minimized and accommodated.

In Chapter 9, Table 9.3, there are additional chemical attributes that must be met for Ph. Eur. [5] waters if the water system is intended to comply with these compendial requirements. There are no commonly used online analyses for these attribute analyses to date, so grab sampling and laboratory testing are the usual options for assuring conformance with these attribute specifications.

12.2.2   Sampling for Steam Systems

For a Pure Steam distribution system that is well designed (e.g., steam trap locations, line sloping), maintained (e.g., frequent steam trap inspections for proper drainage), and operated (e.g., POU flushing times, sampling condenser hook-ups), there should be no microbial growth concerns because of the high system temperature. Typical parameters requiring quantitative monitoring in Pure Steam systems include:

- Superheat

- Non-condensable gases

- Dryness

- Bacterial endotoxins

- Conductivity

- TOC

Bacterial endotoxins, conductivity, and TOC are tested on condensate samples from the Pure Steam system in a fashion similar to testing WFI. Bacterial endotoxins testing is not required if the steam is not used in parenteral applications [4].

The monitoring of superheat, non-condensable gases, and dryness parameters is performed on the live steam samples rather than its condensate, typically using the methods and specifications of the European Standard EN 285 [41]. Usually these attributes are only required where the steam is used for SIP (Steam-in-Place) of product-contact equipment, related parts autoclaving, and for porous product autoclave loads.

Less guidance generally exists for Pure Steam system validations, though performance testing, strategies, and sequencing are similar to high purity water systems. The time duration of the PQ, which is protracted in water systems because of the time associated with slow biofilm development, is significantly reduced in steam systems because of the extreme antimicrobial hostility of steam systems eliminating the potential for biofilm development. For further information, see the *ISPE Good Practice Guide: Approaches to Commissioning and Qualification of Pharmaceutical Water and Steam Systems (Second Edition)* [9].

12.3   Acceptance Criteria

The acceptance criteria for the QRM-based C&Q of the CDEs/CAs, traceable to the CQAs/CPPs, can be documented as an output of the final design review during design qualification and approved by QA.

The acceptance requirements for compendial water for many of the world's major pharmacopeias are listed in Chapter 9, Table 9.3. These requirements represent the minimum acceptance criteria that should be used as part of a validation program. After developing some operating history on a system, pharmaceutical manufacturers may elect to adopt more stringent alert and action levels for process control purposes. These stricter alert and action limits allow for improved system operation and earlier detection of excursions, although the acceptance specification for the system remains consistent with regulatory requirements. For a more complete discussion on the topic, refer to the *ISPE Good Practice Guide: Sampling for Pharmaceutical Water, Steam, and Process Gases* [33].

12.3.1   Chemical Attributes

Compendial requirements may vary from country to country and often companies follow the most stringent requirements for products marketed globally. The most recent version of the pharmacopeia(s) for the area(s) where products will be sold should be documented as the basis for the selection of acceptance criteria. The examples below (US, Ph. Eur., JP) are intended to show differences between the compendial requirements and are not intended provide an overall compendial view.

For products to be marketed in the US, the requirements for the associated waters and steam are found in the USP (USP 42) Purified Water, Water for Injection, and Pure Steam monographs, which further reference General Test Chapters <643> for Total Organic Carbon (TOC), <645> for Water Conductivity, and <85> for Bacterial Endotoxins Tests [4]. These USP chapters provide detailed testing instructions as well as chemical specifications, which are identical for both water grades and Pure Steam.

For systems used in manufacturing products to be marketed in Europe, the chemical requirements are referenced in European Pharmacopoeia (Ph. Eur. 9.0) monographs [5]. Water conductivity, TOC, and the bacterial endotoxins test methods and specifications for the Ph. Eur.'s WFIs are similar to those in the USP [4]. The overall Ph. Eur. PW specifications for water conductivity are less stringent than those of the USP, and oxidizable substances testing is allowed as an alternative to TOC. There are additional wet chemistry tests for the Ph. Eur. waters. Again, these specifications are summarized in Chapter 9 Table 9.3 and may be used as the minimum acceptance criteria in a validation program, but testing to USP specifications plus performing the Ph. Eur. wet chemistry tests would satisfy both compendia for these attributes. As above, if tighter alert and action levels are used for better process control, then the action levels may be used as the acceptance criteria.

For systems used in manufacturing products to be marketed in Japan, the chemical requirements are referenced in analogous JP (JP 17) monographs [6]. These requirements are nearly identical to USP's for TOC and water conductivity (with the exception that no Stage 3 conductivity testing is specified). There are no additional wet chemistry tests. These specifications are summarized in Table 9.3 and may be used as the minimum acceptance criteria in a validation program. As with the other pharmacopeia, if tighter alert and action levels are used for better process control, then the action levels may be used as the acceptance criteria.

12.3.2 Microbial Attributes

Microbial testing and values that could be used as acceptance criteria are not defined in the USP, but were originally published in the 1993 FDA Guide to the Inspection of High Purity Water Systems [40] and are discussed in the General Information Chapter <1231> Water for Pharmaceutical Purposes [4] This General Information Chapter provides guidance, but also notes that other microbial enumeration methods could be evaluated to find one more suitable for enumerating the microorganisms that may be unique to a particular water system. Similarly, this non-mandatory chapter also provides a suggested maximum action level that is the highest that should be considered for QC, and further suggests that lower microbial levels derived from trend analysis be employed for process control purposes. For new water systems, usually insufficient data is available for meaningful trending, so the suggested specification level listed in USP's <1231> typically is used as the acceptance criteria.

The Ph. Eur. is more prescriptive regarding microbial enumeration test methods that appear within the water monographs along with an appropriate action level, identical to USP's non-mandatory maximum action level for the respective waters [4, 5]. By their appearance in the Ph. Eur. monographs, the test method becomes a referee test and the appropriate action level becomes a specification limit rather than a process control value as implied by its name. Therefore, the Ph. Eur. microbial enumeration test method should be used during the system validation program and thereafter if marketing products in Europe, unless a superior method can be demonstrated for the user's water system. Similarly, the Ph. Eur. action levels may be used as the acceptance criteria, unless tighter acceptance criteria are more suitable.

The JP is similar to USP with its placement of suggested microbial test methods and appropriate and generally applicable action levels in its non-mandatory informational Chapter <21> Quality Control of Water for Pharmaceutical Use [6]. However, the JP suggests that different test conditions be used for QC testing versus process control testing. The action levels mentioned in this informational chapter are the same as mentioned in USP [4] as well as Ph. Eur. [5].

12.4   Change Control and Maintaining the Qualified State of the System

Changes in the water or steam system should be coordinated through an appropriate change management program. A risk-based approach should be used when assessing the impact of the change and measures need to be put in place to minimize the potential risk and demonstrate that the system remains in a qualified state. Where changes may alter or compromise the quality or the state of control, remedial actions should be implemented to avoid a loss of control.

For systems that have gone through multiple individual changes over a period of time, it is necessary to evaluate that the accumulation of changes has not affected the qualification of the entire system. This evaluation could result in an abbreviated or full system requalification, or simply a formal historic data review, depending on the collective number and significance of those changes.

CQA monitoring or CPP monitoring supported by existing quality systems (e.g., maintenance, calibration, change control, SOPs, training, etc.) and performance monitoring programs can eliminate or reduce the need to periodically review critical utility systems. Refer to Chapter 9 of the *ISPE Baseline® Guide: Volume 5 – Commissioning and Qualification (Second Edition)* for additional details [10].

13 Microbiological Considerations for Pharmaceutical Water Systems

13.1 Introduction

Issues related to controlling microbial proliferation in a water system require consideration throughout:

- Conceptual Design

- Detailed Design

- Construction

- Qualification

- Operation

- Maintenance

- Monitoring

Although the highly purified waters, such as those prepared for pharmaceutical uses, have very low levels of inorganic and organic contaminants, these waters are sufficiently rich in nutrients to support the growth of several types of microorganisms. This microbial growth in water purification, storage, and distribution systems should be controlled to reasonable levels or prevented where required. Otherwise, the water purification unit operations may fail to perform as intended and the finished water may be unsuitable or unsafe for use in pharmaceutical, biopharmaceutical, and medical device applications, or with patients and consumers who use products prepared with this water.

13.2 The Microbial Growth Process in High Purity Water Systems

It is useful to understand how microorganisms are able to thrive in nutritionally austere environments and to understand both how to control or prevent this microbial growth as well as the consequences of not preventing their growth. This chapter focuses on the development and spread of microbial growth within high purity water systems and how it can change over time.

13.2.1 Low Level Nutrient Behavior

To understand the growth of microorganisms, it is necessary to understand how the thermodynamic properties of nutrients affect their molecular behavior.

Microbial nutrients in high purity water systems are primarily the incompletely removed trace-level organic impurities from the water, as well as subsequent contaminants of the water entering through vent filters and leaching from system materials such as elastomeric diaphragms and seals or plastic components. These organic molecules have both hydrophilic and hydrophobic properties, as do the water system's materials of construction. These organic molecules tend to adsorb to water system surfaces through their hydrophilic or hydrophobic interactions, allowing both the water system surfaces and dissolved organic nutrient molecules to achieve a more thermodynamically favorable lower energy state. In so doing, these nutrient molecules tend to become more concentrated on surfaces than dissolved in the water.

Aquatic bacteria that can use these low organic nutrient levels (oligotrophs), can exploit the slightly higher nutrient levels on these surfaces by attaching to and growing on those surfaces in preference to growing in suspension as planktonic flora, where the dissolved nutrient levels may be too low to be utilized. When microorganisms grow on such surfaces, the resulting biomass takes on the form and characteristics that are called biofilm.

13.2.2 Planktonic Cell Characteristics

The development of biofilm in water systems can start with a single bacterial cell with the structural, genetic, and biochemical characteristics referred to as a pseudomonad (named after the family of bacteria *Pseudomonadales* possessing the genetic traits that allow them to proliferate in the extremely low nutrient environment of pure water systems). This bacterial cell may enter the water system with the source water or perhaps is introduced during routine maintenance. Initially, it floats planktonically along with the water flow and may use its flagella for locomotion. It typically is not able to grow using the dissolved organic nutrients because of their low concentrations, but maintains its cellular integrity and flagellar locomotion by using its limited internal energy stores. A structural component of the cell wall surface of this pseudomonad is a lipopolysaccharide (also called endotoxin, which is well known for its pyrogenic or fever-causing properties). It gives the cell surface a slight hydrophobicity and stickiness that enhances its ability to adhere to surfaces.

13.2.3 Biofilm Initiation and Growth

If this cell touches a surface, it has an initial tendency to loosely and reversibly adhere to that surface. Typically, the layer of water adjacent to the attachment surface is moving slightly, and that force, when combined with the forces exerted on the cell by other molecular motion within the water (Brownian Motion), can exert a shear force on the cell stronger than the cell's initially weak adhering force and almost immediately detaches the cell back into the flowing water. The longer the cell remains loosely adhered to the surface (in terms of seconds to minutes), the more likely that Brownian Motion or the water movement could have the opposite effect and actually "push" more of the cell surface into contact with the substrate. This allows yet more of those weak adsorptive forces to come into play and adhere the cell more securely, making it unlikely to be sheared from the surface. It can remain there long enough for the cell to detect the presence of the surface-concentrated nutrients, triggering a complex series of gene expressions and suppressions that prepare the cell for a non-motile life on the surface (where nutrients are in greater abundance than in the water).

Those genetic expressions cause the production of enzymes and other proteins necessary to the absorption and metabolism of the particular nutrients on the surface and for anchoring the cell more firmly to the surface, making it nearly impossible for the shear forces of even turbulently flowing water to dislodge the cell.

Within hours to days of the initial adherence, depending on the species of microorganism and the surface nutrient levels and types, the nutrients are metabolized to supply the supplementary energy and building blocks for cell replication, so proliferation of additional strongly anchored cells begins.

During this same period, these naked cells also begin to exude a sticky glue-like, mostly polysaccharide, exopolymer. In the following days, this slimy Extracellular Polymeric Substance (EPS, also known as glycocalyx) firmly anchors the cells to the substrate surface and continues to be produced as the cells proliferate within the protective slimy matrix. The stickiness of this EPS begins to trap debris particles and other planktonic bacterial cells. Additionally, the EPS may trap flocs or chunks of cell-imbedded biofilms that may have been sloughed from the fragile surface of thicker biofilms in other locations by the turbulent shear forces of the flowing water or other system vibrations. All the bacteria in these biofilms begin to thrive in the localized nutrient-rich community. Wastes from cells already present plus nutrients provided by the new arrivals and trapped debris are added to the growing biofilm community.

Biofilm formation on a new surface also can begin by the deposition, possibly in an eddy or other low flow location, of a sloughed fragment or multicellular floc from an upstream biofilm location; but once deposited the growth process is identical.

13.2.4 Biofilm Regulation and Behavior

As the biofilm grows larger, its development is complexly orchestrated by quorum-sensing chemical signals produced by some of the biofilm cells. The resulting reactions of those signals within the biofilm collectively affects its shape, growth rate, the death of specific cells within the biofilm, as well as the development and release of planktonic pioneer cells after the biofilm is well developed. The biofilm's focus is on adapting and surviving in the local environment and dispersing to other locations.

13.2.5 Biofilm Microbial Selectivity

The diversity of the species that participate in a biofilm at a given location in a water system is affected by:

•   Planktonic species present in the water at that location

•   Ability to adapt to use the nutrients available locally

The primary source of the planktonic organisms is the feed water. Planktonic organisms may also enter the system during its construction, as well as from biofilms on replacement bed matrices (exchange type media beds such as cation, anion, mixed bed, etc.), filters, and chemical additives, including regenerant chemicals, antiscalants, and chlorine neutralizers.

For example, the biofilm member species in an activated carbon bed grow on a rich source of many different organic molecules adsorbed by the activated carbon granules. Biofilm member species may have favorite foods among the nutrient choices. A large diversity of available nutrients encourages the potential for a large diversity of biofilm participants. Where flocs of biofilm, or pioneer cells from the biofilm, move downstream to environments with more limited nutrient concentrations and fewer nutrient types, many of those cells may not find a surface or existing biofilm with suitable nutrient choices or levels to accommodate their nutrient specializations. These cells eventually starve to death. Cells that have more highly adaptable nutrient utilization diversity are more likely to find a surface or existing biofilm where they can grow.

This selective survival process occurs at each successive purification step until cells able to survive the nutritional limitations and variability arrive at the finished water distribution system. These microorganisms are likely to be the most nutritionally diverse of the biofilm-forming microorganisms because they must be able to survive and grow on a wide variety of types and levels of chemical impurities that could be present from time to time in the finished water coming from, for example:

•   Additions of system materials and components

•   Atmospheric vapors around a tank vent filter

•   Vent filter changing or other system maintenance

•   Impurities not removed by the purification process

Water systems can be unique in types and levels of impurities, while remaining compliant with regulatory chemical specifications, favoring the emergence of a few naturally selected and resilient microorganisms. The microbial diversity can be influenced significantly by:

•   Source water, which often is the cause of final impurities (including microorganisms)

•   Variable unit operation selection and arrangement

•   Quality of design, installation, and operation

Factors such as the frequency of sanitization may influence the survival of microorganisms. The initial microbial population in a newly commissioned water system is probably very low, representing only recent arrivals. It may be distinct both in population density and diversity in an older water system with well-established biofilm flora.

13.2.6 Microbial Diversity as a Function of Seasons and Water System Ageing

As any water system ages, the initial microbial populations have opportunity to develop into larger and probably more complex communities, as different survivors make their way into the finished water distribution system, perhaps from eventual unit operation maintenance procedures, a contaminated bed matrix, chemical addition, or as a function of changing seasonal source water chemistry or microbial populations.

During this system ageing process, biofilms will have had the opportunity to find the most hospitable locations to grow and survive any microbial-control efforts applied. Seasonal changes in source water temperature, system temperature changes from cooler or warmer utility buildings, outdoor storage tanks, frictional heating from circulation pumps, heat from UV units, use of substantially more or less water, etc., can collectively cause a temperature change of as little as a few degrees and lead to a shift in the microbial density, growth rate, and species composition of associated biofilms.

Such water system microbiome changes can also occur over time as a function of:

- Changes in source water flora as a function of the seasons or switched water sources in municipal drinking water systems

- Unit operation efficiency changes

- Intentional changes in system maintenance practices

As a result, no two water system's biofilms are exactly alike. A high purity water system in operation for a period of time may have different, and possibly more or less diverse, flora than were observed just after commissioning. The test methods used to recover microorganisms in the water system during its original qualification may be less optimal for microbial recovery in the mature water system, possibly resulting in lower than actual counts or longer growth times for countable colonies to develop.

Optimizing a microbial enumeration method to suit a more mature system flora (e.g., by using different media or incubation temperatures or durations) may impact the validity of historic data, including those generated during system qualification, and potentially have regulatory consequences. Such impacts usually are not considered sufficient reason to stay with an inferior method that fails to reveal the accurate nature of the flora in a water system or delays timely response to system control issues because of inordinately long incubation, as long as there is reasonably adequate documented evidence that an alternative method is superior. To demonstrate the relationship between the data from a new, well-justified approach to the data from a previous approach, a bridge period of concurrent testing with both approaches should be executed (longer is better).

