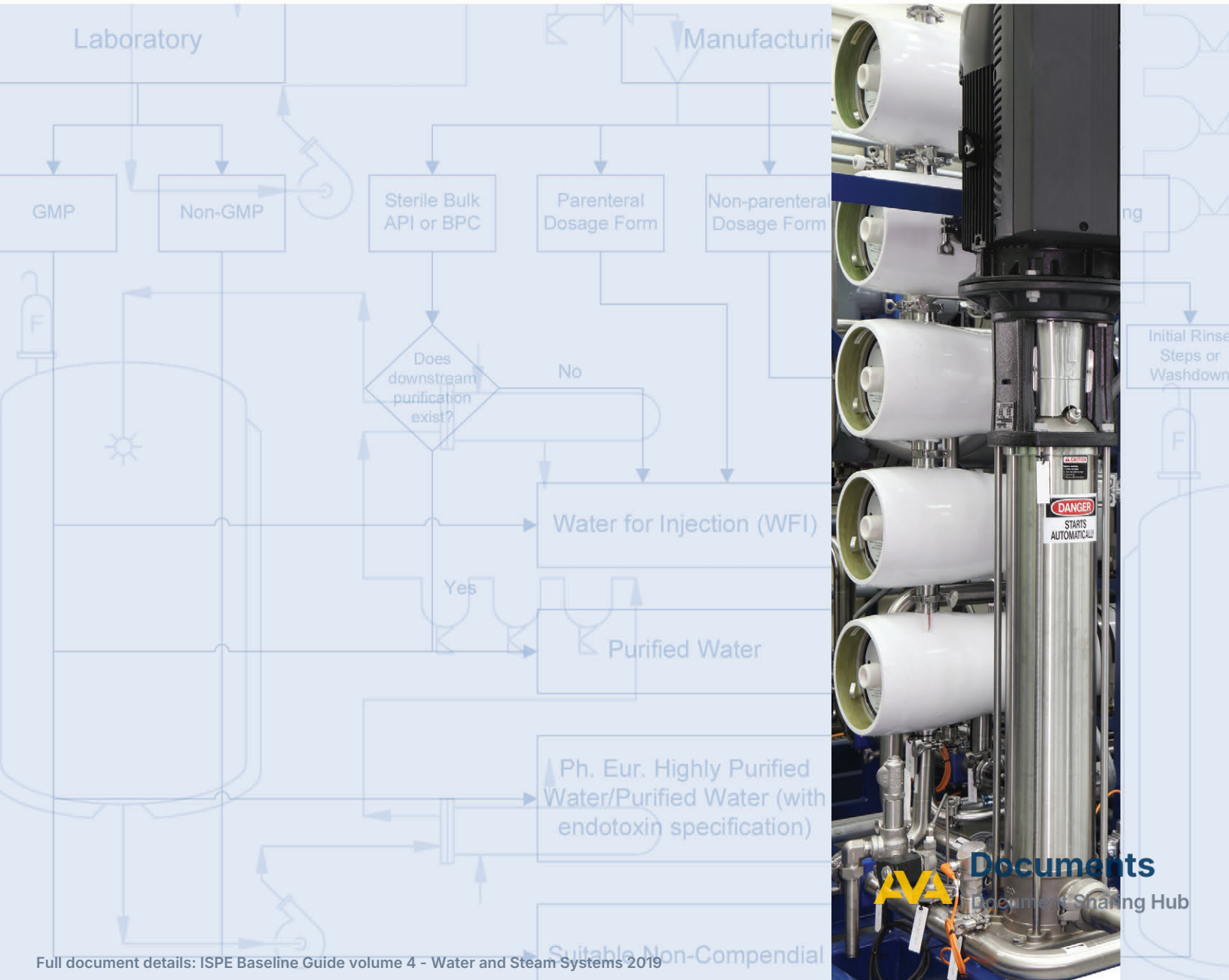
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Preface

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.

