



GOOD PRACTICE GUIDE:

Sampling for Pharmaceutical Water, Steam, and Process Gases



Design of
Sample Valves

Minimize OOS
Investigations

Best Sampling
Practices and
Techniques

Representative
Documents
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Sampling for Pharmaceutical Water, Steam, and Process Gases

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Preface

Product Quality is of paramount importance in all industries, but it is of particular importance in the Life Sciences industry and sampling is a critical part of this process. When any step of the sampling process isn't done properly, errors may be introduced and misrepresentative data can **cost companies thousands if not millions of dollars** by creating costly and unnecessary investigations and corrective actions.

Sampling can help us understand if a system is delivering the critical utility to use points in the facility or if the characteristics are changing between the generation and use of the utility.

Sampling is an involved and complicated process and very little regulatory guidance exists on this topic. *The ISPE Good Practice Guide: Sampling for Pharmaceutical Water, Steam, and Process Gases* provides expert guidance on all aspects of sampling from valve design, the number, location, and placement of sample valves, sampling technique, frequency, and sample storage including delivery to the testing laboratory.

This Guide is an indispensable tool to all users of water, steam, or process gases and impacts facilities, production, and quality control personnel within a facility. As such, this Guide applies to manufacturers of pharmaceuticals, medical devices, biologics, cosmetics, and related products as well as equipment manufacturers, vendors, and other industries outside of the pharmaceutical world.

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1 Introduction

1.1 Background

Effective sampling is of paramount importance to the success of any pharmaceutical critical utility system. Unfortunately, there is very little regulatory guidance with regards to sampling. Extracting a representative sample from a utility system is an involved and complicated process and error may be introduced due to:

- Environmental conditions
- Sample valve design
- Sample point location
- Technique
- Container type
- Sample handling
- Sample storage and transport
- Other factors

The impact of these factors is widespread and occurs throughout industry. Errors due to sampling are so common that the 1993 US FDA “Guide to the Inspection of High Purity Water Systems” [1] specifically addresses sampling errors in recommendations to their field inspectors by stating that, *“it is expected that [Water For Injection systems] be essentially sterile. Since sampling frequently is performed in non-sterile areas and is not truly aseptic, occasional low level [bacteria] counts due to sampling errors may occur.”*

Improper sampling may be responsible for generating Out Of Specification (OOS) data and prompting investigations when a system is actually producing and delivering acceptable quality. Conversely, improper sampling may also create a more dangerous scenario where the quality is actually OOS but the data incorrectly indicates that the quality is acceptable. In either case, there could be negative impact on company image, cost, productivity, ethics, and regulatory liability, resulting from improper sampling. Identifying the elements of proper sampling and eliminating the underlying reasons for these negative consequences formed the primary driving force behind this ISPE Good Practice Guide.

1.1.1 What is a sample?

Simply stated, the intent of sampling is to take a small but representative portion of a much larger stream, where the sample collected accurately represents the content of the larger stream. The sample collected should not be altered or changed in any way because the sampling process, but this is an almost impossibly difficult proposition as all sampled utilities come into contact with air, containers, etc. during the sampling process.

1.1.2 Why do we sample?

It is most desirable to monitor quality parameters using in-line, on-line, or at-line monitors, which minimize and, in some cases, eliminate, sample handling issues completely. However, when the quality attribute of concern cannot be analyzed with an instrument or where an instrument is not present, a sample has to be removed from a stream and evaluated off-line. In most cases, these attributes are microbiological or endotoxin in nature, but sampling for Total Organic Carbon (TOC) and conductivity are commonly done as well.

The goal of sampling really depends on why the sample is being collected. Sampling generally occurs for one or more of the following reasons:

- Regulatory requirements
- Quality control purposes
- Process control purposes
- Technical, investigational or diagnostic purposes
- Test method validation purposes

Each of these purposes is described below.

Regulatory monographs establish compendial requirements for Critical Quality Attributes (CQAs) in a critical utility system. Industry must demonstrate that the utility's CQAs are being met through instrumentation or sampling. There are usually established sampling frequencies, and some of these frequencies may be established by authorities and regulating agencies. In this sampling guide, we will refer to sampling for these purposes as **sampling to meet regulatory requirements**.

In some cases, the utility being sampled is an ingredient or comes into direct contact with a pharmaceutical product. In this case, sampling is done to ensure that the quality of the utility meets established quality parameters. In these instances, samples must be taken in the exact way that the utility is removed from the delivery system during manufacturing. Stated a bit differently in the case of taking a water sample, samples shall be collected from the end of a hose or pipe in a manner that replicates exactly how the utility is used during manufacturing. Samples need to be tested for all quality attributes that are specified for the grade of the utility. There are usually established frequencies for sampling, and frequencies may be established by regulatory authorities as well as by internal Standard Operating Procedures (SOPs). In this Good Practice Guide, we will refer to sampling for these purposes as **sampling for quality control purposes**.

In other cases, sampling may be done regularly, but at a different frequency than samples taken for quality control purposes. Samples of this type would be taken to confirm that a particular process is operating under a state of control. Here, the goal of sampling is completely different in that the purpose is to determine if a specific contaminant is being reduced to the levels established for that particular treatment process. The acceptance level for the contaminant being removed may be different from the final product quality attribute level because the attribute is being tested midway through a multi-step purification process. In this case, it would be a waste of resources to test the sample for anything other than the contaminant that the process has been designed to remove. There is no requirement to test for anything other than the established quality attributes for the treatment step. Sampling for all quality attributes of the finished material and this location would provide data with little meaning. When sampling for these purposes, it is critically important that the sample removed from a system be as representative as possible of the material flowing through the system. Great care should be taken to ensure that samples are not contaminated. Careful consideration should be taken in flushing or preparing these lines, for example by spraying with alcohol prior to or immediately following sample collection. In this guide, we will refer to sampling for these purposes as **sampling for process control purposes**.

If other instances, sampling may be done only as needed, e.g., if an Alert Level is reached for a critical quality attribute, investigation into the root cause of the excursion would suggest sampling from locations that are not part of the regular testing program. The frequency of sampling for these purposes will vary from the frequency of sampling for all other purposes and would typically occur on an as needed basis as established in SOPs. In this sampling guide, we will refer to sampling for these purposes as **sampling for technical, investigational, or diagnostic purposes**.

While there is no established regulatory requirement, a robust sampling program should periodically go through a method validation process where duplicate samples are taken from a small number of sample points to document the consistency of the data and therefore the accuracy of the method. Sampling for these reasons represents **sampling for method validation purposes**.

Note: there is no purpose classified as **sampling for informational purposes only**. While industry has used this description in the past, and many in industry continue to use this designation, every sample point should have a specific purpose and the authors of this guide are recommending abandoning the “for informational purposes only” designation as being too vague and non-specific.

When developing a sampling program and considering sampling at a particular location, the purpose the sample point will serve should be considered. Sample valves should always be installed for a specific purpose and this purpose should be documented. The purpose of a particular sampling point is used to establish the frequency as well as the attributes monitored. For each sampling point, a risk-based approach should be utilized to establish or adjust sampling frequencies based on data collected over time. As an example, an effective sampling program might sample for bacteria and endotoxin after a carbon filter both before and immediately following a sanitization.