The microbial recovery difference observed and the microbial count differences observed between the current data (from both methods) and the data generated during initial system qualification should be used to determine the need to repeat a full or abbreviated requalification to establish a new baseline for current system performance.

Water systems with continuously sanitizing distribution systems are unlikely to demonstrate microbial changes as a function of system ageing. Microbial changes in the purification train may be obscured by the sanitizing conditions in the distribution system. Ageing changes may not be evident in the distribution system microbial counts, but microbial changes within the purification train could cause chemical purity changes in the finished water, as discussed in Section 13.3. This may provide justification for a root cause investigation or an abbreviated requalification focused on the chemical attributes in the distribution system, and microbiological and chemical evaluations in the purification train.

13.3 Detrimental Effects of Biofilm

The presence of biofilm in a high purity water system has consequences that are rarely beneficial. These detrimental effects are why so much activity and cost are expended in attempts to control it and minimize the damage it can cause. Biofilm in a high purity water system can impact both the surfaces it colonizes and the water that passes over those surfaces.

13.3.1 Potential Impact of Surface Alteration

If the biofilm is growing on a surface that has a function within the water purification process, the activity of that surface can be altered. Possibly the only beneficial biofilm colonization phenomenon occurs with coarse filtration. Sticky biofilm grows on the surface of multimedia bed grains or on the elements of coarse mesh filter cartridges, functionally increasing their adherence and sieving properties, as well as the size of the grains or mesh. This reduces the size of the holes in the filtering sieve and increases particulate filtration efficiency by trapping even smaller particles than those for which the filters were designed. Conversely, this causes lower dirt loading and faster blockage of the filtration step, along with biofilm sloughing and pioneer cell release.

If the colonized surface is the upstream side of an RO membrane, water will not be able to freely permeate that portion of the membrane, effectively blocking or fouling it, leading to reduced permeate flow, which, if compensated for by increasing pressure, results in poorer permeate quality.

If the colonized surface is an IX resin bead, water and its ionic impurities cannot as easily reach the active sites on and within the resin bead, effectively reducing IX efficiency. This surface occlusion also may significantly slow the penetration of any regenerant chemicals and their post-regeneration free-rinsing, further compromising the purifying IX functionality of the surface.

A common biofilm colonization phenomenon occurs within Granular Activated Carbon (GAC) beds. These beds remove organic compounds which serve as food for biofilm development. They also remove chlorine, which has modest antimicrobial activity against the naked pioneer cells (but nearly no effect on EPS-coated biofilm). The highly porous surface of the carbon granules provides an ideal environment for biofilm because of the:

- Enormous surface area on and within each granule

- Organic nutrients concentrated on those surfaces

- Absence of any antimicrobial chlorine

If allowed to continue without control from frequent backwashing, fast forward flushing, or hot water sanitization, the organic removal capacity of the carbon bed can be lost rapidly, and the bed quickly can become the source of high-level downstream contamination from released biofilm flocs and pioneer cells.

13.3.2 Potential Impact in Water Used

When biofilms develop in distribution systems, they typically do not harm the functionality or chemical inertness of the surfaces of the piping and valves on which they are growing. Harm is caused by gradual sloughing off into the water stream and exiting the water system with the water at POU into the applications requiring water. It is in these applications where these biofilm-derived organisms or their by-products can be detrimental.

If the water is used for dry products, such as solid oral dosage forms, the low water activity of the formulation, or possibly heat or solvents used in processing, usually are lethal to the biofilm-derived microorganisms, or minimally, are unfavorable for continued growth. These dosage forms are ingested, so even if the microorganisms survive in the dosage form, the hostility of the digestive tract usually will kill them.

If the product is a liquid formulation not intended to be sterile, and is contaminated with sloughed flocs of biofilm containing cells imbedded in protective EPS, these contaminants could evade product or preservative effects that would kill "naked" cells. They could survive for an extended period of time or even proliferate to high numbers in products that otherwise may have been deemed as suitably preserved by the "naked" cell challenges of compendial antimicrobial effectiveness tests; therefore, biofilm should be appropriately controlled in pharmaceutical water systems used for liquid non-sterile formulations.

If not properly controlled, the presence of specific biofilm-derived species also may be potentially harmful to patients using the dosage form, especially if the dosage form is:

- Directly administered to, or contacts, sensitive tissues, such as those of the respiratory tract or abraded/inflamed skin or mucous membranes

- Used where normal immunity is compromised by an underlying disease or a medical treatment

- Used with patients whose age or underdeveloped immune systems render them much more susceptible to infections, such as the very young and the very old

Most aquatic biofilm microorganisms are specialized for growth in their austere habitat and are unable to survive in a host or become pathogenic. A few highly adaptable species are considered opportunistic pathogens because they can cause infections in certain patient exposure situations when present in relatively high numbers. Examples are *Pseudomonas aeruginosa,* known for causing pneumonias as well as burn infections and an emerging opportunistic pathogen, and *Burkholderia cepacia* complex (also called BCC, a group of about 20 closely related *Burkholderia* species with similar metabolic, chemical resistance, and potentially pathogenic properties), which also has been associated with lung, skin and other infections, particularly in immuno-compromised individuals.

The concern originates from susceptible patients who were treated with products contaminated with these microorganisms that have often originated from a manufacturer's contaminated water system. These microorganisms can form and live in water system biofilms and also are capable of growing in or, at a minimum, surviving in otherwise seemingly well-preserved or hostile product formulations, even sanitizers such as povidone-iodine and other disinfectant solutions that have notoriously been contaminated with opportunistically pathogenic water system organisms [94]. Their presence in a water system should be a serious concern if the water is used for susceptible formulations or patients.

The products and uses most susceptible to the effects of water system biofilms are parenteral (or injected) products. These are sterile products, but the water used in these applications also must be free from bacterial components, such as the lipopolysaccharides (pyrogens) from cell walls of Gram-negative biofilm bacteria. Pyrogens are pharmacologically active at extremely low concentrations and should be at extremely low levels or absent in the water used for susceptible formulations.

The pyrogenic cell wall component is released by biofilm bacteria into the slimy EPS surrounding the cells as well as into the water outside the biofilm. Killing the cells in the biofilm producing this lipopolysaccharide does not destroy it, and may cause the release of even more of the pyrogenic lipopolysaccharide into the water, as the killed cells lyse or no longer retain cellular integrity. The best way to effectively control the presence of such harmful compounds in the water is to prevent the development of biofilm in the distribution system, and assure that any pyrogens present in the source water and pretreatment part of the system, are prevented from entering the finished water. When such precautions are taken, the resulting low or absent endotoxin levels are likely to be suitable for water used in manufacturing injection products.

13.4   Microbial and Biofilm Control Strategies

Effective microbial-control strategies typically include more than one approach, involving microbial-controlling design features, activities in multiple locations and implementation at different times. These controlling features and events are intended to work together to achieve control of microbial proliferation within a water system as biofilms. These strategies can be applied locally to individual unit operations or more broadly, such as to the entire storage and distribution system. Their combined success is related to their individual effectiveness. The elements discussed below can be incorporated into an overall microbial-control strategy.

13.4.1   Design and Operational Parameters

Understanding how biofilm responds to commonly used design and control approaches helps predict how well they should work and which approaches justify design and operational costs, based on the level of control that should be achieved. General control strategies usually include:

*   High flow rate and frequent backwashing or fast forward flushing

*   Weld and surface smoothness and material type

*   Use of hostile regenerant, sanitizing or passivating chemicals

*   Use of heat

*   Use of UV

*   Use of filtration

*   Use of ultrapure water (18 MΩ, TOC < 5 ppb)

Individually, these approaches work with varying degrees of thoroughness. When several compatible approaches are combined, the effects tend to be better and last longer.

Most water system biofilm-forming microorganisms are generally equivalent in their susceptibility to these microbial-controlling conditions. However, in a protective, slimy biofilm form compared to their naked planktonic cell form, the differences in susceptibility between these forms is substantial, by factors of as much as 10,000-fold, depending on the thickness and age of the biofilm and how much protective EPS has been allowed to be produced by the biofilm. A microbial-control program, therefore, should be aimed at the more vulnerable planktonic or thin/young biofilm microbial forms in order to prevent or reduce biofilm formation and growth.

Purification measures that enhance the chemical purity of the water can also control the proliferation of biofilm and reduce the presence of endotoxins in the water, since these microorganisms can be a source of endotoxins. Endotoxins in the water also may have originated from bacteria upstream of the distribution system (possibly from biofilms growing within the purification train as well as the incoming source water). Complete control of endotoxin should include microbial control within the system and direct removal of endotoxin from the incoming water by purification unit operations capable of separating these macromolecules from water. Unit operations suitable for this purpose include:

*   Distillation

*   UF

*   RO

*   Anion-exchange resins and positively charged membranes (to a limited extent)

- TOC-reducing UV irradiation units

Given sufficient concentration and contact time, ozone also can destroy endotoxins.

13.4.1.1 Effects of Flow Rate on Biofilm Control

As a biofilm grows larger, it tends to grow outward from the surface where originally attached, as the flow rate shear forces allow. If left undisturbed in stagnant or slowly moving water (0–about 0.1 m/s velocity), the biofilm can form column or mushroom-like shapes that maximize its surface contact with water-borne nutrients; however, taller biofilms are fragile and particularly susceptible to the shear forces of flowing water, especially under changing velocities including pulsations from water hammer. If a biofilm that developed in slowly moving or stagnant water experiences any sudden increase in flow rate or directional change, such as from backwashing or sampling, large portions of the outer biofilm structures may shear off and be carried planktonically with the water flow.

This is the expected and desired consequence when backwashing a granular purification bed such as media filters, activated carbon, softeners, deionizers, or other similar devices. When performed effectively with the entire granular bed being lifted and fluidized by the rapidly reverse flowing water, such backwashing should partially remove the buildup of biofilm and trapped debris. If the biofilm is given sufficient undisturbed time to accumulate in the spaces between granules, particularly downstream of chlorine removal, or where chlorine levels are minimal, it effectively may bond the granules together making them highly resistant to being fully fluidized during backwashing. This agglomeration also impedes the penetration of sanitizing hot water or regenerant chemicals to bed granules.

In distribution systems, when biofilm forms in POU valves and their connecting side legs (possibly as well as in downstream hoses), a preliminary flush of the outlet to drain may be required to first remove the bulk of the loose biofilm. This helps to avoid the presence of sloughed biofilm in water used from the outlet.

A zone of laminar flowing water beneath what is called the boundary layer always exists next to the solid pipe surface, even in highly turbulent water. The less turbulent the bulk water circulation, the thicker this boundary layer. At a typical loop recirculation velocity of about 3 ft/s, this laminar zone is about 120 µm thick, and even at the optimal outlet flushing velocity of 8 ft/s, this laminar zone is still about 50µm thick [95]. Its relationship with flow rate is asymptotic and never goes significantly below 20 µm, even in the fastest flowing water, leaving more than adequate space for biofilm to grow on piping surfaces beneath the turbulent zone.

Thus, even in the most turbulently flowing water, causing the thinnest possible boundary layer, a several-cell thick tenacious biofilm can develop, though with a much thinner and simplified structure compared to stagnant water biofilms. If such a biofilm continues to grow and extends above the laminar zone into the turbulently flowing water, or the turbulence momentarily penetrates into the boundary layer, the outer fragile biofilm layers may be sheared off into the water flow, probably as small multicelled, sticky flocs of intact biofilm. Flow-sheared flocs of biofilm, along with any intentionally released biofilm pioneer cells, may find their way to a downstream boundary layer, surface imperfection, or crevice to establish a biofilm or leave the water system along with the water drawn from a POU.

Microbial and biofilm growth rate is dependent on nutrient levels. In nutritionally equivalent systems with nearly stagnant flow versus fast, highly turbulent flow, the biofilm growth rate tends to be slightly faster in the higher flow scenario because of an increase in the passage of nutrients across the biofilm and more opportunities for nutrient molecule capture by biofilm microorganisms. The shape and associated tenacity of the biofilm develop to accommodate the continuous shear forces of the water.

Alternatively, in ultrapure water systems with mineral and nutrient deprived environments (18 MΩ, extremely low TOC levels) almost any water flow has been shown to dramatically slow the development of biofilms in a distribution system. This "Nutrient Deprivation Model" for microbial and biofilm control is well known and documented in the microelectronics industry.

Water use and sampling create flows in a stagnant system as well as slower moving or stagnant parts of flowing systems (such as sampling ports and some POU valve configurations). The shear forces of this flow can detach multicelled flocs of biofilm from the fragile outer layers of adhering biofilm (this is the rationale behind flushing outlets before use or sampling). Where the water is continuously turbulent, minimal biofilm floc shearing occurs from any tenacious, surface-hugging biofilm that may be growing there. Plate counts of those samples may give the misleading impression of large differences in levels of biofilm development, where this may not be the case. Highly turbulent flow is considered advantageous in reducing the shedding of biofilm by inducing it to grow less erectly and attach more tenaciously to the surface. Turbulent flow also is necessary for thorough mixing of sanitizing chemicals and hot water into short side legs and valves connected to the main piping. Turbulence and flow rate have very little impact on the rate of biofilm initiation or growth.

13.4.1.2 Effects of Surface Smoothness and Composition on Biofilm Control

Controlled studies have shown that using expensive ultra-smooth surfaces virtually free from surface scratches and imperfections, such as PVDF or electropolished SS, offer only a moderate advantage in delaying the initial cell adsorption of biofilm development. The hydrophobic surface of many high technology plastics also shows a similar moderate delay in initial colonization compared to hydrophilic SS surfaces. These delays are possibly only several hours under highly turbulent flow conditions. Unfortunately, some studies show exactly the opposite effects of hydrophobic versus hydrophilic surfaces, so the phenomenon may be species-specific. What is clear is that once biofilm growth has begun, the resulting biofilms demonstrate an equivalent tenacity on a surface, irrespective of the material's "phobicity" or finish. Once the surface has biofilm-covered areas, the surface of the biofilm becomes the preferred site for further microbial attachment, and that surface is identical whether the biofilm initially formed on a smooth or rough, hydrophilic or hydrophobic surface.

The presence of surface imperfections, however, can have a significant impact on the ability of the surface to be cleaned or sanitized chemically. Crevices caused by microscopic cracks or pits in the surface, in macroscopic gaps at gasket/seal edges of hygienic connections, at imperfect welds, in hoses, or in the pinched septa of hygienic valves offer protective areas from poorly penetrating chemical cleaners and sanitants, allowing survival of at least a portion of the cell population within biofilms growing in these areas. These macroscopic imperfections probably provide the greatest survival advantage to biofilm from sanitization efforts.

The relatively high cost of ultra-smooth and hydrophobic surfaces should be evaluated against the modest delay in biofilm formation and marginal improvements in cleanability, particularly in heated or continuously sanitized systems, which tend to never form biofilms anyway. Efforts to minimize macroscopic imperfections and crevices are worthwhile and should be considered.

13.4.1.3 Effect of Water Purity on Biofilm Control

As the purity of water increases, the rate of microbial growth and biofilm development decreases. When ultrapure water conditions are approached, the lack of nutrients may create conditions almost completely inhibitory to bacterial growth, although, low levels of nutrients may still be present (typically concentrated at solid surfaces) and some microbial growth will still occur at an extremely slow rate. High purity water that has resistivity near 18 MΩ-cm, with TOC levels in the low ppb (single digits) tends to allow only very slow biofilm development and growth.

Water at an ultrapure level is well beyond the purity generally needed for most pharmaceutical manufacturing purposes or required by the pharmacopeia. It is challenging to produce water of this quality and several paradigm shifts may be required, but microelectronic and semiconductor ultrapure water systems have a proven track record for effective microbial and biofilm control without requiring regular sanitizations. Designs of this type may be a consideration for use in pharmaceutical applications where such purity levels are desired, for example in research or laboratory applications or in certain manufacturing or formulation scenarios.

13.4.1.4 Effect of Water Temperature on Biofilm Control

Temperatures about 10°C–40°C (50°F–104°F) tend to encompass the operating temperatures of water systems considered to be ambient. The ambient air temperature of a manufacturing or utility area typically is around 20°C–25°C (68°F–77°F). The incoming water temperature may be lower, but frictional heating from the circulating pumps, water circulation, UV units, etc. can increase the water temperature 1°C–2°C per pass. Rapidly recirculating water systems, whose circulating temperatures are not appropriately moderated by cooling heat exchangers, could reach a temperature equilibrium with the environment of 30°C–35°C (86°F–95°F) or higher, which represents an ideal growth temperature for many water system bacteria. Since chemical and biological reaction rates increase with temperature, warmer temperatures tend to encourage faster microbial growth.

Most firms consider distillation processes to be immune from microbial problems because of high operating temperatures intolerable to bacteria; however, wet, cooler locations within the still, such as the cooling condenser, or in stills that do not operate continuously, may not be at microbial-inhibitory temperatures and appropriate microbial-control precautions may be required.