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Acknowledgements

The Guide was produced by a Task Team led by:

Nissan Cohen	Biopharmaceutical Water Doc	USA
Brian Pochini, CPIP	Sanofi	USA
Gary Zoccolante	Plymouth Rock Water Consultants	USA

The work was supported by the ISPE Critical Utilities Community of Practice (CoP).

Core Team

The following individuals took lead roles in the preparation of this Guide:

Jamie Evans	GC Biotherapeutics	Canada
Michelle Gonzalez	Amgen Inc. (retired)	USA
Brian Hagopian, CPIP	Clear Water Consulting, Inc.	USA
Joseph Manfredi	GMP Systems, Inc.	USA
Brian McClellan	Aqua-Chem Inc.	USA
Chris Peterson	AbbVie	USA
T.C. Soli, PhD	Soli Pharma Solutions Inc.	USA
Philip E. Sumner	Pfizer Global Engineering	USA
Steve Wisniewski	CAI	USA

Other Contributors

The Team wish to thank the following individuals for their significant contribution to the document.

Robert M. Augustine	Eli Lilly and Company	USA
Andrew Baird	Jacobs Engineering	USA
Anthony Bevilacqua, PhD	Mettler-Toledo Thornton Inc.	USA
Robert C. Coleman	IHL Consulting Group, Inc.	USA
Martin Emery	AveXis	USA
Diana Fischer	Bausch & Lomb, Inc.	USA
W. Roderick Freeman	Kite Pharma	USA
Ariel Kehati	Omrix, Johnson & Johnson	Israel
Shlomo Sackstein	Biopuremax Ltd.	Israel
Ian Shanahan	MECO Ireland Ltd.	Ireland
Roland Thoendel	Takeda	Austria
Anders Widov	Wiphe AB	Sweden
John Walker	VWS/Elga	United Kingdom
Paul Whitehead, PhD	VWS/Elga (retired)	United Kingdom

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600 N. Westshore Blvd., Suite 900, Tampa, Florida 33609 USA
Tel: +1-813-960-2105, Fax: +1-813-264-2816

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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.

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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

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- 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.

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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.