The results derived from an effective sampling program provide us with greater knowledge and understanding of these critical utilities. Sampling brings a greater understanding of when a piece of equipment is operating properly and when it may require adjustment or routine service in order to keep a system operating under a state of control. Results of an effective sampling program can be used to establish normal operating levels for a purification process or distribution system, or for the end product quality. In most cases, data collection and review allows for the establishment and future adjustment of Alert (2σ) and Action (3σ) Levels based on actual operating conditions.

Sampling can help us understand if a system is delivering the critical utility to use points in the facility or if the characteristics are changing between the generation and use of the utility.

1.1.3 Who is responsible for sampling?

Ultimately, the quality control function is responsible for sampling, but other stakeholders may become involved with sampling including quality assurance, utilities, facilities, manufacturing, production, or regulatory.

1.1.4 How often do we need to sample?

Sampling frequency depends on the system and the grade of the critical utility. In the case of Water For Injection (WFI) grade water, it is an expectation that water samples will be taken from each Point Of Use (POU) and sample location in the distribution system at least once per week during validation. Industry has continued to utilize this same sampling frequency beyond the completion of the Performance Qualification, although it is not mandated. By contrast, purified water has no such preconceived sampling requirements, so the end user is not mandated to follow any specific schedule during or following validation, although many companies also having WFI systems default to the same frequency used on WFI systems. Pharmaceutical steam, compressed air, and process gases have different frequencies during validation and ongoing operation. When no sampling frequency is specified, a risk-based approach may be utilized in conjunction with the purpose of sampling to establish initial sampling frequencies. As data is generated and an operating baseline is established, the collected data should be reviewed to determine if the operating limits, Alert and Action Levels, and/or the sampling frequency may be adjusted (increased or decreased) based on data generated on system operation and as established within operational SOPs.

1.1.5 Where do we need to sample?

Sampling locations are determined by the purpose of sampling and the information expected from the sampling location. Careful consideration and sound engineering judgment should be utilized to distinguish between sampling locations for Regulatory Compliance, Quality Control, Process Control, or Investigational and Diagnostic purposes.

1.1.6 *Are all quality attributes uniformly distributed in a system?*

The answer is a resounding no, and this is one of the most important paradigm shifts that the reader should understand when defining and evaluating a sampling program. In pharmaceutical water systems, if a quality attribute is a chemical constituent (e.g., nitrates, conductivity, dissolved metals, TOC) then the constituent is considered uniformly or homogeneously distributed (Second Law of Thermodynamics). However, if the quality attribute is biological in nature (e.g., bacteria, endotoxin), then the quality attribute will not be uniformly distributed. Non-uniform or heterogeneously distributed attributes are much more challenging to sample accurately as these attributes may vary from point to point in a system. A significant portion of this Guide is devoted to providing guidance on the most effective methods for accurate sample collection involving these heterogeneously distributed quality attributes.

In pharmaceutical steam systems, compressed air, and process gas systems, attributes may or may not be uniformly distributed and sampling programs must take this into account.

1.2 Overview

This Guide affects users of water, steam, compressed air, or process gases and impacts facilities, production, and quality control personnel within a facility. This Guide applies to manufacturers of pharmaceuticals, medical devices, biologics, cosmetics and related products, as well as equipment manufacturers, vendors, and other industries outside of the pharmaceutical arena.

1.3 Scope and Purpose

This Guide has been assembled to provide assistance to designer engineers, process engineers, facilities engineers, quality assurance staff, quality control staff, production staff, and any other group, team, or individual that may be impacted by the results of a sampling program.

This Guide covers the critical utilities of pharmaceutical water, pharmaceutical steam, and pharmaceutical process gases in the chapters that follow.

While the focus of this Guide is geared to the pharmaceutical, biotechnology, and other life science industries, the ideas, concepts, and methods detailed in this Guide may prove valuable and applicable to other industries incorporating the utilities covered in this Guide. In the life science industries, it is important to remember that the product manufacturer is ultimately responsible for all quality attributes that impact raw material and finished product quality.

This Guide covers all aspects of sampling from valve design, the number, location, and placement of sample valves, sampling technique, frequency, and sample storage including delivery to the testing laboratory.

The scope of this Guide stops when the sample is delivered to the laboratory for analysis. This Guide does not include the actual testing performed after the sample is turned over to the laboratory. Further, this Guide does not cover the interpretation or analysis of data generated by the sampling programs referenced in this Guide. While this data is usually collected and compiled to establish alert (e.g., standard deviations (2σ) from the mean) and action (e.g., three standard deviations (3σ) from the mean) levels for the parameter being measured, a thorough discussion of data interpretation is outside the scope of this Guide.

This Guide does not cover Heating, Ventilation, and Air Conditioning (HVAC) systems for cleanrooms, environmental monitoring, Active Pharmaceutical Ingredients (APIs), or finished products.

1.4 Benefits

This Guide aims to:

- Provide industry with standards and best practices for sampling in a comprehensive single reference.
- Help to minimize sampling errors and their contribution to Out of Specification (OOS) results, which can cause costly work and production stoppages, investigations, and disruptions in manufacturing, Quality Control (QC)/Quality Assurance (QA), and engineering organizations.

This Guide is expected to be of benefit to laboratory, QC/QA, engineering, facilities, and operations personnel.

1.5 Objectives

This Guide aims to establish good practices for sampling to minimize sample contamination from human contact, error, atmospheric, or environmental conditions which could alter laboratory results and provide inaccurate data.

1.6 Key Concepts/Terms

Alert Level

A level or range that, when exceeded, indicates that a process may have drifted from its normal operating range. May be established at two standard deviations (2σ) from the mean. Constitutes a warning and does not necessarily require a corrective action.

Action Level

A level established that, when exceeded, indicates that a process from its normal operating range. Typically established at three standard deviations (3σ) from the mean. Corrective actions should be taken to bring the process back into its normal operating range.

Contaminant

Any foreign component present in another substance; used synonymously with impurity in this Guide.

Impurity

A foreign agent that is introduced as part of a process; used synonymously with contaminant in this Guide.

2 Pharmaceutical Water

2.1 Introduction

Water is one of the most widely used materials in the pharmaceutical industry and is commonly used as a:

- Product or Ingredient
- Cleaning agent
- Sterilizing media
- Analytical agent
- Formulation aid

When water is used for pharmaceutical purposes it needs to be tested to ensure that it meets monograph requirements or other specifications for applicable CQAs. When water is extracted for sampling purposes at any point in a system for any reason, proper sampling is the key to ensuring that the collected sample accurately represents the quality of the water at that particular point in the system. When water is sampled in the same way as it is used during manufacturing, sampling is considered the best indicator available of the quality of water going into a product.

2.2.1 Background

Extracting water from a system into a container for subsequent laboratory analysis is the most common sampling utilized by pharmaceutical companies to determine the levels of CQAs. This testing methodology is also the most frequently used method for determining the microbiological and endotoxin content of water. As the accuracy and reliability of instrumentation has increased, establishing the equivalency between the conventional “sample and laboratory test” method and the “continuous monitoring with an instrument” method may allow an increasing number of CQAs to be verified continuously. This can substantially reduce the frequency of water sampling from a system. In order to determine if an attribute is a candidate for monitoring with process instrumentation, the uniformity of distribution of the attribute within a water system needs to be understood.

In pharmaceutical water systems, CQAs or other impurities may or may not be uniformly distributed in a distribution system. The homogeneous or heterogeneous nature of distribution of CQAs in a system should be understood prior to formulating a sampling plan.