Chilling water distribution systems may be used for process or personnel safety reasons. In systems operating below ambient temperature, pipes and tanks usually are insulated to avoid greater energy expenditure and condensation. Chilling has the benefit of keeping the water temperature low enough (typically 2°C–8°C; 35.6°F–46.4°F) to slow the development of biofilm. However, biofilm eventually will develop, even in cold water. A continuously cold system will select for colonization by psychrophilic (cold-loving) microorganisms. These bacteria will preferentially grow in the warmer places of the cold-water system. Their growth rate will be slow, but may be faster than the typical mesophilic (moderate temperature-loving) microorganisms at the same location. Psychrophiles typically are susceptible to heat kill at lower water temperatures than mesophiles.

Continuously cold systems require constant attention to maintain low temperatures throughout, particularly with circulating pumps, uninsulated POU, or uninsulated portions of the system adding heat. In addition, if enumeration of the psychrophilic microbial population uses a cell cultivation approach, it may require cooler incubation conditions (20°C–25°C; 68°F–77°F) that are more suited to their optimal growth temperatures. This usually requires extended incubation times (perhaps doubled) because of their slower growth rates compared to those of mesophilic microorganisms. A cold-water system should not be considered as advantageous for microbial control because of capital and operational cost (as well as timelines for monitoring results). However, a cold-water system offers intermittent heat sanitization advantages that may be within the heat tolerance range of several plastic materials unable to withstand the elevated water temperatures required for sanitizing mesophiles.

Finally, a cold-water system represents challenges in collecting clean samples due to unavoidable condensation at sampling and POU ports, and the biofilms that grow on these moist outside surfaces. Collecting samples and using water at cold outlets in a fashion that avoids contamination from these outside surfaces requires much greater care than with ambient temperature systems.

13.4.2 Effective Sanitization Concepts

Sanitization of individual purification unit operations, including storage and distribution systems, aims to improve the functionality of that unit operation over the long term, as well as the microbial quality of the water passing through it. Sanitization normally is achieved by exposing microorganisms in the water, and the biofilm growing on associated surfaces, to a physical condition or chemical that kills them. In practice, sanitization can be frustratingly inadequate if not performed properly, if the system components (or their absence) prevent sanitant penetration or coverage, or if the materials of construction limit sanitization options to less effective approaches. Misinformation or ignorance of efficacious parameters often leads to ineffective sanitization. Inadequate sanitization that leads to frequent or excessive system contamination can be the cause of significant cost in terms of labor, lost production time, and if not performed when required, potential negative product, safety, and regulatory consequences. A few basic, rational concepts, discussed below, should be considered when sanitizing a water system to be assured of success and improve the microbial quality of the water system in the longer term.

13.4.2.1 Frequency of Sanitization

Continuous Sanitization

Continuously sanitizing conditions that prevent the initiation of biofilm development is considered the ideal sanitization frequency in the pharmaceutical industry. The cells targeted are usually naked newcomers that have yet to develop a protective EPS coating. This allows sanitization conditions to be of minimal potency because of the ease of target cell destruction.

For continuous sanitization to be practical; however, the sanitant needs to be rapidly removable and leave no residue to be flushed out of the system. This limits the acceptable sanitizer choices to heat and ozone (at time of Guide publication) because not only are these sanitizers quite lethal at the right doses, they are the two for which system features can be designed to continuously tolerate their lethal or chemically reactive properties as well as rapidly neutralize them in situ without residue.

Continuous sanitization is considered the most effective approach to microbial control and frequently is employed for WFI systems, where any level of distribution system biofilm development is generally intolerable. Continuous sanitization for PW systems is used less frequently because of cost and logistical considerations, and the awareness that some minimal level of biofilm growth may not be problematic.

Intermittent Sanitization

Systems may use intermittent sanitization for microbial and biofilm control, particularly where a low microbial level in the water does not negatively impact product quality. A sanitization frequency that prevents significant biofilm development during the intervening non-hostile periods between sanitizations is considered fundamental to the success of this approach. Once biofilm has developed its protective EPS coating, it becomes much harder to kill with chemical agents because of poor penetration to the cells imbedded in this EPS. When biofilm has had opportunity to develop in crevices that also impede sanitant penetration, this resistance is more pronounced. If significant biofilm has been allowed to develop between sanitizations, particularly within protective crevices, the ability of even the most aggressive chemical sanitants to give lasting microbial control may be permanently compromised or require extreme efforts to remediate.

13.4.2.2 Kill and Remove the Biofilm

For lasting microbial control, biofilm should be killed and the dead biomass removed. This biomass is a rich source of nutrient for any pioneer cells that may appear and attach to it after the sanitization process is complete. In the presence of such rich nutrients, biofilm regrowth is more rapid. Complete biofilm degradation and removal also assures that complete biofilm kill has been achieved. If the biofilm is only partially killed and partially removed, then biofilm regrowth by the remaining live cells, nourished by the dead biomass, may rapidly rebound after a brief period of low microbial counts.

13.4.2.3 Use an Effective Sanitizing Agent

The sanitizing agent should be deadly to the microbial cells that thrive inside biofilms. Some sanitizers may work by penetrating and killing the biofilm, but leaving it in place (such as heat and chlorine dioxide), while other sanitizers work by chemically degrading the biofilm starting at the outside and killing cells as they are exposed (e.g., most oxidizing or caustic). The oxidation potential is a factor in the efficacy of an oxidizing sanitizer; this is related to its ability to degrade strong covalent bonds in the complex organic molecules associated with the biofilm, including the EPS and cellular components, such as endotoxin. If heat is used as the sanitant, it usually has no difficulty in penetrating through to the base of the biofilm and then into crevices where biofilm may be growing. Heat needs to be of a sufficient temperature to be lethal to biofilm microorganisms after environmental heat losses to distal system components like sampling ports and POU valves. In addition, heat has no direct ability to remove biofilm or to degrade the endotoxin present in the biofilm slime and on the killed cells.

13.4.2.4 Use an Effective Sanitization Procedure

Appropriate sanitizing agents should be used at adequate concentrations and exposure times to be effective. What constitutes "adequate" depends on the resistance of the biofilm to the attack and the properties of the sanitizing agent. There are no universally effective treatment parameters. If an oxidizing chemical is used, its efficacy is related to its reactivity (for oxidizers, expressed as oxidation potential) as well as its concentration, contact time, and possibly its temperature. Chemical sanitization failure often is the result of inadequate sanitizer contact time and insufficient sanitizer concentration, leading to incomplete destruction of the biofilm and a rapid post-sanitization regrowth.

Another significant cause of sanitization failure is the growth of biofilm in crevices or cracks created by sub-optimal construction techniques and materials. Within such protected locations, a chemical sanitant is unlikely to penetrate sufficiently to kill all the biofilm developing within, so once the sanitizing conditions are removed, the biofilm resumes growth, possibly accelerated by a rich supply of nutrient from killed, but still present biofilm material.

Heat is considered an extremely effective approach to killing biofilm because of its ability to penetrate even thick biofilms easily, and the susceptibility of biofilm microorganisms to relatively modest levels of heat. The concerns with effective hot water sanitization focus on temperature and contact time, as affected by the balance between heat distribution and heat loss.

The duration of the heat treatment should be based on the temperature at the coolest or slowest-to-heat-up point in the system. The temperature of the return water may not be a good indicator of this temperature. This is particularly important for systems that are intermittently hot water sanitized and may not be well insulated against heat loss, making them very slow to equilibrate to a sanitizing temperature. Plastic systems are also a concern for this approach, because plastics do not as readily conduct heat to surfaces at the distal parts of sampling and POU valves. In these situations, momentarily flushing the hot water through these valves using proper safety protocols will allow the penetration of the sanitizing heat to these moist surfaces.

A follow-up chemical treatment after an infrequent hot water sanitization may be necessary to remove sizeable dead biofilm deposits, which might otherwise fuel rapid biofilm regrowth.

Wet locations that could support microbial growth should experience a heat or chemical sanitizing treatment for sufficient time to kill the microorganisms. Sanitant contact with **all** surfaces in need of sanitization is important to the success of the process for both chemical and heat sanitization, including:

- The unfilled head space portion of holding tanks (usually using sprayballs, except in the case of ozone sanitization)

- Valves (especially sampling and at POU)

- At-line or in-line unit operations like heat exchangers

- In-line flow metering devices (with moving parts)

- Hoses (including their fittings and gaskets)

- Filter housings (including vent/drain ports and installed filters, if compatible)

- Parallel/backup pumps and associated piping

- Piping/tubing (direct and side stream) to and including instruments

- Other appropriate components or hardware

Following sanitization, the sanitizing agent should be removed to render the water usable again (except with hot water when compatible with products). With continuous sanitizing agents, this process should be achieved *in situ* with no system flushing required. For intermittently used chemical sanitants, the sanitant, along with any associated released debris, usually needs to be flushed out of the system. In such sanitizing applications, sloped and drainable systems have the advantage of allowing more rapid and efficient sanitant removal with minimal flushing to completely remove any residue.

Although not recommended, if steam is used for sanitization, sloping and use of condensate bleeding valves or steam traps are considered essential. Where flushing of sanitant residues is needed, microbiologically and chemically high-quality water should be used to avoid contaminating and reinoculating the system immediately after sanitization. This water can originate from a volume of water reserved just prior to sanitization or it can be the water freshly produced by the system normally after sanitization. System flushing and rinsing capability should be designed into the water system from the start.

13.4.2.5 Minimize Recolonization

Once a system has been sanitized and the biofilm has been reduced significantly, an ongoing process to minimize recolonization may be useful to prolong the time between sanitizations. These approaches generally work by removing or killing all or most new pioneer cells and floating biofilm flocs coming from the water purification units before they can enter and recolonize the storage and distribution system surfaces. This typically is done by controlling biofilm growth and its' potential for sloughing or shedding in the step prior to the distribution system, or killing the planktonic organisms before or as they enter the storage and distribution system.

A number of approaches are commonly used, such as:

- An in-line UV treatment unit (sometimes called a UV Sanitizer or UV Disinfection Unit) with or without a downstream microbial-retentive filter

- Continuous ozonation of the distribution storage tank, so that incoming water is initially ozonated and recirculated water receives routine periodic ozonation, both at germicidal ozone doses

- A final purification unit operation that is resistant to microbial growth or does not allow microbial passage, such as a still, or a hot water sanitizable RO unit or UF unit

An in-line microbially retentive filter may be used in conjunction with other upstream control measures such as UV treatment units. In the absence of control measures immediately upstream, the filter is likely to have only a short retentive life span. The live microorganisms and flocs form a biofilm on and within the filter membrane, and may rapidly penetrate or grow through the filter. This may become a source of downstream contamination after a relatively short period (possibly only a few days), rather than acting as a permanent absolute barrier.

13.5   Sanitizer Choices

Generally, sanitizers can be grouped as physical or chemical. Physical sanitization options, such as UV sanitizers, may exert only a local effect; others may exert only a temporary effect, such as microbial-retentive filtration. Heat is considered a more conventional physical sanitant, either as hot water or as steam, in pharmaceutical water systems, the latter of which is no longer recommended, as discussed in Section 13.5.1.4.

There are a number of chemical sanitizer choices, several of which are oxidizing agents with various oxidizing capabilities and other attributes that affect their lethal, penetrative, and biofilm-destructive properties and usefulness as water system sanitizers. In addition, a number of non-oxidative sanitizers may be used with varying degrees of success and often in special sanitization applications.

13.5.1 Physical Sanitizers

13.5.1.1 Ultraviolet Irradiation

UV light is maximally absorbed by the pyrimidine bases in DNA across the UV wavelengths of 240–280 nm. The absorbed energy makes these bases reactive, causing them to covalently bind to neighboring pyrimidine bases in the DNA, which prevents microbial replication and protein synthesis and ultimately kills the cells. The UV light emitted by low-pressure mercury vapor lamps has an intense emission at 254 nm and is the type of bulb used in UV treatment units. At the appropriate flow rate, water can flow through a chamber containing such bulbs and be in contact with the UV light long enough to kill 99% or more of the microorganisms in the water. As much as 1% may not be killed and no bacteria are killed outside of the exposure chamber. Those that survive the journey through the exposure chamber may do so because of being attached to an opaque particle (such as rouge) or imbedded in the center of a biofilm floc, where they are shielded or shadowed from the deadly light rays.

Many users incorrectly assume that in-line UV treatment units sanitize the entire water system, constituting continuous sanitization. Such in-line UV treatment units can kill only what they actively shine on. Surviving microorganisms can form downstream biofilms. In-line UV sanitizers slow the downstream development of new biofilms from planktonic cells that pass through the chamber suspended in the water flow. UV is most valuable where the downstream biofilm has been eliminated by an aggressive, highly effective approach. In this scenario, continuous UV treatment helps reduce the need for frequent sanitization.

The remaining 1% of microorganisms that survive the UV treatment can be captured or significantly delayed from passing further downstream by placing micro-retentive filters downstream of the UV treatment unit, further extending the period between sanitizations. Filters installed post UV also safeguard downstream piping in the unlikely event of UV damage resulting in a broken bulb or quartz sleeve. See Chapter 5 for a more complete discussion.

Low-pressure amalgam UV lamps used in TOC-reducing UV treatment units emit a higher energy, hydroxyl free-radical generating wavelength of 185 nm in addition to the antimicrobial 254 nm wavelength. It is these free radicals that oxidatively attack and degrade the TOC in the water. For a more complete discussion of TOC-reducing UV units, refer to Chapter 5.

13.5.1.2 Filtration

Application of filtration ranges from the coarse filters used to remove multi-micron sized particles from incoming water or to protect downstream unit operations from debris-shedding granular beds, to the ultra-fine RO filters whose permeability is so fine that essentially only water molecules can pass through. In water systems, there are usually several grades of filters between these two extremes intended for various retention purposes.

Coarse Filtration

Coarse filters are not intended to retain bacteria and are not used for microbial control. Where left in service for excessive periods, however, coarse filters can add to the microbial content of the passing water. The large surface area of these filters usually becomes heavily colonized by biofilm (even in the presence of incoming chlorinated water), which then sheds microbial contaminants into its effluent water, particularly during the surge of start and stop operations. They may present a more serious microbial contribution where they are used between unit operations within the purification train to protect downstream unit operations from escaped bed granules and fragments. The back pressure that develops over time in coarse filters may be more because of biofilm occlusion than debris loading. With such heavily colonized locations able to shed large amounts of biofilm bacteria, their maintenance or replacement frequency, based on back pressure, may need to be assessed on the microbial sensitivity of the downstream unit operation, rather than on the manufacturer's replacement recommendations.

Micro-Retentive Filtration

Micro-retentive filters with ratings of 0.22 µm, 0.2 µm, 0.1 µm, 0.05 µm absolute traditionally have been used to filter sterilize processed liquids prior to aseptic packaging.

There is a long-held misconception that absolute-rated filters are absolute in their removal capability, that the filter's rating is its maximum pore size, and that the filter functions solely as a sieve to remove bacteria and other similarly-sized particles. None of these beliefs are true for most membrane filters. Such filters' pore sizes are actually a range of sizes with the largest possibly being up to two or three times larger than its labeled rating, meaning that a small percentage of particles larger than the rating could get through. Bacterial capture by the 0.2 µm and 0.22 µm-rated filters is based on a mixture of sieving effects and a cell adsorption phenomenon occurring within the filter matrix; organisms tend to stick to the surface of matrix fibers as they flow through the filter along an intrinsically convoluted path created by the matrix.

In fact, and in spite of a filter's validated absolute retention of the challenge organism *Brevundimonas diminuta,* microbial penetration of these supposedly absolute 0.2 µm and 0.22 µm-rated filters occurs, and is especially prevalent with water system microorganisms. In water systems, it occurs well before any hint of back pressure has developed. In fact, by the time there is any barely detectable additional back pressure, the filter may have been passing large numbers of bacteria for quite some time.

The occurrence of this microbial passage phenomenon is unarguable, but its mechanisms are still debated. One theory is that particularly small cells (smaller than *B. diminuta*) and/or cells with low surface hydrophobicity (less hydrophobic than *B. diminuta*), like those found in water systems, eventually happen upon one of these larger pores, avoid hydrophobic adsorption to the filter matrix, and manage to simply "go through" the filter. Another theory involves "grow through" in which the bacteria colonize the filter's internal matrix surfaces and through the cellular elongation that precedes binary fission, some of the newly formed daughter cells are incrementally pushed along these surfaces and through small gaps, eventually all the way to the downstream side.

Microbial penetration of 0.2 µm-rated filters by water system organisms typically occurs when micro-retentive filters are kept in liquid filtration service too long. Among other variables, the length of time for which these filters should be kept in service depends upon the size, surface properties, and level of viable bacteria impinging on the filter, as well as the composition and pore size distribution of the filter, flow-rate effects, and a number of other variables.

There is no generally applicable time before filter penetration occurs. Where allowed by regulatory expectations, an appropriate usage period can be determined empirically and validated for a given filtration application [40].

Note: The FDA disallows these filters to be in service for unvalidated use periods or in situations where the filters are used to mask poor water quality because of poor system design and maintenance [40].