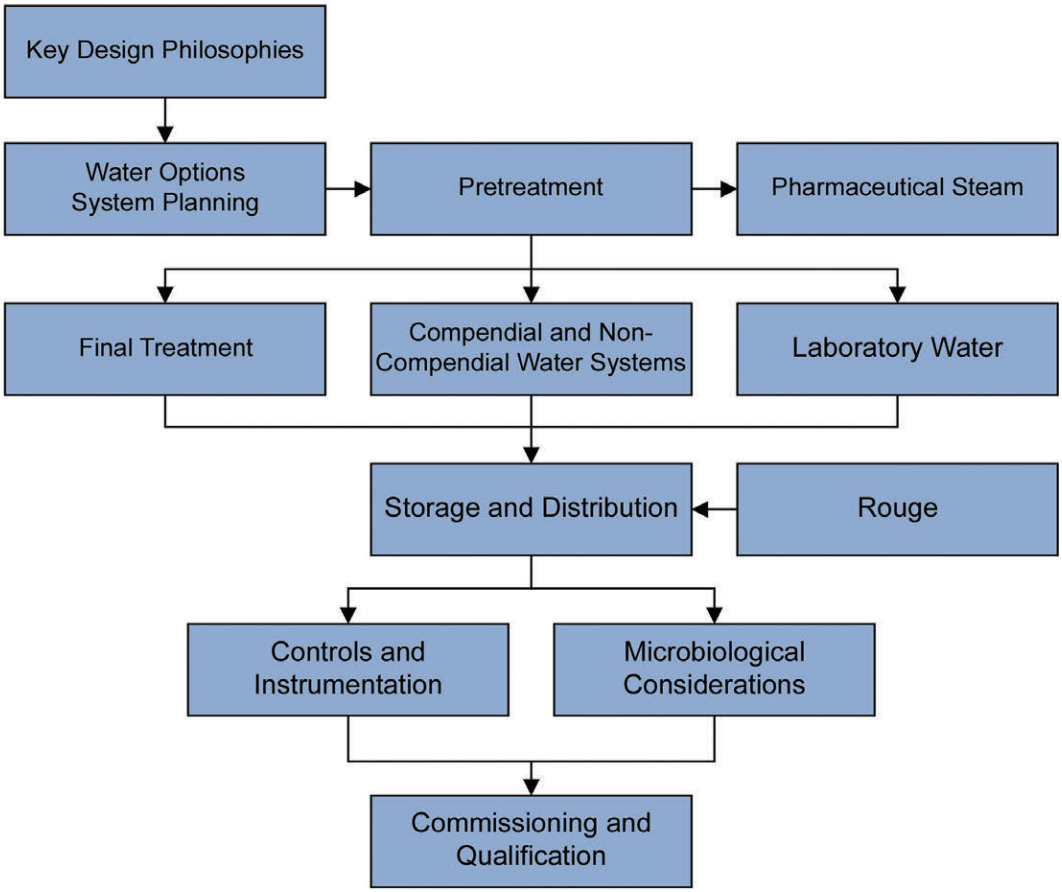
1.4 Guide Structure

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.

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Figure 1.1: Structure of the ISPE Baseline® Guide: Water and Steam Systems



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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.

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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.

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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.

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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.

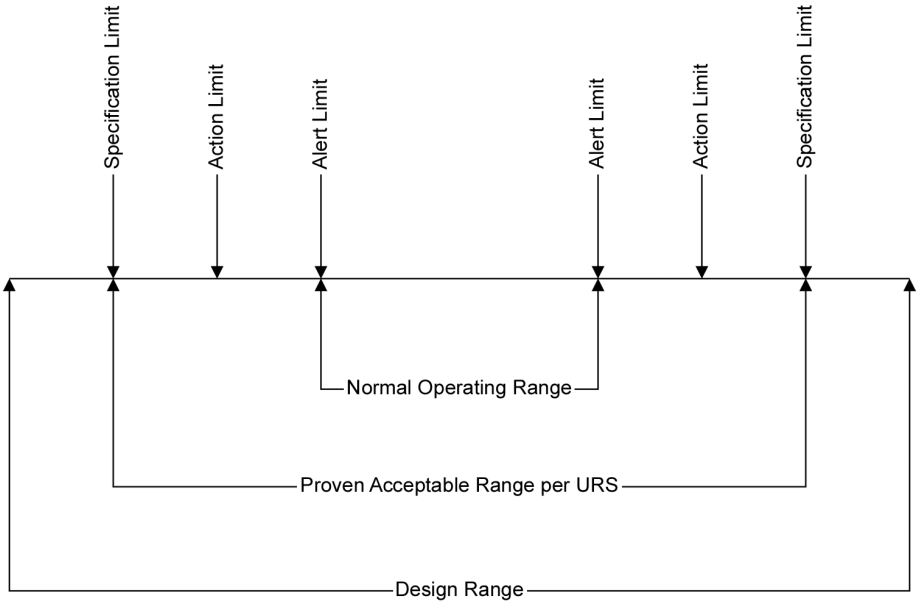
While a water or steam system should meet all stated design conditions, the acceptability of the system for operation from a GMP standpoint depends on operating within the proven acceptable range.

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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.

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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.

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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]

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- 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.

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- 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.