2.1.1.1 Homogeneously Distributed Impurities

Chemical impurities, small particulates, and other soluble impurities are typically expected to be homogeneously distributed throughout a distribution system because of the solubility and nature of these impurities, and because of chemical equilibrium processes. Since the impurity levels at any one location in a distribution system should be identical to the impurity levels at every other location within the distribution system, sampling for homogeneously distributed impurities may not be required at every POU and may be performed at a limited number of locations, provided that there is no likelihood of downstream sources of contamination.

Homogeneously distributed impurities are candidates for continuous monitoring using on-line, in-line, or at-line instruments if the impurity levels at the instrumentation locations have been validated through sampling and laboratory analysis to be predictive of the levels at all POUs. When validated in this manner, the resulting data may be used for quality control or water release purposes. Sampling and testing of these impurities is typically done at the return of a distribution loop, but may be done in other locations. Impurities falling into the homogeneously distributed impurity category include:

- Ionic impurities (detected non-specifically as electrical conductivity or resistivity)
- Organic impurities (detected non-specifically as TOC)
- Nitrates (EP [2] requirement for Purified Water (PW) and Water For Injection (WFI))
- Heavy metals (EP [2] requirement for PW¹)

Localized sources of chemical impurities may be introduced to a system downstream of a particular point within a distribution system. For example, chemical contamination sources after a POU valve, such as from hoses, gaskets, or a POU heat exchanger may contaminate the water as it exits the system at one particular location. Chemical contamination sources within a sub loop, parallel loop, or other isolated portion of the system could contaminate the water in only that portion of the system. The purity of the water in these sub loops and POU locations may not, therefore, be accurately represented by on-line, in-line, or at-line instrumentation installed in the main distribution system. In system sub loops, additional on-line, in-line, or at-line instrumentation may be required in order to accurately measure these impurities, or manual testing by sampling may be utilized at POUs within these sub loops.

2.1.1.2 *Heterogeneously Distributed Impurities*

Bacteria and endotoxin are attributes that are not uniformly distributed throughout a water system. The reason is that most bacteria present in the system are not free floating, but are part of a biofilm that is attached to system surfaces within a water system. It is generally understood that the majority of bacteria present in a system (99.9 to 99.99%) reside in biofilm. It is the small fraction (0.01 to 0.1%) of free floating or planktonic bacteria that contribute to the bacteria and endotoxin levels detected by sampling.

Biofilm development occurs more rapidly in areas of low or no flow where bacteria are able to attach to surfaces more easily. Bacteria and endotoxin populations may, therefore, vary widely because of variable local flow conditions. Examples of low flow areas that allow bacteria to attach to a distribution piping system include:

- Within any non-flowing side connections of any length, including dead legs
- On the upstream or wet side of valve sealing surfaces
- On the water stopping sealing surfaces within the valve
- On the downstream side of the valve surfaces (which may remain wet or moist)
- On the fitting and gasket used to connect a hose or other connector
- Within the hose or connector to the actual location of water use
- Within any additional external device connected to the system through which the water flows, such as:
 - Flow meters
 - Pressure regulators
 - Heat exchangers
 - Check valves
 - Hoses, fittings, adapters, etc.

¹ According to the EP [2] if Purified Water meets the conductivity limits for WFI, then heavy metals testing is not required.



Localized low flow conditions throughout a system and at POU's creates differing conditions and variable bacteria and endotoxin populations at these locations. For this reason, sampling is required of each POU location to confirm the presence or absence of bacteria. Sampling the supply and return may indicate the general condition of the distribution system, but is simply not sufficient to establish the bacterial characteristics and population of the entire distribution system.

2.1.2 Purpose of Sampling

The purpose of sampling should be identified and documented for each potential sample location within a system as early as possible during the design process. This process should justify and document the requirement for sampling and identify the reason for sampling at a particular location.

The purpose of any potential sampling location should fall into one or more of the following categories:

1. Regulatory requirements
2. Consensus standards
3. Process control purposes
4. Quality control purposes
5. Technical, investigational, or diagnostic purposes

The justification for a potential sampling location should also consider:

- The impurities of interest at the potential location
- The type of valve and other accessories that are best suited for or are contra-indicated for the potential location
- Should sampling should be performed at this location at an established frequency
- Should sampling be performed on an event based frequency (i.e., reaching an alert or action level)
- Is the potential location readily accessible to staff
- Can the sample be taken safely by staff at the potential location
- Any special considerations for sample handling after a sample is taken

The purpose of a sampling location may impact the impurities of concern as well as the sampling frequency.

2.1.2.1 Regulatory Requirements

All pharmacopoeias define two bulk grades of water for pharmaceutical purposes:²

1. Purified Water (PW)
2. Water For Injection (WFI)

² Highly Purified Water (HPW) is an additional pharmaceutical grade of water as defined by the European Pharmacopoeia.

While there are some differences between the various pharmacopoeias on the exact specification for some impurities, the general consensus is that the following impurities should be monitored:

- Conductivity
- TOC
- Endotoxin (for WFI only)

Some pharmacopoeias also require testing for heavy metals and nitrates. Consult applicable monographs for exact specification.

While bacteria testing is not a monograph requirement, all pharmaceutical companies sample and test for bacteria. The pharmaceutical industry references the 1993 US FDA "Guide to the Inspection of High Purity Water Systems" [1] which stipulates the following maximum bacteria action limits for pharmaceutical water systems:

- Bacteria action limits at or below 100 cfu per ml for PW
- Bacteria action limits at or below 10 cfu per 100 ml for WFI

The pharmaceutical industry has universally adopted these action limits as specifications for PW and WFI and pharmaceutical water systems are sampled and tested for:

- Conductivity
- TOC
- Endotoxin (WFI only)
- Bacteria

2.1.2.2 Consensus Standards

Consensus standards may be utilized as a source for water quality specifications if the use of water within the facility or a portion of a facility is consistent with those standards. Consensus standards such as the International Organization for Standardization (ISO) [3], the American Society for Testing and Materials (ASTM) [4], the Association for the Advancement of Medical Instrumentation (AAMI) [5], or the Clinical and Laboratory Standards Institute (CLSI) [6], have application specific standards for water purity. These water quality specifications may be found in Appendix 1.

2.1.2.3 Process Control Purposes

Monitoring a water purification system for process control purposes involves monitoring the performance and success of the various treatment processes for specific attributes of concern and includes following the quantitative trends of those or related attributes of interest. When data trends from this monitoring indicate that some aspects of the water purification system or other physical or procedural process controls are not performing as intended, then investigations and targeted remedial interventions can be instituted to bring the process back into normal operational control before the finished quality of the water is sufficiently affected to adversely impact its quality specifications.

It is considered appropriate to monitor only those attributes related to the monitoring or control of a given function in the purification process. For example, it may be appropriate to monitor a carbon bed for the reduction of chlorine, the reduction of TOC, and the effluent (outflow) microbial level since carbon beds are installed to impact these attributes (microbial levels being an adverse effect of installing a carbon bed) and high levels of these contaminants could negatively impact the operation and maintenance of downstream unit operations. However, it would not be appropriate to monitor hardness or conductivity at this location, as the carbon bed is not impacted by these

it intended to impact, these attributes. The selection of the appropriate attributes to monitor should be tailored to the unit operation's function as well as potential downstream impact. The attributes selected for process control monitoring may be different than attributes selected to meet compendial requirements.