Filters rated at 0.1 µm, which purportedly are impenetrable by small bacteria found in water systems, may also be an option. The microbial challenge tests for filters with this rating are less standardized and may be more difficult to perform, so the retentive properties are harder to verify and not all filters with this rating are equally effective at retaining certain aquatic bacteria (e.g., *Hydrogenophaga pseudoflava*) [96], although this organism is unlikely to be found in pharmaceutical water systems. The finer filter matrix for some of these filters may create greater flow resistance than 0.2 µm-rated filters, necessitating a greater number of 0.1 µm-rated filter cartridges to achieve the same flow rate as 0.2 µm-rated filters.

Depending on the application, the potential sacrifice in flow rate and cost may be warranted, but these filters also may clog with tiny particulates or biofilm more quickly than 0.2 µm-rated filters, adding to the cost with more frequent replacement. However, note that some filter manufacturers have fine porosity filters (with even less than 0.1 µm-ratings) that use hollow fiber designs for filtration and do not suffer from flow-rate losses compared to conventional 0.2 µm-rated filters because of a larger filtration surface area and its pseudo-tangential flow design.

As mentioned in Section 13.5.1.1, the use of microbial-retentive filters immediately downstream of UV sanitizers is considered to be a more effective and sustainable filter application. The UV treatment units (or upstream ozone) kill the majority of cells before they impinge on the filters. The filters capture the killed or mortally damaged cells and the remaining small viable population, preventing them, for a time, from getting through the filter and downstream to recolonize new distribution system surfaces. These tandem unit operations help to prolong the usable life of the filter, possibly from only a few days without upstream UV to up to many months, depending on the water's microbial content at that location and the efficiency of the UV sanitizer. The combination of UV sanitizer and 0.2 (or less) μm-rated filtration should be used without interruption or even being momentarily bypassed, and the downstream system should have been previously sanitized with almost all downstream biofilm killed.

If the water is allowed to bypass these units during maintenance, for example, to replace lamps or filter elements, or to bypass these units to facilitate sanitant rinse out, biofilm colonizers may be allowed downstream into the system to begin forming new biofilms or repopulate freshly destroyed but unremoved biofilms. In such situations, system sanitization should be performed again soon afterward to re-establish a system-wide condition of near-freedom from biofilm, which the UV/filter combination is intended to prolong.

Ultrafiltration

These filters have minute pores and are able to screen out large organic molecules to a rated MWCO. The use of ultrafilters for endotoxin removal from water is reasonably common for non-distillation systems, particularly downstream of RO or deionization systems. For this application, JP XVI Information Chapter G8 [6] cites a MWCO of 6,000 Daltons; however, because endotoxin invariably exists in PW in an agglomerated, multiple-molecule state, higher MWCO of 10,000 or 20,000 Daltons also have been used effectively for endotoxin removal. Ultrafilters are discussed in Chapter 5 in greater detail and are commercially available in pore sizes with molecular weight exclusion ratings of 3,000–100,000 Daltons.

Reverse Osmosis

RO units can offer a barrier to microbial and endotoxin penetration, but with unverifiable membrane and assembly integrity issues. They typically are sanitized with chemicals, but with the added impediment that only a few sanitizers are compatible with RO membranes and a reduced ability to sanitize the permeate side of the RO membrane, which may lead to downstream biofilm development and potential generation of endotoxins by that biofilm. Some proprietary sanitants, such as those containing peracetic acid/hydrogen peroxide mixtures, have molecules small enough to penetrate RO membranes to sanitize permeate surfaces. RO units may be designed to be hot water sanitizable and simultaneously contact all upstream and downstream surfaces. Concerns with ROs include:

- Frequency and efficacy of chemical cleaning and sanitization

- Possibility of permeate side biofilm development

- Non-absolute microbial retention and unverifiable membrane integrity

These concerns are greatly reduced if the RO can be periodically sanitized with hot water.

13.5.1.3 Heat Sanitization with Hot Water

In high purity water, biofilm growth typically is either minimal or absent above approximately 45°C (113°F). Temperatures above approximately 50°C (122°F) usually are hostile and slowly lethal to biofilm-forming organisms in water systems. Higher temperatures such as 65°C (149°F) and 80°C (176°F) often are used for hot water sanitization. EU GMP (Annex 1, Item 59) [21] suggests using > 70°C (158°F). The higher the temperature, the quicker the microbial death, but it is so fast even at 65°C that temperatures at or above this temperature (e.g., 80°C (176°F)) are essentially instantaneously lethal [97]. Hence, even hotter temperatures, which would kill even faster, are not necessary to kill these relatively heat-susceptible biofilm organisms.

While aquatic thermophiles capable of withstanding the hot water temperatures used to sanitize a pharmaceutical water system exist in nature, they do not exist in high purity water systems because of the absence of their essential nutrients [98]. Designing sanitization cycles or monitoring techniques to kill these thermophiles, or detect their presence, is considered unnecessary and an inefficient use of energy and analytical resources.

Because of this, water distribution systems operating ≥ 65°C (149°F) generally are considered to be self-sanitizing; 80°C (176°F) is an often-used target temperature. When used continuously, biofilm does not have an opportunity to form in locations at those temperatures, so the water can be maintained in essentially a sterile state. It is common for WFI systems to be operated in a continuously self-sanitizing condition, because the system has little tolerance for microbial/biofilm growth, one of the possible sources of systemic endotoxins that is tightly regulated in this grade of water. PW systems also may be operated under continuously sanitizing temperatures, either to assure trouble-free microbial control or because of process needs.

However, since WFI system owners often need to use ambient temperature water for manufacturing purposes, it is common for continuously hot WFI distribution systems to have either POU heat exchangers, or entire loops or sub-loops operated intermittently or continuously at an ambient temperature condition. It is in these cooler parts of otherwise hot distribution systems where biofilms can develop if not periodically heated to the same self-sanitizing temperature as the main distribution loop. This should be done at least weekly if not more often, such as daily. The system operators are cautioned that if using cooling heat exchangers, adequate time must be allowed for the heat exchanger to reach a sanitizing temperature during sanitization; the return temperature of the water is often not a good indicator of remaining slow-to-heat locations within the cooling heat exchanger. Refer to Chapter 5 for a more thorough discussion of heat exchanger design, failure modes, and their sanitization.

Intermittent hot water sanitization is more common in PW systems. Hot water sanitization has the advantage of penetrating, by heat conduction, into wet crevices where biofilm could be growing and where chemical sanitizers may never reach (see Section 13.5.2.). Conduction-mediated heat penetration may reduce the concerns of microbial control in crevices associated with seals, gaskets, and surface imperfections. The temperatures generally used are 65°C to > 80°C (149°F to > 176°F). Sanitization efficacy issues can be accommodated with the timing for the treatment beginning when the target temperature is reached at a determined coolest point (which may not be the return to the tank). Treatment times of 0.5–4 h are common for ≥ 80°C (176°F) sanitizations, with longer times required for more complex designs, to assure heat penetration to all moist surfaces.

Care should be exercised with 65°C (149°F) sanitizations since heat losses during conduction-mediated heating can cause a temperature drop of as much as 10°C–15°C (50°F–59°F) across a metal POU valve to downstream moist valve surfaces, yielding minimally or non-sanitizing conditions on those distal surfaces. Longer exposures may be required if relying solely on heat conduction for sanitizing these surfaces. In such situations, safely flushing the hot water for a few seconds through the valve can effectively overcome the otherwise minimally sanitizing condition. This approach is considered particularly useful for heat-tolerant non-metallic (PVDF) systems, because of poor heat conduction through system materials.

Occasionally, heat-tolerant, non-metallic systems (and SS systems) are considered for hot water sanitization when chemical sanitization has failed to achieve microbial control. In such situations, these non-metallic systems may not have been designed to be heated and may not be fully compatible with typically-used sanitization temperatures. The non-metallic systems theoretically may be tolerant of the stresses of marginally sanitizing temperatures of 55°C–60°C (131°F–140°F). However, great care should be exercised before attempting this since there may be inordinate heat losses due to long uninsulated and unsupported runs of piping, as well as thermal expansion (which could cause permanent sag), and physical strength/stress issues that could cause a catastrophic failure in pipe or tank integrity, or even an unanticipated heat-incompatible component that may be part of an otherwise heat-tolerant unit operation.

Sanitizing under sub-optimal conditions may cause several additional concerns, including:

- The requirement for extended treatment time to accommodate a slow heat-up, prolonging the risk period to system integrity

- Heat losses in the system may require water hotter in the initial stretch of piping downstream of the heat exchanger than the treatment temperature; thus, heat compatibility in this location is particularly important.

- Non-metallic tanks may need to be sanitized in a minimally filled condition that allows circulation but minimizes hydrostatic stress on the tank walls when hot.

- Not achieving a sanitizing temperature in all parts of the system due to heat losses

A disadvantage of using heat as a sanitizing agent is that although it is quite lethal to the organisms that could inhabit a water system as biofilms, it does not remove those heat-killed biofilms. It leaves the dead organic biomass in its original location, which could serve as food for future biofilm development by new arrivals (see Section 13.4.2.2).

13.5.1.4 Heat Sanitization with Steam

Steam can be used to sanitize water systems, although it is typically no more effective in system microbial control than hot water and considerably more complicated. It increases component wear, increases rouging in SS systems, and may have higher safety concerns than hot water. Traditionally, steam under pressure (and more recently superheated hot water under pressure) has been used in sterilization methods, and generally is perceived (incorrectly) as more effective than using plain 65°C–80°C (149°F–176°F) water for water system sanitization because of steam's higher temperature and greater lethality. Water systems can be designed to be steam sanitized, but the temperatures this approach can achieve are far in excess of those necessary to kill biofilm organisms that may be growing in the system.

Sterilizing conditions of steam may be perceived as required to kill extremely heat-resistant exogenous organisms that may have entered a water system through a compromised vent filter or rupture disc, or prior to initial system start-up. However, such potentially heat-resistant organisms are not aquatic, typically do not produce endotoxins, and are not the types of organisms that could become established, form biofilms, or proliferate in a water system. They are transients that do not survive very long in water systems. A hot water sanitization and system flushing is usually all that is required to eliminate these microorganisms, but system sanitization with steam is an alternative, albeit archaic, approach.

If steam is used for in situ sanitization within a water system, USP Pure Steam [4] should be used. If this purity of steam is not available, precautions should be taken to ensure component compatibility and post-sanitization flushing to make certain that all steam additive residues and particulates have been removed after steaming. This is such an arduous and time-consuming task that Pure Steam is almost exclusively used.

During design and construction of a steam-compatible system, consideration should be given to:

- Choice of materials and design features to accommodate the extreme temperature differentials between ambient routine use and sanitization

- Piping insulation

- Ability to completely drain the system prior to steaming

- Air venting before steaming (to remove trapped air pockets and hamper heat transfer) and after steaming (to relieve the vacuum related to steam collapse)

- Pipe sloping to facilitate condensate drainage

- Condensate removal through properly piped steam traps at all low points

- Steam injection valve design and locations to assure temperature uniformity during steaming

- System designs for steam injection, air venting, and condensate bleeding that do not compromise the hygienic design of the water system while producing and distributing water

- Quantity of steam needed for large water systems

Insulation is important for safety and to avoid heat loss and poor heat distribution in long piping runs, large tanks, and granular beds, as well as to reduce the amount of steam needed. If such features are improperly installed or fail (e.g., condensate accumulation near a clogged steam trap), the accumulating water may not be sufficiently hot for even hot water sanitization in that section of a system. The use of steam for sanitization may increase the maintenance requirements of a system, including issues related to material stress and faster rouge development. It is important to ensure material compatibility, including the use of chloride-free insulation with SS.

If steam is used to sanitize unit operations, such as GAC beds, without the proper steam injection design, the heating of the carbon in the bed may not be uniform and the sanitization will be ineffective because of the tendency for steam to channel through the bed rather than flow evenly through it. GAC beds are more thoroughly sanitized by first backwashing to separate any biofilm-agglomerated granules, followed by a flow of hot water to kill that biofilm; adequate temperature and contact time are essential.

Generally, using steam is an outdated approach for the heat sanitization of pharmaceutical water systems. Steam is far hotter than necessary, stressful to system materials, often difficult to achieve uniform targeted temperatures throughout the system due to distal heat losses, and creates the necessity for engineering design features that could become dead legs or water-retaining areas, which can compromise water system microbial control under normal system operating conditions.

The use of hot water is automatable, more energy efficient, and makes it much easier to achieve sanitizing conditions without the typical manual interventions needed to execute a steaming operation and to monitor steam trap functionality. Designing a new pharmaceutical water system for steam sanitization is not recommended when the use of hot water for sanitization is clearly superior. This does not mean that legacy water systems designed for steam sanitization must be converted to hot water sanitization; however, understanding the risks of a steam-sanitized system is essential for instituting appropriate monitoring during a steaming process to ensure its intended efficacy.

13.5.2 Chemical Oxidizing Sanitizers

The effectiveness of oxidizing sanitizers depends on the combination of their oxidation potential, concentration, stability, and contact time. Generally, the higher the oxidation potential, the more reactive it is against strong covalent bonds in organics and the more rapid it is against the weaker bonds. It penetrates poorly into thick, well-developed biofilm because of its reactivity at the outside layers. The penetrability can be improved by using high concentrations and prolonged contact times. This apparent disadvantage is balanced by the potential to completely degrade and remove the biofilm, which is desirable for prolonged microbial control in water systems. Biofilms growing into crevices may be almost impossible to kill with chemical sanitizers because of the limited exposed surface area. Understanding the properties of a chemical sanitant helps in using the sanitant to its greatest effectiveness. Table 13.1 gives the absolute oxidation potential of various sanitants and some of their active components. The table also depicts a relative oxidative effectiveness compared to chlorine gas (historically used as a sanitant in potable water).

Table 13.1: Oxidative Effectiveness of Various Sanitants and their Reactive Components [97]

Agent/Chemical	Oxidation Potential[1]	Relative Oxidative Activity[2]
Fluorine (F_2)	3.06	2.25
Hydroxyl Free Radical (•OH)	2.80	2.05
Ozone (O_3)	2.07	1.52
Peroxyacetic Acid[3] (CH_2COOOH)	1.81	1.33
Hydrogen Peroxide (H_2O_2)	1.77	1.30
Perhydroxyl Free Radical (•OOH)	1.70	1.25
Hypochlorous Acid (HOCl)	1.49	1.10
Chlorine (Cl_2)	1.36	1.00[2]
Bromine (Br_2)	1.09	0.80
Chlorine Dioxide (ClO_2)	1.57 (~1.0)[4]	1.15 (~0.7)[4]
Hypochlorite Ion (OCl^-)	0.94	0.69
Iodine (I_2)	0.54	0.40

Notes:
1. Oxidation potential expressed in Electron Volts.
2. Oxidative activity expressed relative to Chlorine as 1.00.
3. Commonly known as Peracetic Acid.
4. Possesses multiple oxidation states with the lower value most functional in water with biofilm penetration as a gas.

13.5.2.1 Ozone

A thorough discussion of the use of ozone as a sanitizing agent for pharmaceutical water systems can be found in the *ISPE Good Practice Guide: Ozone Sanitization of Pharmaceutical Water Systems* [34]; however, an overview is presented in this section.

Ozone is triatomic oxygen (O_3). Its instability (short half-life) and explosive reactivity at concentrations above 10% prevent it from being supplied as a compressed gas. It is frequently and economically generated by two primary commercial methods, one of which is passing diatomic (O_2) oxygen gas through an electrical coronal discharge (corona discharge) where a portion of the O_2 is converted to O_3. The resulting ozone gas is then sparged into water to dissolve it. The oxygen gas should be as pure and as dry as possible, because the presence of even small amounts of nitrogen gas in incompletely dried air can lead to the formation of nitrogen oxides within the coronal discharge, which can corrode the coronal electrodes and, when dissolved, become nitrates and degrade the water conductivity.

Electrolytic technologies also are used, which require no feed gas, and create ozone from the electrolytic splitting of water molecules, with the ozone dissolved directly in the water as it is formed. Ozone created through electrolytic technology usually is purer than that created by coronal discharge, and although electrolytic ozone is more effectively dissolved in the water, it may not be able to attain the higher ozone concentrations achievable at a lower capital cost by coronal discharge.

Ozone is a sparingly water-soluble gas and an aggressive oxidizer in its own right, but when it reacts with water, it generates more aggressively oxidative hydroxyl free radicals by the reaction:

$$O_3 + H_2O \rightarrow 2 \text{ •OH} + O_2$$
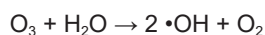
Both the ozone and the hydroxyl free radicals react with organic molecules with sufficient energy to break most types of covalent bonds, and if sufficient dissolved oxygen is present, to insert an oxygen atom where a bond is broken. The organics tend to degrade into CO_2 and carboxylic acids, which affect the water conductivity, and may need to be addressed with system flushing after periods of low water use, or with deionizing polishing and appropriate precautions. See Section 13.5.1.1.