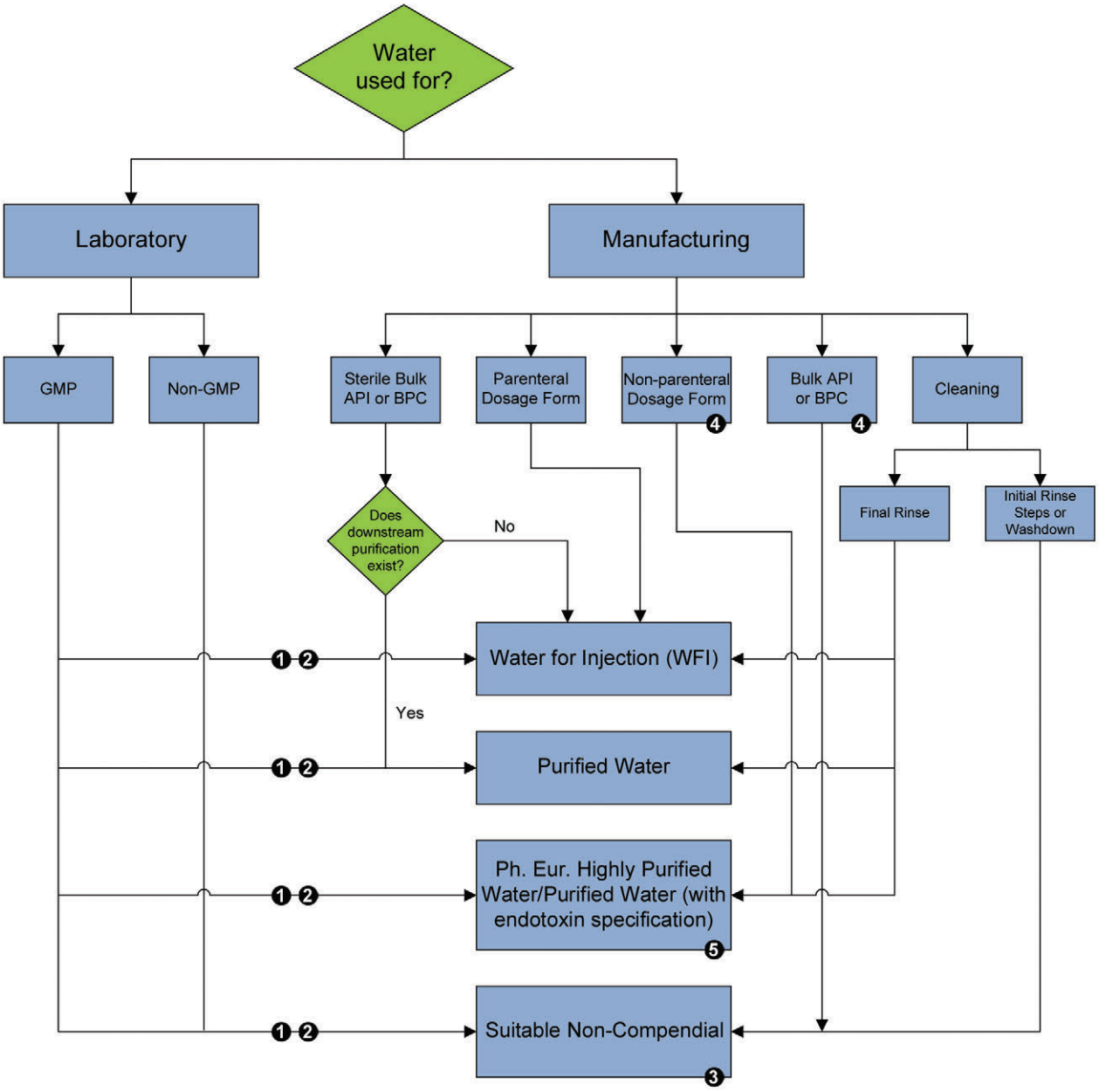
Figure 3.1 shows a decision tree that can be followed by manufacturer organizations to determine appropriate requirements for water used throughout their pharmaceutical manufacturing processes. The completed diagram should be accompanied by documentation supporting the options chosen with review and 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.

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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]

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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

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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

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- 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.

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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.