Process control sampling points may be strategically located throughout the water purification system. They may be located at the beginning and end of distribution loops or near critical POU's which are typically not used by manufacturing. They may also be located at POU valves in the distribution system that is used by manufacturing. In these cases, sampling may be limited only to final product CQAs such as conductivity, TOC, bacteria, and endotoxin (WFI only). POU valves with built in upstream sampling ports may be utilized for process control monitoring.

Biological attributes such as bacteria and endotoxin that are not homogeneously distributed throughout a water system have the potential to contaminate the attribute being monitored at a process control sampling location as water is sampled. In these cases, efforts should be made to prevent or minimize sample contamination from these attributes.

Process control indicating trigger values, such as Alert and Action Levels, are typically used to assist in identifying when the process is deviating from its normal operating capabilities.

Alert Levels

Alert Levels should be set at levels that are near the top edge of normal data trends. Alert levels may be based on analysis and trending of historic performance data and are usually set at two standard deviations (2σ) from normal operating levels.

An occasional Alert Level excursion that is barely above the Alert Level could be considered a normal expectation, as it is within the upper reaches of the normal operating trends for the system. Though such a level could be an early indication of a growing control problem, it could also be simply the variability of normal operating data. Responses to Alert Level excursions should include notification of appropriate quality, manufacturing, and maintenance personnel, along with closer attention being paid to the routine data. Frequent excursions beyond the Alert Level should not be expected and might also be considered out of trend.

When data begins to drift outside of the normal trends and expected performance, notification of those who may potentially be affected, as well as resampling, may be appropriate to verify if the data trends are consistently higher (a possible developing control problem) or not (a possible sampling inconsistency or normal data variability).

Where Alert Level excursions occur concurrently at multiple locations or sequentially at the same location, this may be an indication of a need for investigation and remediation and may be escalated to an Action Level excursion.

Action Levels

Historic data trending should be used to establish Action Levels, which are typically set at three standard deviations (3σ) from normal operating levels. Action Levels should be established at values that are:

- Above the normal data trends and indicative of routine process controls beginning to fail
- Far enough from the specification so that remedial action(s) can bring the process back under control before a specification excursion occurs

Resampling and retesting should be one of the first corrective actions (along with the usual notification of appropriate parties such as for Alert Level excursions) to see if the excursion conditions are an indication of a true process control problem or the result of a sampling problem.

Where high values are confirmed by retesting, or if the original value is following Alert Level excursions, appropriate remediation activities should be instituted to restore control and determine the cause(s) of the excursion. Solving corrective measures can preclude recurrence and remediate any potential impact to quality specifications.

2.1.2.4 Quality Control Purposes

When monitoring for quality control of the water, the intent is to:

1. Exactly duplicate the quality of water that is being used for manufacturing by collecting samples at routine intervals
2. Collect water samples at the beginning of a period when the water is being drawn from the system for manufacturing use

Exact duplication of the preparatory procedures utilized by manufacturing should be used during sampling, and should include the use of the same:

- Outlet sanitization practice, if applicable
- Hose and gasket
- Outlet flush procedure (if any)
- Attached devices such as heat exchangers, reducers, adapters, check valves, and flow meters

The purpose of including all of the potential sources of contamination in the flow path for sampling is to attempt to duplicate the water quality delivered to the manufacturing process, including any heterogeneously distributed contaminants coming from the associated biofilms on or within these components.

Hard piped or otherwise permanent connections between the water system and manufacturing equipment, as well as automatic valves, create challenges for obtaining samples that duplicate the way that water is used by manufacturing. One engineering solution may be to utilize a three way divert valve that may be installed on the manufacturing equipment. This could facilitate sampling by diverting water to obtain a sample. Alternatively, there could be a sample port on, or near, the equipment isolation valve that could allow a sample to be collected when the water is first being discharged into the processing tank or other POU. Another approach (if feasible) may be to simply disconnect the interconnecting piping and direct the water flow toward a sample container, instead of allowing it to flow into the manufacturing equipment.

While POU valves with a built in upstream sample port may be used when sampling for process control purposes, they are typically not used when sampling for quality control purposes. The only exceptions that may allow use of a built-in sampling port on the POU valve would be:

- The conduit is routinely sanitized with a validated procedure prior to water use for manufacturing with sanitization occurring by hot water, steam, or chemicals so that the conduit provides no added contamination to the loop water
- There is no feasible engineering solution that allows sampling exactly as used during manufacturing
- The relevant attributes at that particular POU were not microbial, i.e., only the homogeneously distributed chemical impurities, e.g., for a washer whose cycle ends with a hot (> 60°C air) drying step that would kill any microbial contaminants in the transferred water

The test data from quality control sampling should be used for comparison with the quality control requirements or specifications for the water.

Alert, Action, and Out Of Specification (OOS) Levels

Sampling could be performed from the same sample location for process control and quality control purposes. Different Alert and Action Levels could be established; however, process control levels may typically be established at tighter values than those for quality control.

For an excursion above a specification limit, an investigation should be performed to determine, correct, and prevent the cause of the excursion from occurring in the future. In this case, the particular investigation would be an OOS investigation and the impact of this water on the product should be assessed.

2.1.2.5 Sampling for Technical, Investigative, or Diagnostic Reasons

Sampling performed for technical, investigative, or diagnostic reasons may include:

- Gathering data to better understand (or pinpoint) the root cause of a process deviation or specification excursion
- To determine the extent of contamination within a system
- To spot check the long-term efficacy of a particular remedial action (e.g., from a CAPA response) by checking specific attribute levels at a specified location

Additional sampling points, installed for technical, investigative, or troubleshooting purposes may not be routinely sampled. For instance, if a Reverse Osmosis (RO) membrane was prematurely scaling with hardness, it would be appropriate to sample upstream and downstream of a water softener to determine if hardness reduction levels were being achieved throughout the softener use cycle or if the water hardness increased since the equipment was originally set up.

Data from technical, investigative, or diagnostic sampling can also be used to establish a baseline for non-routinely measured water attributes (such as the chemical attributes of the potable feed water during initial commissioning or validation) which may be valuable in future investigations. Samplings of this nature are typically done only occasionally and only when needed for long term profiling, or as part of an investigation.

2.2 Determining Sampling Locations

Locating sample points to ensure samples are taken from suitable process locations before and after unit operations, at points of use and elsewhere, should assure a successful water system monitoring program. Since many technologies and unit operations may be employed to produce pharmaceutical grades of water, sampling locations are best identified during the conceptual and detailed design phases. A Risk Analysis (RA) may be performed to help determine sample locations. The RA can provide a rationale for the sampling points in a water system and can help to define the intended purpose of each sampling location, based on established CQAs and Critical Process Parameters (CPPs).

These sample locations should provide samples that are representative of water quality at the sample location. This cannot be accomplished without serious consideration to the physical location of these valves and the methods that should be utilized to obtain the sample. Sample valve locations should be addressed not only on a P&ID but should also be addressed during the equipment and piping installation. Components, hardware, or other items that interfere with correct sampling techniques should be avoided through careful planning and appropriate field execution. Considerations should include the disposition of waste from flushing, location of sample ports relative to other equipment, local environmental issues, and any other appropriate concerns. Design in consultation with QA, QC, and Microbiology Subject Matter Experts (SMEs) is desirable.