Ozone used as a water system sanitizer typically is in concentrations of 0.1–0.2 ppm, although higher and lower concentrations are also used, but usually not less than 0.03 ppm

When ozone is used as an intermittent sanitant, increased concentrations may be required because the ozone may be attacking the EPS-coated biofilm, which it penetrates poorly. Biofilm is killed by ozone via attack from the outside. It penetrates the biofilm only as the outer layers of EPS, endotoxin, and bacterial cells are degraded. If the biofilm has had ample time to develop and is thick, ozone has little chance to completely kill it without prohibitively lengthy, repeated applications. Only thin biofilms can be completely killed by ozone, thus, using ozone as a periodic sanitant should be timed such that any EPS-coated biofilm formation is in its very early stages. The frequency depends on factors unique to each water system, but daily to weekly treatments have been found to be effective at minimizing or preventing recolonization and in interrupting biofilm regrowth.

Continuous ozonation of the storage tank into which the loop return and makeup water from the purification system is fed may be used to prevent recolonization. This normally is achieved either by adding ozone into the recirculated water just prior to its return to the storage tank or by sparging ozone into the tank; either technique creates an ozone-filled hostile environment in the tank water. The ozone can be destroyed by $UV_{254\,nm}$ before the first POU.

Periodic loop sanitization with ozone can be achieved by de-energizing the ozone using destructive UV. Consideration should be given to ensuring that sanitizing levels of ozone are present throughout the loop to compensate for its natural degradation and reactivity with any biofilm or organics present in the loop. The minimal ozone concentrations effective as a continuous sanitant in the tank may be ineffective as an intermittent sanitant in the loop; therefore, the ability to increase ozone concentration during loop sanitization may be significant to this approach.

When ozone is used as a sanitant, its destruction may be as important as its formation. For USP waters, ozone should not be present in water used from the system. If ozone is present in this water, it both violates the pharmacopeial water monograph requirement of containing no added substance [4], and is so reactive that it could degrade ingredients or surfaces the water contacts. In addition, it may create a health hazard to the operators in the environment, as the ozone outgases into the room air.

Ozone is degraded easily by germicidal $UV_{254\,nm}$ sanitizers; however, it is usual to size these units at 90 mJ/cm^2 (three times the UV intensity used for germicidal activity) to ensure the complete destruction of > 1 ppm of ozone, which is a much higher ozone level than typically used in pharmaceutical water systems. The irradiation activates the ozone to react with water to form transient, highly reactive hydroxyl free radicals and diatomic oxygen by the following reaction:

$$O_3 + H_2O + UV_{254\,nm} \rightarrow 2 \bullet OH + O_2$$

The ozone destroying process adds a final surge in lethality; viable organisms in this water stream are unlikely to survive an encounter with the free radicals or the UV. Although the free radicals exist only for a fraction of a second, care should be exercised with very high purity water to avoid de-ozonated water contacting sensitive applications in the first few seconds after ozone inactivation.

Ozone is an extremely potent and reactive oxidizer, which is quickly lethal to naked bacteria cells not imbedded in slimy flocs, and given sufficient time, can degrade biofilm directly along with its components, such as EPS, endotoxin, and the bacteria cells. Ozone can be used to help reduce TOC and endotoxin levels.

Ozone normally is used for continuous sanitization of complete or parts of water distribution systems (for eliminating biofilm re-colonizing pioneer cells) at low concentrations. It is removed easily by germicidal UV irradiation, eliminating the requirement for removal by system flushing. As an intermittent sanitant, ozone is effective against naked planktonic bacterial cells and on early (thin) biofilm formations that have produced minimal EPS slime.

Ozone tends to react superficially on thick biofilms and does not penetrate well because of its extreme reactivity with all organic molecules and its low concentrations. Ozone has minimal efficacy against thicker, older biofilms embedded in substantial EPS, even after many hours of contact time with ppm levels of ozone. The key to the efficacious use of ozone as an intermittent sanitant is to use it frequently, before thick biofilm has an opportunity to form.

The extreme reactivity of ozone also may affect system materials; although it is well tolerated by SS and PVDF piping materials as well as PTFE and some but not all vendors' EPDM, and Viton, gaskets/sealing materials. It is particularly aggressive toward most other plastics and elastomers. The incompatibility of ozone with system components may be a significant limiting factor associated with its use.

Ozone is toxic to humans at low atmospheric concentrations and care must be taken during use, particularly in the vicinity of the ozone generators and tank vents. Flushing use points with ozonated water to sanitize the outlets should be carefully controlled. For proper system design and safety precautions, refer to the *ISPE Good Practice Guide: Ozone Sanitization of Pharmaceutical Water Systems* [34].
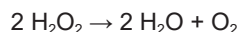
13.5.2.2 Hydrogen Peroxide

Hydrogen Peroxide (H_2O_2) is used as an intermittent sanitant. The energetic and unstable peroxy (-O-O-) bond in this molecule is its source of oxidative reactivity. It also can form the highly reactive hydroxyl free radical in water upon $UV_{254\,nm}$ irradiation:

$$H_2O_2 + UV_{254\,nm} \rightarrow 2 \cdot OH$$
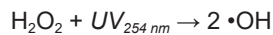
Hydrogen peroxide is widely available as a 30% solution, but technical grades are stabilized with ppb levels of certain metals and salts that may be unsuitable for use in high purity water systems. Reagent grades contain the less objectionable low ppm levels of stabilizers. Hydrogen peroxide has been used effectively for water distribution system sanitization at concentrations of 3%–10%, with contact times of several hours (the longer the better). It is reportedly compatible with most surfaces, including thin film composite polyamide RO membranes (at low concentrations).

Hydrogen peroxide decomposes over time to water and oxygen gas, which are not considered added substances as they are present in water.

$$2\,H_2O_2 \rightarrow 2\,H_2O + O_2$$

After hydrogen peroxide sanitization, the sanitant solution should be flushed out of the system because of the stabilizers in the concentrate and the organic molecules and debris potentially released by biofilm degradation. Quick test kits and test strips are available for confirmation of post-sanitization rinsing efficacy, but are usually quantitative only down to 1 ppm, which may not be sufficiently sensitive, therefore, additional flushing may be needed.

Hydrogen peroxide is not particularly temperature stable so its use is limited to ambient temperature systems, which should not exceed 25°C (77°F) for maximum stability. The pH stability of hydrogen peroxide allows it to be combined with sodium hydroxide to form an exceptionally good sanitizer and biofilm remover. Hydrogen peroxide can be combined with ozone to make a particularly aggressive sanitant based on the prolific formation of hydroxyl free radicals. The compatibility of hydrogen peroxide with other similar acting oxidizers and their free-radical potentiating effects also has been exploited with other proprietary sanitants (see Section 13.5.2.4).

When hydrogen peroxide is used, depending on the amount of biofilm present, there may be a substantial evolution of oxygen gas facilitated by cellular catalase; the relief of developing pressure should be considered. Although the lethal activity is almost instantaneous for naked bacterial cells, the process is much slower for developed biofilm that is degraded from the outside, so sufficient exposure time should be allowed for the sanitization and biofilm removal to be as complete as possible. The higher the concentration of the sanitant, the more rapid the action; treatment durations of many hours are common. The amount of time required for a given system will depend on the level of biofilm development allowed since the previous sanitization; an efficacious treatment time can be determined only by experience.

After a sanitization cycle, the sanitant should be flushed from the system.

13.5.2.3 Peracetic Acid

Peracetic acid also is known as peroxyacetic acid (CH3COOOH), and is generally a less commonly used intermittent water system sanitant. (It is often used as a vaporized or aerosolized sterilant for enclosed environmental surfaces such as sterility test isolator chambers.) An energetic peroxy bond is the source of its oxidative reactivity. It is available as a 40% solution, but should be stabilized with the same types of metals and salts as hydrogen peroxide. It may work in a similar way to hydrogen peroxide with similar, if not better, effectiveness. It naturally decomposes to acetic acid and oxygen:

$$2\ CH_3COOOH \rightarrow 2\ CH_3COOH + O_2$$
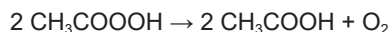
Peracetic acid has been used at concentrations ranging from 50–40,000 ppm. It is considered safe for use with polyamide RO membranes at a 1% concentration. It is not susceptible to the temperature instability of hydrogen peroxide, but is less stable than hydrogen peroxide at high pH, since it is susceptible to alkali dissociation. Peracetic acid is suitable for mixing with other oxidants for potentiated oxidizing activity. Because of this, its use as a solo sanitant in water systems is largely being replaced by proprietary oxidant mixtures.

Sanitization treatments usually are several hours, the duration of which should be determined by experience and is a function of the concentration used and the amount of biofilm that has developed.

At the correct concentrations peracetic acid is compatible with sensitive surfaces, such as TFC polyamide RO membranes. It possesses moderate stability, including at elevated temperatures, so using an additional chemical to maintain an effective concentration over long treatments usually is unnecessary if the initial concentration is sufficiently high. Using peracetic acid at higher temperatures significantly increases its efficacy. Its interactivity with other oxidizing sanitizers creates an exceptional release of extremely reactive and lethal hydroxyl free radicals making the mixture more reactive than either sanitizer alone.

Peracetic acid is unstable at high pH so combining it with certain other high pH agents such as un-neutralized sodium hypochlorite or caustic is not feasible. It is also moderately volatile and toxic to inhale, so use at elevated temperatures, which increases volatility, should be accompanied by appropriate precautions. After a sanitization cycle, the sanitant should be flushed from the system. Depending on local codes, neutralization of the acidity and oxidative reactivity may be required before discharge to the sewer. Redox, conductivity, or TOC instruments should detect its presence when assuring post-sanitization rinse out completeness.

13.5.2.4 Hydrogen Peroxide and Peracetic Acid Mixtures

Hydrogen peroxide and peracetic acid mixtures are obtainable as proprietary combinations, which claim to be more effective than either ingredient alone, even when used at much lower concentrations. According to material safety data sheet information, several products contain approximately a 5:1 ratio of hydrogen peroxide to peracetic acid (e.g., 22%:4.5%), which is intended to be used at a 1:100 dilution of the concentrated mixture. At this concentration, it reportedly is safe for most water-contact materials often found in high purity water systems and is considered to be highly effective at killing naked aquatic bacterial cells as well as killing and removing biofilm. The correct contact time should be allowed for complete biofilm kill and removal, which may be affected by TOC content of the water and the depth of the biofilm that is being treated. An effective contact time should be determined by experience. For minimal or very thin biofilm development and high water purity situations, contact times of 1–2 h are common; significantly longer times and/or multiple treatments usually are required where thicker biofilms have developed.

Commercially available mixtures commonly are used in water systems with testimonials for efficacy. Test strips are available for assessing the correct treatment concentrations and post-sanitization rinsing efficacy (for the latter, test strip sensitivity may not be sufficient). The treatment concentration is effective and not harmful to sensitive surfaces, such as TFC polyamide RO membranes.

The diluted mixture has a limited shelf life. Hydrogen peroxide and peracetic acid combinations are unstable after dilution to concentrations appropriate for use, at elevated temperatures, and high pH. At the conclusion of treatment, the chemical and any associated organic debris should be flushed from the system. The acidic nature of the chemical may require pH neutralization before discharge to the sewer, depending on local codes.

13.5.2.5 Chlorine Gas

The use of chlorine gas (Cl_2) for disinfecting water has a long and accepted history, primarily for potable or drinking water. When chlorine gas is dissolved in water, it reacts to form hypochlorous acid (HOCl), which is the most potent form of this sanitant molecule:

$$Cl_2 + H_2O \rightarrow HOCl + H^+ + Cl^-$$

The use of chloramines has largely replaced the use of free chlorine in drinking water because of the more reactive chlorine's tendency to break down organics in the water and form carcinogenic THMs and haloacetic acids.

Chlorine gas is rarely used in the pharmaceutical industry to sanitize PW systems because of issues of safety and practicality. It may be used occasionally in a pharmaceutical organization's private source water purification process or to supplement low chlorine levels in municipal drinking water.

The larger concern with chlorine in water is the water's further purification and the requirement to remove it to avoid damaging sensitive unit operations. Highly reactive chlorine (as well as chloramines) can seriously damage anion-exchange resins, EDI units, and TFC polyamide RO membranes. It also can indirectly cause pitting and crevice corrosion by attacking the passive layer of SS, which is particularly serious at high temperatures, such as in distillation units. There are several processes that may be used to remove chlorine (and chloramines), including activated carbon beds, reducing agents, and strong UV irradiation.

The use of chlorine gas as a water sanitizer is very economical in terms of materials cost. There is a long history of its use in treating large quantities of water with low ppm doses and it is a familiar compound. When used at EPA-regulated levels [29] for purifying privately sourced water to become potable or to supplement municipal water chlorine levels, it does not need to be removed prior to direct human consumption, and its removal prior to further purification typically is already designed into water systems.

Chlorine is extremely hazardous to humans in concentrated gas form and requires special handling equipment to prevent leaks, as well as safety alarms for airborne discharges. It is impractical to use for creating the high dissolved chlorine levels required for water distribution system sanitization. The low chlorine levels associated with the potable feed water to the system can kill pioneer cells given sufficient contact time, but otherwise does very little to control biofilm growth.

13.5.2.6 Sodium Hypochlorite

Sodium hypochlorite (NaOCl) is used frequently and is familiar in the form of household disinfectants and laundry bleach. Typically, it is obtained as concentrated solutions of sodium hypochlorite (from the 6% concentration in household bleach to industrial solutions as high as 21%). Such solutions are usually adjusted to approximately pH 12 to enhance stability and prolong shelf life. The most active moiety is hypochlorous acid (HOCl) with the hypochlorite ion having less than 2/3 of its oxidation potential (see Table 13.1) resulting in far less than 1/10 of its antimicrobial activity. It has a pKa of 7.4, so at pH 7.4 it exists in equal amounts as undissociated hypochlorous acid and dissociated hypochlorite anion. Above pH 9 or so, the hypochlorite ion predominates as the more stable but less reactive form (see Figure 13.1).

Figure 13.1: Chlorine Equilibrium Curves as a Function of pH

Reprinted from Water Research, Vol. 42 /Issues 1-2, Marie Deborde, Urs von Gunten, Reactions of chlorine with inorganic and organic compounds during water treatment—Kinetics and mechanisms: A critical review, Pages 13-51, Copyright 2008, with permission from Elsevier.
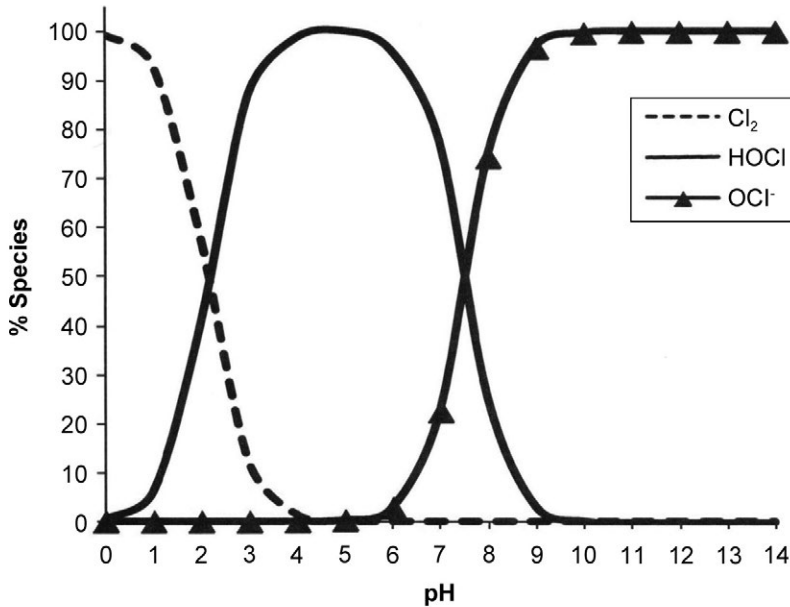
The equilibrium formula for chlorine, depicted in Figure 13.1, is as follows:

$$Cl_2 + H_2O \leftrightarrow HOCl + H^+ + Cl^- \leftrightarrow OCl^- + 2H^+ + Cl^-$$
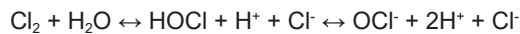
This equilibrium makes the activity of this sanitant highly pH dependent, with neutral to moderately acidic pH yielding more oxidative reactivity than at alkaline pH. However, the more reactive it is, the less stable it is, so acidic pH reduces its stability. When diluted for use as a sanitant, its efficacy can be enhanced by adjusting the pH of the final solution to below neutrality for maximal activity in its non-ionized form, as hypochlorous acid. However, in this acid form, it is in equilibrium with the very hazardous chlorine gas form which tends to outgas from the solutions, so care should be exercised when neutralizing these solutions in their concentrated forms. It is moderately heat stable, so increasing the system temperature during sanitization, where compatible with the materials of construction, can significantly increase its activity (the general thermodynamic rule is 2-fold for every 10°C increase). Simply increasing the treatment concentration may provide an equivalent effect to that of heating or pH neutralization, as there is no limitation on the maximal concentration that can be used during sanitization, except perhaps by cost (this compound is widely available and relatively inexpensive).