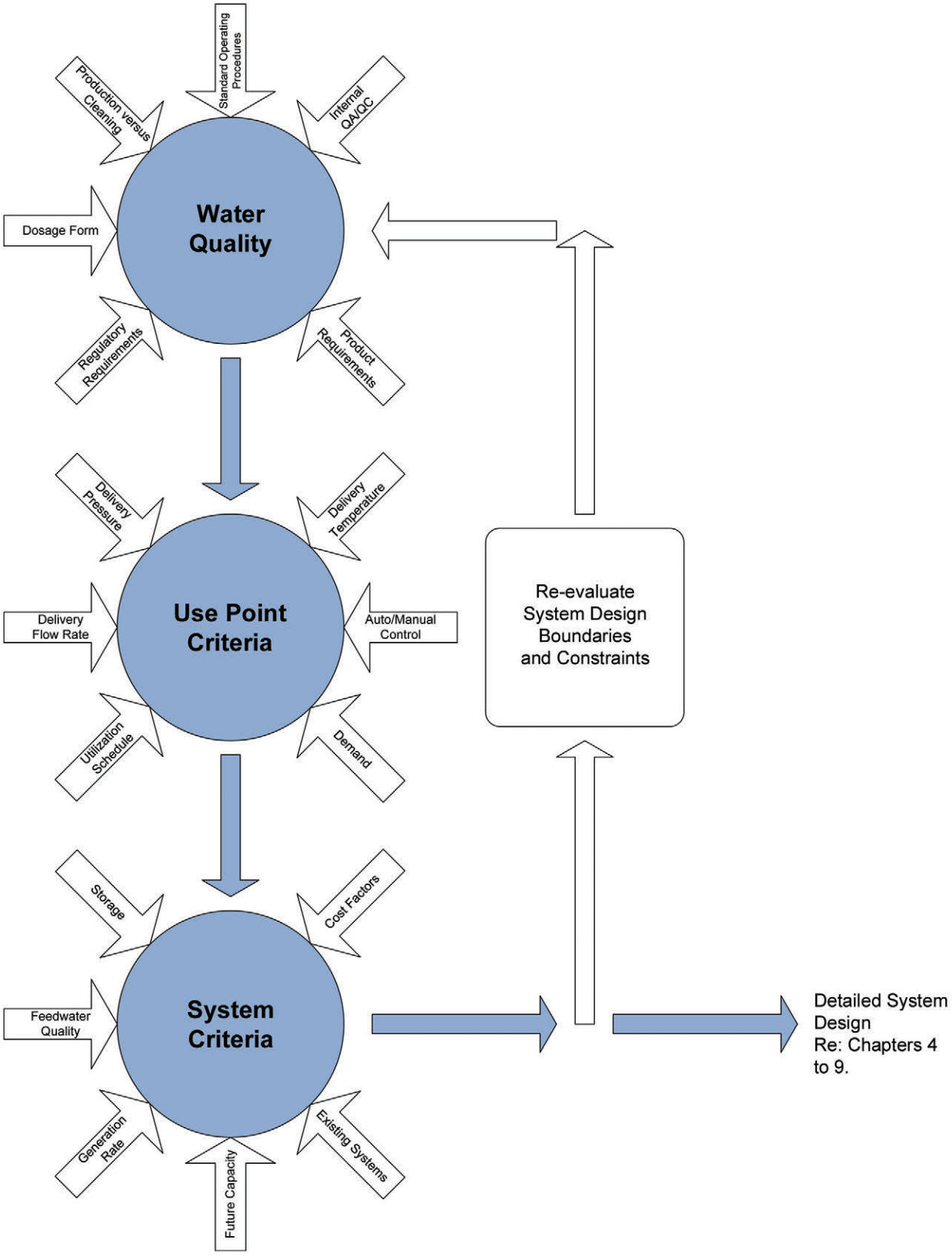
Certain restrictions can necessitate a specific strategy; however, as long as the decision leads to a result that is within the limits of the established system boundaries, it will most likely be acceptable. An example is a facility that requires a new use point to deliver non-compendial water with microbial 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.