For example, sample valves located in return loop piping that are inaccessible to samplers, sample valves blocked by other equipment or with otherwise limited access, and/or sample valves that cannot be utilized in a reasonable fashion, do not accomplish the goal of ensuring that the samples are representative. Improper location may put a sampler's safety at risk or may yield data with a high degree of variability, and may result in an increase in alert limit, action limit, and OOS findings.

Sampling locations should include all appropriate sections of the system including:

- Source water
- Pretreatment unit operations
- Primary and final treatment
- Storage
- Distribution systems (main loops and sub loops)
- POU and any special POU treatments

Sampling locations should be tabulated. Table 2.1 provides an example of such a table.

Table 2.1: Examples of some Sample Points in a Purified Water System

Drawing No.	Tag	Function/ Classification	Location (Room)	Frequency	Remarks
PW-1	PW-01	Carbon Bed Inlet	Mechanical	Monthly	Chlorine, TOC, bacteria for process control
PW-1	PW-02	Carbon Bed Outlet	Mechanical	Monthly	Chlorine, TOC, bacteria for process control
PW-2	PW-03	Deionizer Outlet	Mechanical	Quarterly	Sodium, silica for diagnostic purposes
PW-2	PW-04	Distribution Loop Supply	Mechanical	Daily/Weekly	TOC, conductivity, bacteria, for quality control purposes
PW-3	PW-05	POU Valve #1	Production Room #1	Weekly	TOC, conductivity, bacteria, for regulatory requirements and quality control

2.2.1 Source Water

Source water feeding any compendial pharmaceutical water system should meet local drinking water standards such as those specified by the WHO, the US Environmental Protection Agency (EPA), drinking water regulations of the EU or Japan, or the drinking water regulations from other competent authorities. Source water that does not meet potable or drinking water standards should be brought into compliance with recognized drinking water regulations prior to being used to feed a pharmaceutical water system.

Chlorination (or chloramination) of municipal water has become common in many areas of the world, for microbiological control. If residual chlorine levels are inadequate for microbial control, rechlorination may be required and should be defined in a SOP and should be monitored on a regular basis through an appropriately located sample port. If rechlorination is required, sampling immediately afterward is also indicated.

Complete chemical analysis of source water that confirms it meets the appropriate potable or drinking water requirements may be performed on a periodic basis to trend incoming contaminant levels and to make system adjustments if required. If a source water storage tank is employed, additional testing, after storage, is advisable before water enters the water purification system.

2.2.2 Pretreatment Unit Operations

Sampling locations should be included before and after each unit operation for diagnostic purposes so that monitoring can be performed as required. Sampling before and after individual unit operations helps in establishing a unit operation's performance.

The following unit operations are examples of monitoring locations that may be considered in a purification system for assessing the performance of the purification step:

- Before and after media filtration (e.g.: multi-media, cartridge, etc.)
- Before and after softeners
- Before and after Activated Carbon Filters³
- Before and after Ultraviolet units
- Before and after chlorination or dechlorination units
- Before and after Reverse Osmosis (RO), Continuous Electro Deionization (CEDI), or ion exchange units
- Before and after any other unit operations within the pretreatment system boundary

2.2.3 Primary and Final Treatment

Primary and final treatment for compendial or non-compendial water may include several different treatment technologies. See the *ISPE Baseline® Guide: Water and Steam Systems (Second Edition)* [7].

Examples of primary and final treatment unit operations equipment include:

- Reverse osmosis
- Continuous electro deionization
- Ion exchange deionization
- Microfiltration
- Ultrafiltration
- Nanofiltration
- Distillation
- Ultraviolet treatment
- Heat exchangers

³ Microbial monitoring may additionally be critical in this location because activated carbon beds tend to promote microbial growth.

Sampling locations should be provided before and after each treatment unit operation as appropriate. Attributes to be evaluated are based on equipment performance expectations and may include:

- Conductivity
- TOC
- Chlorine
- Ammonia
- Hardness
- Silica
- Silt Density Index (SDI)
- Microbial
- Endotoxin

Attributes may be selected for determining the performance of a unit operation and should have Alert and Action Levels that mirror the performance expectations of the respective unit operation.

Final treatment unit output water should be monitored using in-line, on-line or at-line analyzers where possible. Conductivity and TOC analyzers are usually used for these purposes. If on-line instruments are available, then off-line sampling may not be required for process control purposes. Attributes such as pH, chlorine, and ammonia may also be monitored if they are defined as CPPs.

Where multiple final treatment units are present in a facility, there should be a sample point before and after each. Each point should be monitored routinely for process control purposes. One sample point located between unit operations can serve to sample the outlet of one process and the inlet of another.

2.2.4 Storage Tanks

Sampling locations directly on a storage tank may provide valuable information if any microbial buildup (biofilm) is occurring in the tank and also allows testing of the stored water quality since water velocity through storage tanks provides minimal turbulence when compared to distribution lines. A sample valve installed for direct sampling from the storage tank may be required for validation or for diagnostic purposes and may or may not be used for routine sampling.

Sampling valves located at storage tanks should be easily accessible for sampling and should minimize the risk of contamination of the sample and also the storage tank itself during sampling.

Tank water quality can also be assessed indirectly through monitoring of the primary generation supply (incoming water to storage), the loop return (water returning to storage), and the tank outlet which feeds the pumps and subsequently the use points. These samples indicate the water quality prior to entry to the storage tank, after returning from the loop, and at the storage tank outlet, which provides an indirect indication of the impact the storage tank is having on water quality.

2.2.5 Distribution Systems (main loops and sub loops)

Quality control sampling locations in the main distribution system should include all POU's, with sampling occurring in a manner identical to how the water is used by manufacturing as discussed above. Process control sampling locations should be located before the first and after the last POU and at other specified locations. Sampling the loop return after the last POU ensures process control as this location may be the worst case location for water quality in the entire distribution system. Water systems with multiple return loops should have sampling locations in each of the return loops. For one way (non-recirculating) branch systems, all POU's should be sampled.

When temperature changes are required, the distribution system should be designed such that the pharmaceutical water is maintained at a higher pressure than heating/cooling media such as in a heat exchanger to prevent leakage from the non-sanitary utility to the sanitary side of the heat exchanger. If the pressure of the pharmaceutical water is lower than the heating/cooling media, then a double tube sheet heat exchanger design should be employed or the conductivity/TOC of the pharmaceutical water should be monitored through in-line instrumentation or regular testing of the water at a use point downstream of the heat exchanger.

Sampling location selection should also consider those locations in the distribution loop where possible contamination could occur, e.g., locations downstream of a heat exchanger, flow monitor, or other equipment.

Each sub loop returning to the main loop return should have a sampling point before the sub loop connects to the main loop return.

In the distribution loop of a pharmaceutical water system, all use point valves and sample valves should be of a sanitary design. Sample points in a laboratory system may not be sanitary and may contain dead legs such as may be present in a gooseneck faucet. In addition, sample points located between components in a water purification system and used for process control purposes may not be sanitary and may consist of ball valves or other valves that should not be used in a pharmaceutical water distribution system.

2.2.6 Points of Use

A Point Of Use (POU) is defined as the location where the water delivered from the water distribution system is actually used. POU's may be located on the main loop or in sub loops.