Sanitant use concentrations are generally 50–5000 ppm (0.5% sodium hypochlorite) as a function of the required contact time, whether or not pH-neutralized, the TOC content of the water, and the depth and location of the biofilm being treated. Sufficient contact time should be allowed to kill biofilms, but it is questionable how well it will remove them, especially well developed, thick ones and at high chlorine concentrations and high pH, which makes the chlorine less oxidative. Ironically, greater dilutions to lesser chlorine levels (up to a point) also lower the pH by dilution, making lower chlorine levels possibly more effective than higher chlorine concentrations with un-neutralized pH. Dilution of the concentrate with neutral to slightly acidic pH buffers can avoid chlorine gas evolution and maximize antimicrobial efficacy.

At the completion of treatment, the chemical should be flushed from the system along with any organic debris it may have released. If an alkaline hypochlorite is used, the amount of flushing required may be extensive. Simple chlorine test kits may be used and redox instrumentation also is available to determine when system flushing is complete. Water conductivity can be used to reinforce an indication of rinsing completion. If large amounts of hypochlorite have been used, it may require inactivation with reducing agents, such as sodium sulfite or bisulfite before discharge to a sewer.

This sanitant is incompatible with prolonged contact with SS, even at low concentrations and particularly at high temperatures, as it causes chloride corrosion. In addition, it is not compatible with TFC polyamide RO or ultrafiltration membranes; however, it is compatible at a 10 ppm concentration with cellulosic RO membranes.

13.5.2.7 Chlorine Dioxide

Chlorine dioxide gas (ClO_2) is freely soluble in water. It has been used widely in other industries and applications for effectively sanitizing clean rooms and animal research facilities, killing biofilm accumulations in cooling towers and paper manufacturing facilities, and for correcting odor and taste problems in drinking water. It has had limited use in sanitizing water systems. It should be generated at the POU, as it is explosive in a concentrated state. There are several approaches to generating and dissolving chlorine dioxide gas in the system water that will not be discussed here. However, once the dissolved chlorine dioxide gas is present, it is effective over a broad pH range of 1 to 10.

Chlorine dioxide possesses multiple oxidation states, but its relatively low oxidation potential gives it selective organic reactivity, which combined with its existence as a gas rather than a dissolved ion, allows it to deeply penetrate biofilm without reacting with, or being consumed by, the EPS. Once inside the biofilm, it subsequently enters the embedded cells to oxidize sulfhydryl-containing proteins, as well as complex amines and other macromolecules found in living cells, quickly killing the cells. Its low effective oxidation potential, though penetrative and lethal to biofilm cells, does not allow it to degrade and remove biofilm. Its penetrative properties start at a 1.5 ppm level, but can be used at levels as high as 150 ppm.

Treatment times vary depending on the concentration used and the depth of biofilm to be killed, which can be established only from experience. Such treatments may need to be performed by skilled contractors experienced in this work, because of the specialized equipment that may be needed for treatments, as well as human exposure limitations to the moderately toxic gas. Disposal of the sanitant solution directly to the sewer without treatment may be possible, depending on the quantity and local codes.

Chlorine dioxide's ability to penetrate and kill even thick biofilm is its most useful attribute. Test kits to assess residues for rinsing efficacy verification are available.

There is not a long history of previous experience for this sanitant in the pharmaceutical industry. If biofilm removal is needed to avoid post-sanitization accelerated biofilm regrowth, other more oxidative or caustic treatments should be used. Post-sanitization removal is by system flushing.

13.5.2.8 Bromine and Iodine

Bromine and iodine are halogens that have been used occasionally for water sanitization. The reactions of bromine and iodine in water are analogous to the behavior of chlorine in their formation of hypobromous or hypoiodous acids; however, these compounds are far less reactive than hypochlorous acid. Although there are applications for these compounds in sanitizing drinking water, particularly in emergency situations, their use in sanitizing pharmaceutical water systems is rare because of their relative lack of efficacy compared to other sanitizers, as well as their high cost.

13.5.3 Other Chemical Sanitizers

13.5.3.1 Extreme pH Regenerant Chemicals

Frequently regenerated IX resin beds tend to be relatively free from high microbial counts. The extreme pH of the chemicals used for regeneration (typically 4%–6% hydrochloric acid and sodium hydroxide) create hostile conditions on and in the resin beads. If cells that would form slimy biofilms have only recently adsorbed to those resin surfaces and not started producing EPS slime, they are very susceptible to the hostile pH regeneration conditions and are likely killed. The key to such regenerants being effective sanitizers is their frequency of use. Once a layer of slime has been produced (e.g., on the resin surfaces of infrequently regenerated DI beds), short extreme pH exposures have little detrimental effect on biofilm, which, after regeneration, continues to grow further out of control, possibly becoming a serious source of water system contamination.

Biofilm problems may be worse on anion resins, even if these resins are regenerated with caustic, because anion resins tend to adsorb more organic matter from the water (i.e., more food), leading to faster and more luxuriant biofilm growth than on cation resins. Thicker biofilms lead to poorer chemical penetration, possibly affecting regeneration effectiveness. Regeneration using warmer water increases reaction rates and many chemical regeneration systems utilize warmer water to regenerate anion resins for this reason.

Extreme regenerant pH occurs on the active surfaces within the electrical cells of CEDI units. The difference is that those extreme pH regenerant ions are continuously present on the surface of the charged resin beads and membranes. This is a result of the electrolytic effects on the water molecules that keep the resins and membranes continuously regenerated and more easily cleaned.

Very little microbial colonization or resulting biofilm formation is likely to occur on DI surfaces, because of frequent or continuously hostile pH. This advantage applies only when continuous or frequent regenerations occur and are unlikely for exchange (off-site regenerated) resins.

Frequent regenerations can be costly for conventional DI units, create regular non-use periods, and produce more waste chemicals. Where service DI is used, the resin bottles may be replaced every day or two, which may seem to promote this microbial-control phenomenon. The DI resin bottles may have been regenerated many weeks after exhaustion and then stored wet and warm for yet many more weeks, negating the entire microbial-control effect from regeneration. It also could create a significant microbiological problem as fully developed biofilm in a fresh resin bottle sheds into the finished water.

Continuously hostile extreme pH conditions do not exist within a CEDI unit outside of the electrical field in the discharge paths of the concentrated waste water or in the downstream product water discharge path, so biofilm can flourish, if allowed to take hold, fouling membranes and other wet surfaces before the water exits the CEDI unit. This is particularly significant, as a CEDI unit may be the last unit operation in a purification train; any immediately downstream biofilm within a CEDI unit may have a direct impact on the quality of water in a distribution system.

13.5.3.2 Caustic

Caustic, usually in the form of sodium hydroxide (NaOH) (although potassium hydroxide (KOH) has rinsability advantages), has been used successfully to remove biofilm slime in water systems. It frequently is used at a concentration of 0.4%–4% (0.1–1 N), often in a heated state, in order to achieve a pH of about 13 or higher. Caustics are generally compatible with TFC polyamide RO membranes and are useful in restoring biofouled membranes, but will dissolve cellulosic RO membranes.

Caustics work by hydrolyzing the EPS material of biofilm and allowing the extreme pH to penetrate the biofilm and kill the exposed cells by its hostile alkalinity. Its effectiveness has reportedly been substantially enhanced by combining it with pH-compatible oxidative sanitizers such as hydrogen peroxide. It can be used only on oxidation-resistant materials compatible with high pH. Treatment times vary depending on concentration, temperature, the presence of activity enhancing ingredients, and the thickness and accessibility of the biofilm to be killed and removed. Before disposing of the sanitant to the sewer, it usually must be neutralized. A note of caution may be necessary regarding the use of proprietary caustic cleaners in water systems. These formulations are generally optimized for cleaning process equipment and may contain organic ingredients that are difficult to rinse out of water systems, creating TOC issues if not completely removed.

Caustic is a frequently handled material in pharmaceutical facilities; familiarity is an asset to its use. Caustic is relatively inexpensive and moderately effective at removing biofilm slime, depending on pH. It is compatible with the majority of pharmaceutical water system materials. Caustic can be heated or combined with pH-compatible oxidizers to enhance is activity. Rinsing efficacy can usually be verified by a simple pH test or conductivity.

The high pH of a caustic is not compatible with some water system materials. Accommodation should be made for the exothermic dissolution/dilution process of caustic, which also may not be compatible with a number of system materials. Post-sanitization removal is by system flushing, and the volume required may be extensive. Neutralization of flushed out residues is usually needed before discharge to a sewer.

13.3.3.3 Formaldehyde

Formaldehyde is a 1-carbon aldehyde that acts as an alkylating agent (adds methyl groups to susceptible organic molecule locations that typically kill the cells). It volatizes easily. (It was historically used as a gaseous environmental sterilant in aseptic suites and in water systems, but its identification as a carcinogen has reduced its usefulness to those situations where there are few equivalently effective alternatives, and only with appropriate safety precautions.)

One application of formaldehyde is in the sanitization of RO membranes. Although solutions of formaldehyde do little to remove existing biofilm, they can penetrate the biofilm as a gas and kill the cells within. Formaldehyde gas also can penetrate the RO membrane and kill biofilm cells growing on the reject as well as permeate sides of the membrane, which is difficult to reach by most other RO sanitants. Formaldehyde is used rarely for sanitizing other locations in water systems owing to its toxicity and cost.

Formaldehyde is costly in large amounts, and not particularly penetrative to thick biofilms. Post-sanitization removal is by system flushing, and depending on the quantity and concentration, may need to be treated before discharge to a sewer. These concerns largely contraindicate its usage as a sanitizer in modern pharmaceutical facilities, but still may be used in older, non-domestic facilities.

13.3.3.4 Glutaraldehyde

Glutaraldehyde use increased with the concerns over formaldehyde's carcinogenicity, and with its wider use as a hard surface facility sterilant. Glutaraldehyde is a 5-carbon dialdehyde with a different mechanism of action than formaldehyde, although it continues to be classified as a sterilant because of its ability to kill bacterial spores. It is a larger molecule and does not volatize to a gas under normal use conditions. Its effectiveness in sanitizing the entire RO membrane is considerably less than formaldehyde, because it cannot penetrate the membrane as a gas to sanitize the permeate side. Although glutaraldehyde's toxicity and potential for carcinogenicity in humans is less than formaldehyde, its ability to penetrate and kill biofilms is also less, so it is used only occasionally for RO membrane sterilization. Its removal is by rinsing, usually by unit operation flushing, and rinsing efficacy may be demonstrated by TOC or conductivity analyses.

13.3.3.5 Cationic Detergents

Cationic detergents are used as the active ingredients in a number of disinfectants intended for hard surface decontamination, and their mode of action is to disrupt the membranes of bacterial and fungal cells. These agents have little effect on the cells in a biofilm because of poor penetration through the EPS. Cationic detergents are effective on naked cells, which may be planktonic pioneer cells, as well as on recently surface-attached cells prior to development of the EPS. If used for sanitization, cationic detergents should be flushed out of the system, but its surfactant properties make complete rinsability a challenge. Rinsing efficacy may be demonstrated by TOC or conductivity analyses. Neutralization prior to discharge to the sewer usually is not required, depending on local codes.

13.6   Assessing Microbial-Control Success

Processes that may affect product quality should be justified by verification or other indications of their effectiveness; this applies to microbial-control activities for high purity water systems. Assessments are a regulatory expectation and considered good business practice. How these assessments should be performed and how the resulting data should be used to enhance microbial control and assure the water's suitability for use are discussed in this section. The intention is to clarify the purpose and limitations of these assessments.

13.6.1   Microbial Enumeration Issues

Biofilm organisms have a strong preference for growth in water systems only when attached to a surface as part of a biofilm. When biofilm organisms are present in the flowing water, they are either in the form of individual pioneer cells released by biofilms to colonize other surfaces or as multi-celled flow-sheared biofilm fragments or flocs. At a given point in time, a small minority, probably far less than 0.1%, of the total number of microorganisms in a water system are free floating or planktonic, with the remainder associated with the attached biofilms; however, neither the release of pioneer cells nor the shearing of biofilm flocs is continuous over time. Minor transient changes in water purity can affect the release rate of pioneer cells, and minor flow changes or even shock waves from sudden valve closures or vibrations from processing equipment can cause momentary releases of biofilm flocs. Additionally, the act of collecting a sample or using the water at a given valve can cause flow pattern changes in piping or valves that may cause biofilm flocs to be released locally.

To quantify the amount of biofilm developing in a system, the surface growth of biofilm should be assessed directly, by examining typical surfaces from the water system. Sampling devices designed to perform this examination are available. Operational issues associated with retrieving samples from these devices, as well as concerns about biofilm development in these devices being unrepresentative of biofilm development throughout the system, however, have reduced their popularity in pharmaceutical applications.

There continues to be a strong preference and tradition (dating back to pre-biofilm awareness days) for collecting water samples as an indication of the microbial status of a water system, despite microbial variability problems in collecting planktonic samples.

13.6.2   Rapid Microbial Methods

This discussion on RMMs is intended to give the high-level basics of the advantages and disadvantages and is not intended to be a thorough treatise on methods applicable to water systems. There are a number of well-respected references that can be consulted for this information, and the field of available methods is constantly changing as new approaches are introduced and older approaches loose support from their original vendors [100, 101].

The inability to cultivate all viable organisms present in a tested sample is problematic. Specialized nutritional requirements or other factors tend to prevent a single cultivation approach from detecting all the viable cells present. In addition, traditional cultivation approaches can take 2–7 or more days to have countable colonies, depending on the test method conditions used and the flora present. This could be an extremely long time to wait for test results that identify an urgent microbial problem with a need to re-sanitize a water system "immediately". It also may represent an extremely long delay before product made with this water may be released.

Clearly, being aware of the microbial-control condition of a water system or the microbial content of the water used from a water system are important attributes, and the sooner those attributes are known, the sooner remediating actions can be taken. This is where alternative or RMMs have potentially great utility for water systems – they give test results sooner than the conventional cell cultivation approaches where the microorganisms reveal their presence by slowly growing into visible colonies, with each colony representing billions of cells. This many generations of cellular replication takes considerable time depending on the growth rate (and assumes that the collected organisms planted on the nutrient medium can utilize those nutrients to grow into colonies). Rapid methods that do not require this growth to occur, or perhaps only a few replications, are certainly advantageous; however, such rapid methods are not without limitations.

All rapid microbiological methods can generally be segregated into those that:

- Kill or do not capture the original bacterial cells but derive from them a signal of their presence

- Give an early indication of microbial count and retain the viability of the detected cells for further characterization

All of the methods more rapidly reveal an estimate of the total number of apparently viable bacterial cells in a water system sample versus their traditional predecessors.

These RMMs can be further categorized as:

- Those that must be performed in a laboratory setting (i.e., off-line using collected samples)

- Those that are performed online where the instrument detects viable planktonic bacteria (or indicating signals therefrom) in the distribution system in essentially real time

The ability to further characterize and/or identify the recovered bacteria allows the test to be used for QC (as well as for process control), but the rapid methods that destroy or do not recover those organisms for further characterization limit the usefulness of the method primarily to process control. It is noted that there are exceptions to these limitations, which are discussed in Section 13.6.3.

Usually, the most rapid tests are either destructive to the detected bacterial cells or do not capture them at all, thus, preventing their identification. Some of the "slower" rapid microbiological tests (still faster than traditional cell cultivation approaches) do not destroy the bacterial cells enumerated, allowing them to be identified, sub-cultured, or otherwise further characterized and studied. This is an important distinction and affects the applicability of rapid microbiological tests in water system monitoring and water release.

13.6.3 Use of Microbial Enumeration Data for Quality Control versus Process Control

As mentioned, microbial enumeration data has two distinct uses that can determine the testing approach and sample collection method. Discussion in substantial detail on the uses of the microbial test data for QC versus PC purposes, including how to properly collect those samples, can be found in the *ISPE Good Practice Guide: Sampling for Pharmaceutical Water, Steam, and Process Gas Systems* [33].

It is important to consider RMMs in the context of the PC or QC use of the resulting data. For both purposes, the number of planktonic organisms or measured units that correlate with that number in the water is important. For PC, the identity of the organisms that are present is usually less important than the change in microbial counts (or other correlating units). For QC the magnitude of the microbial counts as well as the identity of the organisms responsible for those counts are important. The fact that some RMMs do not allow for the identification of the recovered or detected isolates typically disqualifies these methods for use in QC testing. However, there are exceptions.

Even if an RMM does not allow for further characterization of the quantified bacteria, if the number of those bacteria is zero or inconsequentially very low, there are no bacterial identities that need to be determined. Therefore, with very good quality water, very rapid PC-only RMMs (where test results are available in a short period of time but within the validated sample hold time) could be used for QC testing, assuming the sample has been collected properly. If the quantitative test results are not low enough to make organism identification unnecessary, then the untested remainder of the sample could be tested by another method, including a slower cell cultivation method, which will allow organism identification. Thus, a QC sample could be validly tested by an otherwise PC-only RMM. Likewise, if an online RMM detects in real time an unusually large signal suggestive of high numbers of planktonic bacteria, then a sample can be collected during this period and tested by cultivation in order to confirm the microbial count as well as determine their identities.