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Figure 3.2: Pharmaceutical Water System Planning



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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.

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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.

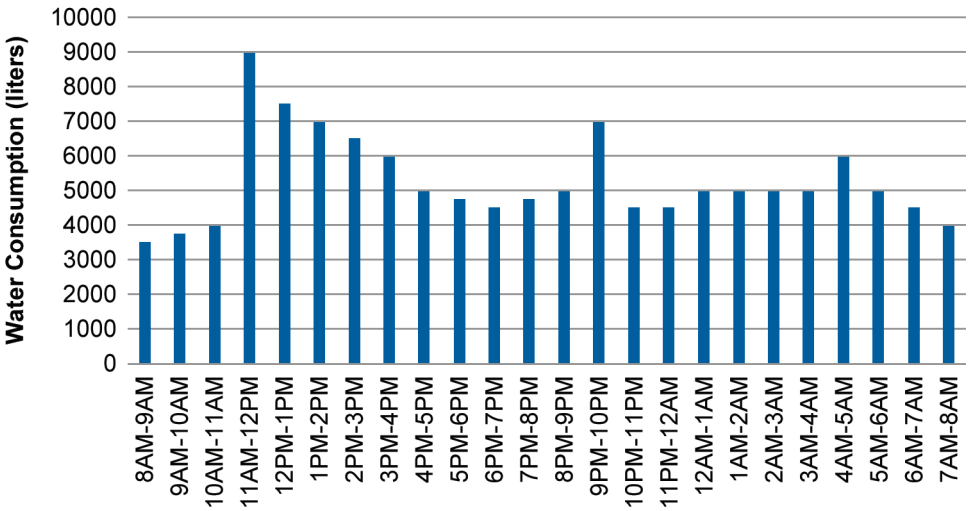
Table 3.2: Example of Point of Use Criteria for System Planning

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.



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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:

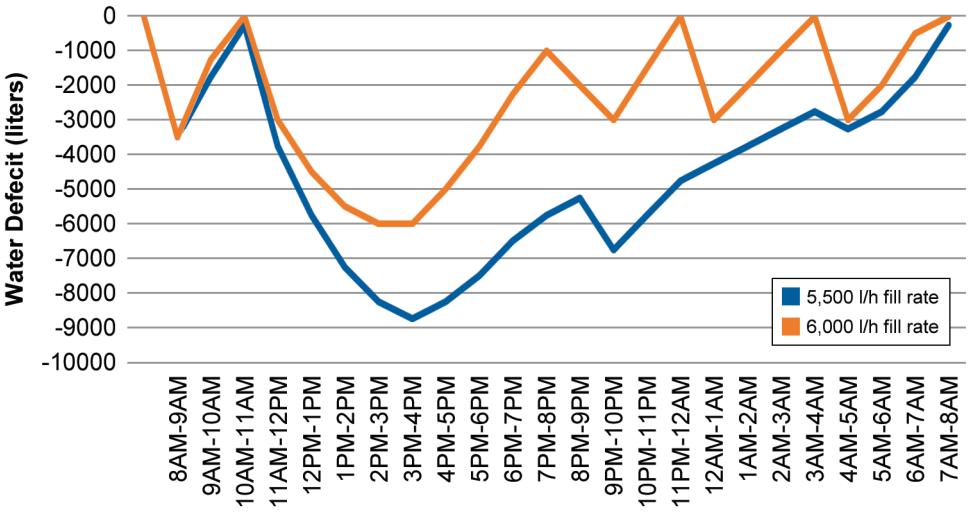
- The system must be available at all times.
- Shutdowns must be limited in number and duration.

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- 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.

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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.

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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)

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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.

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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

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- 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

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- 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.

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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.

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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).

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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).

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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.

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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

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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.

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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.

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