When sampling for quality control sampling purposes, the POU is typically not the valve on the distribution system itself from which the water is taken. Instead, it is the end of the delivery system that transfers the water from the distribution system to the process (e.g., sinks, autoclaves, washers, process tanks). Sampling at POU's should include all components and surfaces along this water delivery pathway (e.g., heat exchangers, hoses, fittings) that the water needs to travel through to reach the process.

When the outlet of a POU cannot be sampled, the next most representative sampling location should be identified. Rationale for the selection should be provided in the risk assessment. Validation and/or routine monitoring data should conclude that the sample location is representative of the POU.

Direct sampling of water from a drop, e.g., to a sink in a wash room where the water is normally used does not require any additional sampling locations as the POU serves both purposes. Water collected for sampling should be collected in a way that represents how water is normally taken from the system during routine use.

Every POU in a water distribution system that is not active should be locked out or tagged out of service and should be appropriately maintained to prevent contamination of the POU or the distribution system.

2.3 Developing Sampling Plans

The frequencies and durations of sampling plans have historically coincided with the phases of the validation program for the water system. Using this rationale, the final phase of validation forms the basis for ongoing sampling frequencies with the goal of ensuring that the system is maintained in a validated state. However, the use of risk analysis tools coupled with periodic data review may be used to alter the frequency of sampling when the data provides overwhelming support for a change (increase or decrease) in sampling frequency. Regular data review should be documented as part of the planning process.

A sampling plan should define and document:

- Potential sampling points and the purpose for each
- Sample locations intended for continuous, regular, routine, periodic, or as needed monitoring
- Attributes to be tested at each sampling location
- The frequency at which samples are required for any given attribute
- The purpose and use of the resulting data for those attributes
- When sample valves and use point valves may be used as the same valve

Sampling plans are required for both new and renovated systems and may involve sampling locations throughout the water purification and distribution systems, including source water. During renovations or modifications, evaluate the changes that will be made and use risk analysis tools to help design a sampling plan appropriate for the significance of the modification and to assess the usability of the water during this time.

In specific circumstances, adequate scientific and statistical rationale may be required to not sample at an installed sampling point.

Sample locations installed for technical, investigative, or diagnostic purposes may not be included in a routine sampling plan and may not be sampled on a regular basis. The purpose and use of these sample locations should be defined, and they should:

- Be used on an as need basis
- Be suitably maintained
- Not pose a contamination risk to the system

Designating sampling locations For Information Only (FIO) or for future use should be avoided.

2.3.1 Background Philosophy

Sample plan development should be based on the expected sampling required during the life cycle of the system.

A typical life cycle scenario for water sampling activities may include activities during the following steps:

- Conceptual and detailed design
- Construction and installation
- Commissioning

- Performance qualification (including worst case test and special scenario testing)
- Ongoing testing during production
- System changes and modifications (major and minor)
- Periodic System Evaluation (PSE)

Sampling guidance is provided in Tables 2.2, 2.3, and 2.4 regarding specific sampling locations, testing frequencies, and the type of monitoring or testing for various activities including commissioning and qualification/verification. This information may apply to new and renovated systems as well as some unique scenarios.

Automated electronic monitoring of conductivity and TOC can provide a comprehensive database from which chemical water quality trends may be observed over time. When analyzed, this information may allow for minimization or elimination of manual chemical testing of the water during routine operations. However, during the Performance Qualification, confirmation that the on-line or in-line readings are representative of water quality used should be verified if this data is going to be used for product release purposes. Where localized, outlet specific contamination could occur (e.g., POU heat exchangers), a downstream instrument, or grab samples would be required for release purposes.

For investigative purposes, *“TOC can be used as a process control attribute to monitor the performance of unit operations comprising the purification and distribution system”*. [8]

Water may be delivered at several different temperatures for use at a single POU. The water sample collected from this point should be collected at the worst case temperature for microbiological control. For example, if water is delivered at both 65°C and 20°C (149°F and 68°F) from the same POU, the sample should be collected at 20°C (68°F).

2.3.2 Regulatory Requirements Related to Monitoring Frequency and Duration

No well-defined regulatory requirements exist regarding routine sampling frequency and duration. Various pharmacopoeias provide specifications for microbiological and chemical contaminants for the various grades of water, but do not define the frequency or duration of sampling. General expectations that can be found in various compendia and consensus standards are provided as follows:

USP General Information Chapter <1231> Water for Pharmaceutical Purposes, [9] states:

Water systems should be monitored at a frequency that is sufficient to ensure that the system is in control, and continues to produce water of acceptable quality”; and “The sampling plan should take into consideration the desired attributes of the water being sampled”.

EP Guidelines to GMP Vol. 4 Annex 1 “Manufacture of Sterile Medicinal Products” [10] states:

“Water sources, water treatment equipment and treated water should be monitored regularly for chemical and biological contamination and, as appropriate for endotoxins”.

The JP16 General Information, G8 Water, Quality Control of Water for Pharmaceutical Use, Section 4.2 Sampling [11] states:

“Sampling frequency should be established based on the data from validation studies on the system.”

ICH Q7 Section 4.20 [12] states:

“All utilities that could impact on quality (e.g., steam, gases compressed airetc.) should be qualified and appropriately monitored and action should be taken when limits are exceeded”.

The 1993 US FDA “Guide to the Inspection of High Purity Water Systems” states [1]:

“The results of the Commissioning & Qualification are designed to demonstrate that all of the process steps and components within a Purified Water or Water For Injection system are capable of consistently providing water meeting the necessary water quality requirements”.

The FDA guide also provides the most specific guidelines for sampling frequency during system validation, but does not stipulate frequency beyond validation and recognizes that more than one approach may be acceptable.

To summarize, routine sampling should always be adequate for the intended purpose. It is necessary to look into the design and operational conditions for each specific water system with frequency and duration decisions based on RA including rationales for the decisions made.

2.3.3 Commissioning and Pre-validation

Water testing of the pretreatment, generation and distribution systems for PW and WFI systems during commissioning is an exercise in Good Engineering Practice. This activity may contribute to developing operational and maintenance practices and procedures that will be confirmed at a later time during qualification [13] and may provide baseline information for the system that may be useful in the future.

The testing activities may include chemical testing, or monitoring as appropriate, for specific unit operations and microbial testing to identify the indigenous microbial bioburden of the system. The duration of commissioning activities may vary depending upon the complexity and size of the system (e.g., 1 to 5 days).

Once the entire system is operating, the effluent of each unit operation should be monitored or tested at least once during the commissioning phase in order to provide baseline values for the system.

It may be necessary to perform extended pre-validation microbiological sampling activities in order to achieve process knowledge and assure system robustness.

2.3.4 Source Water

USP General Information Chapter <1231> Water for Pharmaceutical Purposes [9] states:

“To ensure adherence to certain minimal chemical and microbiological quality standards, water used in the production of drug substances or as source or feed water for the preparation of the various types of purified waters must meet the requirements of the National Primary Drinking Water Regulations (NPDWR) (40 CFR 141) issued by the U.S. Environmental Protection Agency (EPA) or the drinking water regulations of the European Union or Japan, or the WHO drinking water guidelines”.

Various nomenclature may be in use across the globe for drinking water including: potable water, tap water, city water, and feed water, however, the quality intent remains consistently the same.

Note: there may be other additional regional/local area requirements or expectations.

WHO Technical Report Series No. 929, Annex 3 [14] recommends daily sampling of incoming potable water during the early validation phase of the pharmaceutical water system to verify its quality, but this may not be required in all areas of the world.