13.7 Functional Microbiological Pharmacopeial Compliance

At the time of the revision of this Guide, each of the global pharmacopeial references remains different in several aspects of how to manufacture, test, and control PW and WFI [4, 5, 6]. This presents problems when trying to market products in different parts of the world that must comply with the regional pharmacopeia. Differences include:

- How the waters can be prepared

- Chemical quality specifications and tests required to assess those specifications

- Microbiological attributes required or implied and how to assess those attributes

A degree of harmonization has occurred with some of the chemical attributes and tests among the USP, Ph. Eur., and JP [4, 5, 6] (see Chapter 9, Table 9.3). There remain many differences, particularly for microbiological attributes and testing. The Ph. Eur. puts their microbial test methods and specifications directly in the monographs for these waters, which confers a certain level of mandate for their use, but both the USP and JP place different suggested or recommended microbial test method options and suggested action level options in their respective informational chapters, conferring a different level of mandate. A user that markets products globally must comply with all the conflicting pharmacopeias, including choosing the most appropriate microbiological tests and control criteria for their water system.

13.7.1 Microbial Enumeration Test Method

The pharmacopeias agree on microbiological issues only to a limited degree, such as for the enumeration method to be used. The microbial enumeration test method used may have an enormous impact on the numbers and types of microorganisms recovered as well as the delay before data are available due to the incubation period. There is no universally optimal test method because each water system is different and potentially selects for different combinations and levels of flora. However, all pharmacopeias have General Notices sections that allow the use of alternative test methods if proven equivalent or superior to a referee or suggested procedure. An alternative test method may be used, for example, one that takes less time to yield equivalent counts or one that yields higher counts, as long as it is shown to be as good (defined as resulting in no fewer counts or species) or better than the reference test method.

The justification for an alternative test method (and this includes alternative conventional cell cultivation procedures as well as RMMs) generally is achieved by concurrent testing of the equivalent water samples, using one or more candidate test methods, including the reference method, over a suitable period of time. The potential uniqueness of the flora in a given water system and the timeliness of the data availability may justify the use of methods other than those listed in a particular compendium.

13.7.2 Establishing Appropriate Action Levels for Process Control

Action levels are intended for process control purposes, not QC purposes, and ideally are established from normal data trends for each system that take into account the innate variability of microbial enumeration data. In addition, there may be seasonal variations in the microbial control of a given system so that normalcy has cyclic variation over a given year. The intent of action levels is to prevent a water system from deviating out of control sufficiently to generate water that is microbiologically unsuitable for its uses. These suitability for use values, also known as the specifications or limits used for QC testing, should be considerably higher than the action levels for a system. If an action level is exceeded, microbial-controlling remedial actions should be taken to preclude microbial levels from exceeding a specification or fitness-for-use level or being sufficiently high to adversely affect products or patients.

The occurrence of multiple excursions of a lower microbial-control level, sometimes called an alert level may provide a better indicator of microbial process control. Multiple lower level excursions also may trigger equivalent system evaluations and control responses as those triggered by an action level excursion. Sampling procedures should be effective and consistently executed without fault, as poor or inconsistent sampling issues often cause unnecessary excursion responses. These issues are mentioned in Section 13.6.3. and discussed at length in the *ISPE Good Practice Guide: Sampling for Pharmaceutical Water, Steam, and Process Gas Systems* [33].

13.7.3   Using Action Levels from Pharmacopeia

Levels of microbial control routinely achievable are considerably below the action levels stated (with varying degrees of mandate) in the USP, Ph. Eur., and JP [4, 5, 6]. Maximum or reasonable compendial action levels are:

*   100 cfu/ml for PW

*   10 cfu/100 ml for WFI

Waters exceeding these levels are not acceptable to regulators for use with pharmaceutical products; therefore, these compendial action levels may be taken as functional QC specifications, especially in light of the expectation of performing a formal OOS investigation should one of these levels be exceeded.

Functional alert and action levels should be established at lower levels to allow remedial microbial-control activities to occur when the planktonic microbial levels (and therefore the analogous biofilm levels in the system) are in a minimal and more controllable state so that the planktonic levels never exceed these functional QC specifications. The most functional alert and action levels are those derived from an organization's water system data trends while the system is operating optimally and is sampled ideally. Poor sampling is usually the cause of extreme data variability, so sampling must be controlled in order for system data trends to truly be indicative of system control (refer to the *ISPE Good Practice Guide: Sampling for Pharmaceutical Water, Steam, and Process Gas Systems* [33]). These PC indicators are set at levels that are triggered when the monitoring data deviate from normal levels and are reflective of unsuitable microbial control.

When used properly, action levels trigger extraordinary remedial control measures, not ordinary or routine control measures like system sanitization. Alert and action levels should be used to notify users, as well as those responsible for system maintenance, that the routine control measures are no longer working properly and microbial levels have exceeded the normal trends. If one waits for a compendial action level to be triggered before taking microbial-control measures such as periodic system sanitization, then the biofilm causing those high planktonic counts may have become so thick and well developed that routine sanitization measures may not be successful, mandating the use of extreme microbial-control activities that consume much more time, not to mention the time consumed by the required OOS excursion investigations. It pays off in the long run to establish low, trend-based alert and action levels in order to trigger extraordinary, not ordinary remedial actions, bringing the system back under microbial control well before the microbial levels make the water unfit for use or fail a specification.

Regardless of the terminology used for these various levels or the approach employed to establish these levels, process-controlling values should be established at levels that are useful in controlling the microbiological content of a water system so that it is able to consistently and reliably make water compliant with regulatory expectations and suitable for the intended use.

13.8   Microbial and Endotoxin Control in Pure Steam Systems

Pure Steam generation systems are designed to remove any endotoxin from the source water from which the steam is generated. This is achieved by using properly designed mist elimination components on PSG if their feed water contains endotoxins. If the feed water to a PSG has controlled endotoxin levels, such as WFI, then mist elimination within the PSG is usually not necessary. Pure Steam distribution systems (usually branched, dead-end systems) should be designed to bleed all steam condensate from all low points within the system to avoid creating cool flooded areas in piping sections where endotoxin could accumulate. Pure Steam distribution systems are too hot for microbial proliferation or survival, except possibly in areas of substantial condensate accumulation, which is indicative of poor design, poor maintenance, or system component malfunction (see Chapter 7).

In-house specifications for PW (and for Pure Steam used in non-parenteral applications) or WFI (and for Pure Steam used in parenteral applications) often are applied to Pure Steam that has been freshly condensed at a POU during sampling. These specifications may include limits, specifications, or action levels for microbial content, which are inappropriate.

For a well-designed and operated Pure Steam system, testing freshly condensed steam for microbial attributes is not necessary, since the steam, as it is collected, will be immediately lethal to aquatic organisms present in co-exiting condensate. Only where there is a substantial flush of accumulated condensate from a given sample point prior to the exit of live steam is there some chance of any recoveries in microbial testing. In such situations, however, rather than waiting for microbial data to signal remedial action in the steam system, the discovery of accumulations of cooled condensate in the steam lines is cause for immediate remedial action, including possible shut down and/or quarantine of all or parts of the system. Such a discovery is an indication of a serious and intolerable flaw in the system operation that may lead to the generation of bacterial endotoxins within the steam distribution system that, unlike the microorganisms, would not be destroyed by the live steam.

For well-designed and operated Pure Steam systems, microbial testing of freshly condensed steam is essentially assessing whether or not the sampler can collect an aseptic sample, not whether or not the steam system contains any microbial contaminants. Therefore, microbial attributes for Pure Steam is not an important quality indicator for Pure Steam testing. Microbial attributes are intentionally absent from the USP Pure Steam monograph. USP41-Supplement 1 contains the most recent revision of Chapter <1231> where, in Section 3.1.4., it states that microbial analysis of Pure Steam condensate is unnecessary [4].

14 Appendix 1 – References

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15 Appendix 2 – Glossary

15.1 Acronyms and Abbreviations

AAS	Atomic Absorption Spectroscopy
AC	Alternating Current
AI	Artificial Intelligence
API	Active Pharmaceutical Ingredient (also known as Bulk Pharmaceutical Chemicals)
ASHRAE	American Society of Heating, Refrigerating and Air Conditioning Engineers
ASME	American Society of Mechanical Engineers
ASTM	American Society for Testing and Materials
BCC	*Burkholderia cepacia* Complex
BPC	Bulk Pharmaceutical Chemicals
BPE	Bioprocessing Equipment (ASME National Standard)
BSi	British Standards Institute
C&Q	Commissioning and Qualification
CA	Critical Aspects
CAPEX	Capital Expenditure
CCA	Component Critically Assessment
CDE	Critical Design Elements
CEDI	Continuous Electrodeionization
CFS	Chemical Free Steam
CFU	Colony Forming Units
cGMP	Current Good Manufacturing Practice
ChP	Chinese Pharmacopoeia
CIP	Clean in Place (system)
CLRW	Clinical Laboratory Reagent Water
CLSI	Clinical and Laboratory Standards Institute
CPP	Critical Process Parameter

CPVC	Chlorinated Polyvinyl Chloride
CQA	Critical Quality Attribute
CS	Clean Steam
D/A/CH	ISPE Affiliate for Germany, Austria, and Switzerland
DCS	Distributed Control System
DI	Deionized, Deionizing, Deionization
DNA	Deoxyribose Nucleic Acid
DTI&R	Difficult to Inspect and Repair
EDI	Electrodeionization (Osmonics and Generic)
EDQM	European Directorate for the Quality of Medicines & Health Care
ELISA	Enzyme-Linked Immunosorbent Assay
EMA	European Medicines Agency
EPA	Environmental Protection Agency (US)
EPDM	Ethylene Propylene Diene Monomer
EPS	Extracellular Polymeric Substance
EU	Endotoxin Units
FRP	Fiberglass Reinforced Plastic
GAC	Granular Activated Carbon
GEP	Good Engineering Practices
GF-AAS	Graphite Furnace Atomic Absorption Spectroscopy
GMP	Good Manufacturing Practices
GPD	Gallons per Day
GPH	Gallons per Hour
GPM	Gallons per Minute
GRAS	Generally Recognized as Safe (US FDA)
GxP	Good "x" Practices
HMI	Human-machine interfaces

HPLC	High Performance Liquid Chromatography
HPW	Highly Purified Water
HVAC	Heating, Ventilation, and Air Conditioning
ICH	International Council for Harmonisation
ICP-AES	Inductively Coupled Plasma Atomic Emission Spectroscopy
ID	Identification
I/O	Input/Output
IP	Indian Pharmacopoeia
IR	Infrared
ISA	Instrument Society of America
ISO	International Organization for Standardization
IX	Ion Exchange
IU	International Units
JIS	Japanese Industrial Standards
JP	Japanese Pharmacopoeia
LAL	Limulus Amebocyte Lysate
LPD	Liters per Day
LPH	Liters per Hour
LPM	Liters per Minute
LVP	Large Volume Parenteral
MBtu	1,000 British thermal units
MD	Membrane Degasification
ME	Multiple Effect (still)
MF	Microfiltration or Micro-Filter
MOC	Material of Construction
MS	Mass Spectrometry
MSDS	Material Safety Data Sheet

MWCO	Molecular Weight Cut-off
NIST	National Institute of Standards and Technology
NMPA	National Medical Products Administration (China)
NPDWR	National Primary Drinking Water Regulations
NPV	Net Present Value
NTU	Nephelometric Turbidity Units
OD	Outer Diameter
OOS	Out of Specification
ORP	Oxidation Reduction Potential
OSHA	Occupational Safety and Health Administration (US)
P&ID	Piping and Instrumentation Diagram
PAT	Process Analytical Technology
PDE	Permitted Daily Exposure
PE	Polyethylene
Ph. Eur.	European Pharmacopoeia
PID	Proportional Integral Derivative
PLC	Programmable Logic Controller
POU	Point of Use
PP	Polypropylene
PQ	Performance Qualification
PSG	Pure Steam Generator
PTFE	Polytetrafluoroethylene
PVDF	Polyvinylidene Fluoride
PW	Purified Water
QA	Quality Assurance
QC	Quality Control
QRM	Quality Risk Management

Ra	Roughness average
RMM	Rapid Microbial Methods or Rapid Microbial Monitoring
RO	Reverse Osmosis
ROI	Return on Investment
SDI	Silt Density Index
SBS	Sodium Bisulfite
SE	Single Effect (still)
SEM	Scanning Electron Microscope
SI	International System of Units
SIP	Steam-in-Place
SMS	Swedish Manufacturing Standard
SOP	Standard Operating Procedure
SRA	System Risk Assessment
SS	Stainless Steel
SVP	Small Volume Parenteral
TDS	Total Dissolved Solids
TFC	Thin Film Composite
THM	Trihalomethanes
TIG	Tungsten Inert Gas
TOC	Total Organic Carbon
UF	Ultrafiltration or Ultrafilter
URS	User Requirements Specifications
USP	United States Pharmacopeia
USPC	United States Pharmacopeial Convention
UV	Ultraviolet
UVT	Ultraviolet Transmittance
VC	Vapor Compression (still)

VFD   Variable Frequency Drive

VICH   International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products

WFI   Water for Injection

WHO   World Health Organization

15.2   Definitions

Absorption

Assimilation of molecules or other substances into the physical structure of a liquid or solid without chemical reaction.

Adsorption

Adhesion of the molecules of a gas, liquid or dissolved substance to a surface because of chemical or electrical attraction – typically accomplished with granular activated carbon to remove dissolved organics and chlorine. The attachment of charged particles to the chemically active groups on the surface and in the pores of an ion exchanger.

ASME Bioprocessing Equipment (BPE) [37]

An American National Standard that provides the requirements applicable to the design of equipment used in the bioprocessing, pharmaceutical, and personal care product industries, including aspects related to sterility and cleanability, materials, dimensions and tolerances, surface finish, material joining, and seals.

Backwash

The process of flowing water in the opposite direction from normal service flow through a filter bed or ion exchange bed. The purpose of backwashing a sand filter is to clean it by washing away all the material it has collected during its service cycle. The purpose of backwashing a carbon filter is also to clean it, but primarily to eliminate flow channels that might have formed and to expose new absorption sites.

Bacteria

Single-celled microorganisms measured in high purity water by several means: culturing, high power microscope, or Scanning Electron Microscope (SEM). The value is reported as CFU, or colonies per milliliter or per liter. The bacteria in the water act as particle contamination on the surface of the product, or as a source of detrimental by-products. *See Pyrogen.*

Blowdown

The withdrawal of water from an evaporating water system to maintain a solids balance within specified limits of concentration of those solids.

Breakthrough

Passage of a substance through a bed, filter, or process designed to eliminate it. For ion exchange processes, the first signs are leakage of ions (in mixed beds, usually silica) and the resultant increase in conductivity. For organic removal beds, usually small, volatile compounds (THMs are common in activated carbon).

Cation Exchange Resin

An ion exchange resin which removes positively charged ions.

Colony Forming Unit (CFU)

A measure of the number of bacteria present in the environment or on the surfaces of an aseptic processing room; measured as part of qualification and ongoing monitoring. Also applied to the testing of Purified Water samples.

Compendial

Official; purported to comply with USP, Ph. Eur., or JP.

Conductivity

A measure of flow of electrical current through water. This conductance is high with high TDS water and very low with ultrapure deionized water. Conductivity is the reciprocal of resistivity (C=1/R) and is measured in micromho/cm (µmho/cm) or microsiemens/cm (µS/cm).

Contaminant

Any foreign component present in another substance. For example, anything in water that is not H_2O is a contaminant.

Critical Instrument

These are the instruments used to measure critical parameters.

Critical Utility

Utility that has the identified potential to impact product quality or performance in a significant way.

Dead Leg

A space where system design and operating conditions result in insufficient process fluid flow, presenting a risk for particulate, chemical, or biological contamination.

Dissolved Solids

The amount of non-volatile matter dissolved in a water sample, usually expressed in parts per million (ppm) by weight.

Drinking Water

EPA primary drinking water or comparable regulations of the European Union or Japan.

Electropolishing

Controlled electrochemical process utilizing acid electrolyte, DC current, anode and cathode to smooth the surface by removal of metal.

Endotoxins

Pyrogens from certain Gram-negative bacteria. Generally highly toxic Lipopolysaccharide-protein complexes (fat, linked sugars, and protein) from cell walls. A marker for these bacteria with a reputation for persistent contamination because they tend to adhere to surfaces. *See Pyrogen.*

Extractable

Undesirable foreign substances that are leached or dissolved by water or process streams from the materials of construction used in filters, storage vessels, distribution piping, and other product-contact surfaces.

Ferrite

A solid solution of one or more elements in body-centered cubic iron. Unless otherwise designated (for instance, as chromium ferrite), the solute is generally assumed to be carbon. On some equilibrium diagrams there are two ferrite regions separated by an austenite area. The lower area is alpha ferrite; the upper, delta ferrite. If there is no designation, alpha ferrite is assumed.

Good Engineering Practices (GEP)

Standards, specifications, codes, regulatory and industrial guidelines and accepted engineering and design methods to design, erect, operate, and maintain a pharmaceutical facilities taking into account not only regulatory compliance, but also safety, economics, environmental protection, and operability. Standards and specifications are provided by recognized sources such as established engineering contractors and pharmaceutical companies. Codes are provided by local, state or federal jurisdictions, or insurance companies. Guidelines are issued by professional societies, industrial organizations, or regulatory agencies. Engineering design methods have been established in the engineering educational system.