If there is little or no knowledge of the feed water quality at the system inlet, it is recommended to take daily samples for analysis including organism(s) of concern if such local requirement exists. If the potable water quality is already well known and the historical data shows good, stable water quality, a rationale can be made to perform less source water testing during the Performance Qualification (PQ) period. Typically, the potable/drinking water supplier is responsible for the potable water quality up to the property boundary, thereafter the responsibility is transferred to the

property owner/site operator. Keeping in mind that pharmaceutical product manufacturers are ultimately responsible for end product quality, the burden of proof falls on the pharmaceutical manufacturer to assure, through suitable testing, and that potable water quality is maintained, as required, up to the inlet of the water system.

An impact assessment should be performed on potable water depending on the attributes, the treatment technology employed, and the end use of the water.

Depending on the end product or the process purifications steps etc. it may be possible to classify the potable water with different criticality levels. A RA with rationales should be made in order to define the criticality of the potable water. The outcome of the assessment will tell if Good Engineering Practices or validation/verification of the potable water supply is necessary.

2.3.4.1 Pretreatment

Pretreatment is a term that represents designated treatment steps, and typically prior to primary/final treatment. This may also be designated by the unit operations involved such as filtering, softening, or RO. It may be convenient to refer to pretreated water as feed water for the production of PW, WFI and/or pure stream (PS). When used as feed water for WFI or PS, pretreated water does not necessarily need to comply with PW requirements to ensure WFI/PS quality water is obtained. It should be noted that the Chinese Pharmacopoeia (ChP) [15] requires that supply water to a WFI still must comply with PW specification. The USP, EP, or JP does not require PW quality as feed for production of WFI.

In order to ensure that the pretreatment fulfills its purpose, sampling is carried out specifically for each purification step as mentioned in the *ISPE Good Practice Guide: Approaches to Commissioning and Qualification of Pharmaceutical Water and Steam Systems (Second Edition)* [13] and includes:

- For a sand, mixed media, or similar filter, the SDI may be measured before and after the equipment. The worst case sampling time would be just before the automatic back flush.
- For a water softener, hardness may be measured before and after the softener. The worst case sampling time may be immediately before softener regeneration.
- For a carbon filter, the chlorine concentration may be measured before and after the carbon filter. A worst case sampling time may be immediately before the back flush.
- For a RO system, conductivity may be measured before and after the RO unit
- For CEDI, the conductivity may be measured before and after the CEDI

For all purification steps microbiological testing may be required, including before and after the RO if applicable. Acceptable microbiological levels should be defined for each purification step when applicable. There should at least be an Action Level with consideration for adding an Alert level if appropriate.

If, during RA, the pretreatment is determined to be a no impact system, samples should be taken for record purposes during Performance Qualification (PQ) of PW/WFI. There is no regulatory requirement, but if the pretreatment is determined to be indirect impact, a rationale should be developed for the sampling frequency during the PQ of the pretreatment.

2.3.4.2 Purified Water

Depending on the number of POU's and sample points in the distribution system consideration could be given to rotational sampling for chemical tests since chemical contaminants are uniformly distributed in the water. It is generally recommended that several samples be taken from each use point during the PQ period. It should be noted that the worst case testing or special testing may influence the results and should be taken into account. The number of worst case tests chosen may influence the length of the PQ.

Define the microbiological levels as required by intended use of the water. There should be an Alert Level and an Action Level. Testing frequency should be determined based on a suitable RA.

2.3.4.3 Water For Injection

POU sampling plans should rotate through all use points on the system, with the expectation that samples are collected on a daily basis from various use points, and that all use points are sampled on a routine basis based on risk analysis. System representative locations (e.g., supply and/or return) may be sampled on a daily basis for the process control purposes and to aid in the investigation of OOS results from individual use points.

During the PSE of a WFI (or PW) system, sampling frequency may be evaluated. Increases or decreases in sampling frequency should be based on historical data and should only occur when data indicates that more or less frequent sampling is justified based on performance of the use point or system. Sample frequency should not be arbitrarily adjusted without adequate scientific and statistical justification. A decrease in sampling frequency may result in increased regulatory scrutiny. Decreased sampling frequency also puts more product at risk during investigations because of longer periods between acceptable test results surrounding a deviant test result. In short, careful consideration should be given before decreasing sampling frequency relative to the increased number of product batches that will be put at risk.

2.3.5 Sampling for Performance Qualification/Verification

2.3.5.1 Purpose

The purpose of PQ/verification is to document that the stated water quality is delivered from the water system during:

1. Typical (nominal) use conditions
2. Worst case use conditions (system limits)
3. Special scenarios

and that the water complies with the requirements for the grade of pharmaceutical water type specified.

The period for the PQ depends on whether it applies to a completely new system or to modifications made to an existing system.

2.3.5.2 Typical Use Conditions (Nominal)

All PQs include a period of normal operation or simulated normal operation to demonstrate that the water quality during normal operation complies with the requirements for the actual specified pharmaceutical water quality. Normal operational usage ranges are defined with rationales.

2.3.5.3 Worst Case Use Conditions

A worst case scenario tests the limits of the system and is defined as the most extreme situations during the operation of the water system.

Below are a few examples of worst case conditions:

- Conditions of no water consumption (e.g., during a weekend or shut down) can result in a rise in the level of bioburden and conductivity
- Maximum use of the water confirms the system or unit operation is capable of delivering suitable water quality during a period of maximum delivery

- If routine sanitization occurs, just before start of and after the sanitization
- After a maintenance procedure or a periodic event such as derouging and/or passivation

2.3.5.4 *Special Scenarios*

Special scenarios are situations which may occur during normal use either as unplanned or as planned scenarios. Often these special scenarios occur at inconvenient times, and it would be advantageous to validate these scenarios to avoid delays when they occur.

Validation of special scenarios can be part of the ordinary PQ of the pharmaceutical water system, or it can be performed as a specific PQ for only this purpose.

The validation of a special scenario may need to be performed in a worst case scenario and be documented by water quality sampling data. The outcome and conclusion of the validation, based on the data, can decrease time spent on the procedure during daily operation, when going from the special scenario to normal condition, due to less sampling, sanitization, etc.

Examples of special scenarios are provided below:

- Power failure: to document that the pharmaceutical water quality is unchanged after restarting after a defined period of time without any sanitization. A prerequisite for this test is no breach of integrity of the water system.
- Emergency or unplanned maintenance procedures: including unusual or unexpected component failure, system damage from internal or external action, or other situations that may require action but cannot be anticipated. Validation of all emergency or unplanned maintenance procedures is not practical.

Acceptance criteria should be set up for the special scenario properly because if it is not set properly, the PQ may fail. For example, if after a power failure the water retains its quality characteristics for three hours, then a power failure of up to three hours can be followed by normal operation without any sanitization, provided the system integrity is not otherwise compromised and will only require documentation of the actual duration of the power failure. A special scenario test may be performed for a longer period than the period used as the limit, if there is a need for incorporation of a safety factor. The three-hour power failure scenario mentioned above is only **an example** and that shorter or longer times may actually be validated.

2.3.5.5 *Risk-Based Approach*

A risk-based approach to C&Q/verification may be utilized to develop the monitoring and testing strategy. For example, risk analyses or impact assessments may be utilized to determine what equipment or functions of the water system are considered critical [13]. There may be unit operations or process steps within the generation or distribution system that require testing during initial commissioning as well as during ongoing routine operation (e.g., UV treatment, pumps, heat exchangers, etc.) that may not be considered critical.