Gram-Negative Bacteria

A basic classification of bacterial type, along with "Gram positive." These organisms resist staining by the Gram technique. Sometimes considered "bad" bacteria when discussing pollution or contamination; however, this is an artificial and quite broad classification.

Gram Positive

Of bacteria, holding the color of the primary stain when treated with Gram's stain.

Greensand

Used for water filtration – Sedimentary deposit that consists largely of glauconite often mingled with clay or sand.

Halogens

Any of the five elements fluorine, chlorine, bromine, iodine, and astatine that form part of group VIIA of the periodic table and exist in the free state normally as diatomic molecules

Hardness

The concentration of calcium and magnesium salts in water. Hardness is a term originally referring to the soap-consuming power of water; as such it is sometimes also taken to include iron and manganese. "Permanent hardness" is the excess of hardness over alkalinity. "Temporary hardness" is hardness equal to or less than the alkalinity. These also are referred to as "non-carbonated" or "carbonate" hardness, respectively.

Heavy Metals

High molecular weight metal ions, such as lead. Known for their interference with many processes, and "poisoning" of catalysts, membranes, and resins.

Highly Purified Water (EDQM [102])

> *"Following a decision taken by the European Pharmacopoeia (Ph. Eur.) Commission at its 160th session (March 2018), the monograph for Water, highly purified (HPW) will be suppressed on 1 April 2019 from the Ph. Eur.*
>
> *The monograph suppression is a consequence of the recent revision of the monograph for Water for injections (0169), which now allows for purification processes equivalent to distillation for producing water for injections (WFI), in addition to distillation. Hence, the HPW monograph is a duplication of the WFI monograph in terms of quality requirements and production methods, and as such became redundant."*

High Purity Water

Water conforming to USP monographs or equivalent.

Humic Acid

The classical method for fractionating the humic colloids that disperse in the sodium hydroxide extract is to acidify the suspension with sulfuric or hydrochloric acid, which causes a part of the dispersed organic matter to precipitate. The part that stays in solution is known as fulvic acid, that which precipitates out as humic acid, and that part of the organic matter which does not disperse in the alkali but remains in the soil as humin.

Hydrocarbons

Organic compounds containing only carbon and hydrogen. Sometimes broadened to include compounds or mixtures of compounds with small amounts of oxygen also.

Hydrophilic

Having an affinity for water. Its opposite, non-water-wettable, is hydrophobic.

Hydrophobic

The extent of insolubility; not readily absorbing water; resisting or repelling water, wetting, or hydration; or being adversely affected by water. Hydrophobic bonding is an attraction between the hydrophobic or non-polar portions of molecules, causing them to aggregate and exclude water from between them.

Impurity

Any component present in the intermediate or API that is not the desired entity. It may be either process or product related.

Inorganics

Chemical compounds which are not organic in nature. Inorganics that are soluble in water generally split into negative and positive ions, allowing their removal by deionization.

Ion

An atom or radical in solution carrying an integral electric charge, either positive (cation) or negative (anion).

Ion Exchange (IX)

One of the processes used to further reduce the concentration of ions in water supplies referred to as TDS removal. The process uses anion and cation exchange resins to chemically react with and remove the remaining ions or TDS in the water. This process results in water with virtually no TDS.

Ion Exchange Regeneration

The process by which ion exchange resin that can no longer effectively remove ions from the water is recharged. This recharging or regeneration is performed by adding an excess of caustic (NaOH) to the anion resin and an excess of either hydrochloric acid (HCl) or sulfuric acid (H_2SO_4) to the anion resin. These regenerant solutions are allowed to flow through the resin beds at specific flow rates for specific periods of time depending on the type of resin, the ionic load, and the final purity desired. The regenerant solutions react with the ion exchange resin releasing the removed cations and anions which are then carried away to drain by the flow of the regenerant chemicals. The excess chemical is rinsed from the ion exchange resin with Purified Water then the bed is ready for another service cycle.

Ion Exchange Resin

A styrene-divinylbenzene or acrylic copolymer formed into small, spherical, and highly porous beads about the size of a pinhead. These inert beads are chemically treated so that they perform as if they were chemical compounds.

Material Safety Data Sheet (MSDS)

Document produced by the manufacturer that contains the chemical and physical properties of a substance that are pertinent to safe handling and storage.

Megohm/cm (Mohm-cm)

A measure of the ionic purity of water.

Membrane

A barrier, usually thin, that permits the passage only of particles up to a certain size or of special nature.

Micron

The same as a micrometer or 1000th of a millimeter. The typical particle size of importance in deionized water is less than 0.2 μm.

Microorganism

Organisms (microbes) observable only through a microscope. Larger, visible types are called organisms.

Milligrams per Liter (mg/l)

A term used to report chemical analyses. Milligrams per liter refer to the milligrams of the compound or element present in 1 liter (1000 milliliters) of water. Another term often used is parts per million (ppm) which is the same for substances in water. 1 mg/l = 1000, μg/l = 1 ppm.

Mixed-Bed Ion Exchange

The use of both cation and anion-exchange resin mixed together in one tank.

Noncarbonate Hardness

Hardness in water caused by chlorides, sulfates, and nitrates of calcium and magnesium.

Operating Parameter

Any information entered into an automated system used for automated equipment operation.

Organics

Short for organic chemicals; those compounds that contain carbon and hydrogen and are not carbonate related.

Orifice

An opening through which a fluid can pass; a restriction placed in a pipe to provide a means of measuring flow.

Osmosis

The passage of water through a permeable membrane separating two solutions of different concentrations; the water passes into the more concentrated solution.

Oxidizer

A chemical which readily oxidizes more reduced substances. Examples of strong oxidizers are ozone, hydrogen peroxide, chloride, persulfates, and oxygen itself.

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 O_3 and due to reaction with other things rapidly becomes oxygen (O_2). 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.

Particles

A physically measurable contaminant in deionized water. Particles can be bacteria, colloidal material or any other insoluble material. Particle counts are reported as number of particles per liter of a particular size measured in micrometers (microns).

Passivation

Removal of exogenous iron or iron compounds from the surface of stainless steel by means of a chemical dissolution, most typically by a treatment with an acid solution that will remove the surface contamination and enhance the formation of the passive layer.

Passive Layer

A chromium-enriched oxide layer on a stainless steel surface that improves the corrosion resistance of the base metal.

Pathogens

Disease-producing microbes.

Percent Rejection

In reverse osmosis or ultrafiltration, the ratio of impurities removed to total impurities in the incoming feed water. For example, RO membranes typically remove (reject) 90% of the dissolved inorganic contaminants in water.

Permeability

The ability of a body to pass a fluid under pressure.

pH

pH, the negative log of the hydrogen ion concentration, is a measure of the concentration of hydrogen ions (H^+) in a water-based solution. The more hydrogen ions that are present, the lower the pH and the more acidic the solution.

Polished Water

High purity water after it has undergone a second treatment step. Ultrapure water usually undergoes two or more treatment steps. More economical *pretreatment* processes (e.g., reverse osmosis) are used to remove all but a very small fraction of the impurities. Highly efficient *polishing* processes (e.g., mixed-bed deionization) are used to remove the impurities that remain.

Polypropylene (PP)

A crystalline polymer with high heat resistance (for piping an upper limit of 100°C (212°F), stiffness, and chemical resistance with respect to handling caustics, solvents, acids, and other organic chemicals. It is not recommended for use with oxidizing type acids, detergents, low boiling hydrocarbons, alcohols, and some chlorinated organic materials. Polypropylene is a relatively inert material and contributes little in the way of contamination to pharmaceutical water.

Polyvinyl Chloride (PVC)

The most common of the vinyl family of plastics. Overall it has excellent basic properties, may be easily processed and welded, and is exceptionally economical in cost. Because PVC is a thermally sensitive thermoplastic, compounding ingredients such as heat stabilizers, lubricants, fillers, plasticizers, impact modifiers, pigments, and processing aids must be added to make it processible. PVC is prone to produce extractables during start-up in high purity water.

Polyvinylidene Fluoride (PVDF)

A thermoplastic fluoropolymer that has a very linear chemical structure, and is similar to PTFE with the exception of not being fully fluorinated, i.e., having 3% hydrogen by weight. Its drawbacks in the area of chemical resistance include unsuitability with strong alkalis, fuming acids, polar solvents, amines, ketones, and esters. It has a high tensile strength as well as a high heat deflection temperature. It is readily weldable, offers high purity qualities, and is resistant to permeation of gases. PVDF is a relatively inert material and contributes little in the way of contamination to pharmaceutical water.

Potable Water

Water that is suitable for drinking.

Potable Water is not covered by a pharmacopeial monograph but must comply with the regulations on 91 water intended for human consumption of a quality equivalent to that defined in Directive 98/83/EC, or 92 laid down by the competent authority. Testing should be carried out at the manufacturing site to 93 confirm the quality of the water. Potable water may be used in chemical synthesis and in the early 94 stages of cleaning pharmaceutical manufacturing equipment unless there are specific technical or 95 quality requirements for higher grades of water. It is the prescribed source feed water for the 96 production of pharmacopoeial grade waters.

Potable Water (EMA [103])

"Potable Water is not covered by a pharmacopoeial monograph but must comply with the regulations on water intended for human consumption of a quality equivalent to that defined in Directive 98/83/EC, or laid down by the competent authority. Testing should be carried out at the manufacturing site to confirm the quality of the water. Potable water may be used in chemical synthesis and in the early stages of cleaning pharmaceutical manufacturing equipment unless there are specific technical or quality requirements for higher grades of water. It is the prescribed source feed water for the production of pharmacopoeial grade waters."

Precipitate

An insoluble reaction product; in an aqueous chemical reaction, usually a crystalline compound that grows in size to become settleable.

Product-Contact Surface

A surface that contacts raw materials, process materials, and/or product.

Pure Steam (USP [4])

Water that has been heated above 100°C (212°F) and vaporized in a manner that prevents source water entrainment. It is prepared from water complying with the U.S. EPA 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 non-condensable gases are to be determined by the Pure Steam application. **Note:** Pure Steam is intended for use where steam or its condensate comes in contact with the article of the preparation.

Purified Water (USP [4])

Water rendered suitable for pharmaceutical purposes by using unit operations that include deionization, distillation, ion exchange, reverse osmosis, filtration, or other suitable purification procedures. It meets rigid specifications for chemical purity, the requirements of the Federal Environmental Protection Agency (EPA) with respect to drinking water, and it contains no added substances. Cannot be used as raw material for parenterals. Common uses are: a rinse for equipment, vials, and ampoules, and as makeup for cosmetics, bulk chemicals, and oral products. For FDA acceptance, Purified Water must contain less than 0.5 mg/l of TOC (Total Organic Carbon), and less than 100 CFU.

Purified Water (Ph. Eur. [5])

Water for the preparation of medicinal products other than those that require the use of water which is sterile and/or apyrogenic. Purified Water which satisfies the test for endotoxins may be used in the manufacture of dialysis solutions. Purified Water is prepared by distillation, by ion exchange or by any other suitable method that complies with the regulations on water intended for human consumption laid down by the competent authority.

Pyrogen

Trace organics which are used as markers of bacterial growth or contamination. Produced by various bacteria and fungi. Critical pharmaceutical and biotechnological processes have restrictions on contamination by these substances, usually at levels near the limit of detection. Primarily polysaccharide (made of linked sugars) in nature. Fever producing substances when administered parenterally to man and certain animals.

Resistivity

The measure of the resistance to the flow of electrical current through high purity water. This is measured in millions of ohms-cm or Megohm-cm (Mohm-cm). Resistivity is the reciprocal of conductivity (R = 1/C, 1 Mohm-cm = 1 µS/cm). This provides an easy means of continuously measuring the purity of very low TDS water or ionic concentration.

Reverse Osmosis

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.

Rouge

Rouge in stainless steel systems utilized in the biopharmaceutical/life science industry, is a general term used to describe a variety of discolorations on the product-contact surfaces, caused by variations in hydration agents and the formation of metallic (primarily iron) oxides and/or hydroxides from either external sources, or from alteration of the chromium rich "passive" layer.

Salt

Neutral compound formed of two or more ions. The salt disassociates into cations and anions when dissolved in water.

Scale

The precipitate that forms on surfaces in contact with water as the result of a physical or chemical change.

Sedimentation

Gravitational settling of solid particles in a liquid system.

Softening

The removal of hardness (calcium and magnesium) from water. This is a pretreatment process which uses a cation exchange resin to remove the hardness elements from the water. The hardness elements are calcium and magnesium. The cation resin is regenerated with sodium chloride and during the exchange process, the calcium and magnesium are removed from the water and replaces with sodium ions (Na^+). The resulting sodium salts are much more soluble than the salts of calcium and magnesium and do not precipitate which provides better feed water to the RO system.

Stainless Steel

Steel to which a significant amount of chromium and nickel has been added to inhibit corrosion.

Sterilization

Refers to the killing of microorganisms in the distribution system. This is normally done periodically by flushing a sterilizing solution, such as hydrogen peroxide or ozone, through the distribution piping system. In some systems, ozone is continuously injected at low levels for continuous sterilization.

Surface Finishes

This term shall apply to all interior surface finishes accessible and inaccessible, that directly or indirectly come in contact with the designated product in bioprocessing equipment and distribution system components. Final criteria shall be determined by **Ra** values rather than polishing methods. **Note:** For commonly utilized **Ra** readings on stainless steel product-contact surfaces for the biopharmaceutical industry refer to Table SF-3 of the ASME Bioprocessing Equipment (BPE) an International Standard [31].

Surface Water

Surface water is any water where the source is above ground. This can be rivers, lakes, or reservoirs. Surface waters are usually higher in suspended matter and organic material and lower in dissolved minerals than well water.

Thermal Fusion

The joining of two materials (usually metal or plastic) by use of heat only, without any additional material. Usually done by the use of automatic TIG welding in alloy steel tubing welding or with specially designed melting equipment for plastics.

Total Dissolved Solids (TDS)

The term used to describe inorganic ions in the water. Usually measured by measuring the electrical conductance of the water corrected to 25°C (77°F).

Total Organic Carbon (TOC)

Measure of organics in water by their carbon content. This is one of the parameters used to determine the purity of Semiconductor Grade water. Feed water will have TOC measured in ppm. Ultrapure water will have TOC measured in ppb.

Trihalomethanes (THM)

Compounds present in the feed water that are formed by the reaction of chlorine and the organic material in the water. The most common THM found in water is chloroform which is quite difficult to remove. Activated carbon and degasification can serve to reduce THMs.

Turbidity

A suspension of fine particles that obscures light rays, but requires many days for sedimentation because of the small particle size.

Ultrafiltration

Filter technology similar to reverse osmosis that is capable of filtering colloids and large molecular weight organics out of the water. The filter capability of ultrafiltration filters to 0.005 μm particle size. Ultrafiltration also will remove organic material down to about 1,000 to 10, 000 molecular weight.

Ultraviolet (UV) Sterilizer

Ultraviolet lamps used to kill microorganisms in water. These can be placed anywhere in the water system. The wavelength used for control is 254 nanometers (nm).

Ultraviolet TOC Reduction

A UV source which partially oxidizes organic compounds to ionic species which can then be removed. Relies on 185 nm radiation from ozone producing mercury lamps (along with 254 nm germicidal radiation). Generally has a longer contact time than for sterilization alone.

USP Purified Water (see Purified Water (USP [4]))

Vacuum Degasification

The process of removing dissolved and entrained gases from the reverse osmosis product water by creating a vacuum in a tower through which the RO product water flows. The degasifier may be located before the reverse osmosis system, but the majority of the time it will be located after. The most prevalent gas present is carbon dioxide which may be have been generated during pH adjustment of the reverse osmosis feed water. Carbon dioxide can be removed by the anion-exchange resin, but that load can be reduced by using the vacuum degasifier. The other gas of concern in the water is oxygen, which also is removed by a vacuum degasifier.

Water for Injection (WFI) (USP [4])

Prepared from water complying with the quality attributes of "Drinking Water." Purified by distillation or a purification process that is equivalent or superior to distillation in the removal of chemicals and microorganisms. Conductivity in accordance with Stage 1, 2, and 3 tests and Conductivity Tables. Total Organic Carbon limit is at 0.5 mg/l. Typically, viable microbial counts of less than 10 CFU/100 ml for microbiological acceptability. Less than 0.25 USP EU/ml.

Water for Injection (WFI) (Ph. Eur. [5])

Water for the preparation of medicines for parenteral administration when water is used as a vehicle (WFI in bulk) and for dissolving or diluting substances or preparations for parenteral administration (sterilized Water for Injection).

WFI in bulk is produced by a purification process equivalent to distillation such as reverse osmosis, coupled with appropriate techniques such as electrodeionization, ultrafiltration or nanofiltration. The use of non-distillation technologies for the production of WFI requires that notice be given to the supervisory authority of the manufacturer before implementation. Equivalence in quality does not simply mean compliance with a specification but also takes into account the robustness of the production method.

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