If determined to be non-critical, such equipment operation (e.g., multimedia filters, softeners) may be tested only during commissioning as part of the C&Q/Verification process [13]. Testing relating to the continued operation of a unit process may become part of a routine monitoring program based upon the impact to the system and the finished quality of the water as detailed in SOPs and subject to Good Engineering Practices (GEP). Frequency of routine testing could be adjusted based on the consistency of equipment performance. These tests assure proper maintenance and operation of the water system (e.g., regeneration of resin beds, sanitization of equipment, etc.) [13].

A CQA is a test defined as critical, based on the need to meet a specific compendia specification or other defined non-compendial requirements [13]. For example, conductivity may be a CQA of water when measured at the outlet of a PW generation system. Sampling the conductivity at this point would initially occur during C&Q/verification activities [13].

A risk-based approach may also be utilized for determining the sampling approach to qualify changes made to an existing validated water system.

2.3.5.6 Performance Qualification Sampling

The PQ sampling protocol should describe the purpose, scope, and strategy (including justification). The sampling plan and the expected data from in-line/on-line measuring equipment (e.g., for temperature, pressure, conductivity, TOC) should be described in the protocol. The prerequisites and the acceptance criteria for the performance testing should also be stated in the protocol. The protocol should also consider adjusting sampling as appropriate based on production activities (e.g., if there is no production during weekends or if production varies significantly).

All stakeholders involved in the PQ, (production, engineering, quality control and quality assurance) should have an opportunity to review and comment on the protocol.

Communication and information sharing between the different participants before, during, and after the PQ are essential for efficient and successful qualification. Feedback on changes (e.g., missing samples) during the qualification should immediately be communicated to the relevant participants and documented in a deviation.

PQ sampling should be performed for a newly installed water system or for significant changes made to an existing qualified system. When minor changes are made to a qualified system, reduced sampling requirements may be considered. See the *ISPE Good Practice Guide: Approaches to Commissioning and Qualification of Pharmaceutical Water and Steam Systems (Second Edition)* [13] and the *ISPE Baseline® Guide: Water and Steam Systems (Second Edition)* [7] for additional information.

The following provides basic guidance regarding sampling plans during formal validation. Sampling during commissioning provides information that may be used to develop SOPs (e.g., for routine system operation, sampling, cleaning, sanitization, and maintenance).

Initial Sampling

Initial sampling is the most intensive and typically lasts from two to four weeks. Commonly, this period can be satisfied by monitoring and testing all sample and use points in the distribution system and selected other points daily for between 10 to 20 consecutive working days depending upon the design of the system (e.g., overall size, complexity, or number of use points). If the weekends involve no water consumption, the first day of the week may represent a worst case scenario for sampling.

During initial sampling, if consistency in operation is apparent, representative microorganisms that are visually distinct (i.e., physical colony characteristics) and detected during microbiological monitoring may be identified. Since all parts of a water systems are not always completely sterile by design, inherent populations of microorganisms may be found and these populations can vary from system to system. Typically, there are only a few distinct types of microorganisms that make up the resident population.

Initial sampling activities are performed to demonstrate that the production and delivery of water consistently meets the specified compendial requirements. The initial sampling phase of PQ typically starts after Installation Qualification (IQ) and Operational Qualification (OQ) report approval. Initial sampling should demonstrate consistent quality before start of the next phase.

Intermediary Sampling

Intermediary sampling is less intensive and may involve reduced sampling frequency. This phase typically lasts for 10 to 20 working days. The purpose of intermediary sampling is to further demonstrate consistent production and delivery of water (e.g., repeatability) of the required quality within the established ranges when using SOPs.

Intermediary sampling may provide additional worst case data since use points are not as frequently active.

Extended Sampling

The extended sampling portion of the water system qualification activities continue for not less than the remaining balance of one year's time (one year minus the time used for initial and intermediary sampling) [13]. Collectively, the validation process includes an extended sampling study of the system and allows for the system to be challenged by evaluating its effectiveness of delivering water of acceptable quality despite seasonal variations in the potable water feed to the system, the slow development of the system's natural flora, and any other variations that may occur [1]. Typically, the extended sampling plan is reduced in frequency [13], from initial and intermediary sampling activities. Extended sampling monitoring typically forms the basis for the routine monitoring and testing program established once the validation has been completed. During this phase, there may be subtle shifts in the types of microorganisms inherently present within the system due to seasonal changes. Only those isolates from the microbiological testing samples that are visually distinct (i.e., physical colony characteristics) should be identified if not previously characterized.

Table 2.2: Examples of Suggested Source Water and Equipment Testing and Frequencies (Note A)

Equipment Sample Location	Suggested Commissioning and Pre-validation Tests and Frequencies	Suggested Initial Phase Tests and Frequencies	Suggested Intermediary Phase Tests and Frequencies	Suggested Extended Tests and Frequencies (Note B)
Potable Source Water Supply at Inlet to Pre-Treatment	Qualification of a new water source in the facility may involve initial and periodic testing of the source water to verify and ensure continuing compliance with potable water requirements. If the water is from a reliable source, at a minimum, obtain and review testing certificates from the supplier to establish full compliance with appropriate potable water regulations. Based on a risk assessment, it may be necessary to verify, via testing, the supplied water entering the facility complies with all potable water requirements. Local/country requirements should also be followed for water used in the manufacture of products sold in those areas.			
Media Filter	Confirm SDI re-duction	Quarterly or on-line for process control purposes, or at a frequency commensurate with the criticality of the process to the production of the desired grade of water.		
Organic Scavenger Bed	Confirm TOC re-duction	Quarterly or on-line for process control purposes, or at a frequency commensurate with the criticality of the process to the production of the desired grade of water.		
Water Softener	Confirm hardness reduction	Quarterly or on-line for process control purposes, or at a frequency commensurate with the criticality of the process to the production of the desired grade of water.		
Carbon Filter for Dechlorination	<ul style="list-style-type: none"> Confirm free and total chlorine reduction Monitor microbiological levels 	<ul style="list-style-type: none"> Quarterly or on-line for process control purposes, or at a frequency commensurate with the criticality of the process to the production of the desired grade of water. Monitoring microbial levels may be important as needed for process control purposes. 		
Chemical Feed for Declorination	<ul style="list-style-type: none"> Confirm free and total chlorine reduction Confirm sufficient dosage without overdosing (Note H) 	Quarterly or on-line for process control purposes, or at a frequency commensu-rate with the criticality of the process to the production of the desired grade of water.		
Carbon Filter for Organics Reduction	<ul style="list-style-type: none"> Confirm TOC reduction Monitor microbiological levels 	<ul style="list-style-type: none"> Quarterly or on-line for process control purposes, or at a frequency commensurate with the criticality of the process to the production of the desired grade of water. Monitoring microbial levels may also be important. 		
Ultrafiltration for SDI or TOC Reduction (Note I)	Confirm SDI and/or TOC reduction	Quarterly or on-line for process control purposes, or at a frequency commensu-rate with the criticality of the process to the production of the desired grade of water.		
Deionization as a Pretreatment Process	<ul style="list-style-type: none"> Confirm conductivity reduction Monitor microbiological levels 	<ul style="list-style-type: none"> Quarterly or on-line for process control purposes, or at a frequency commensurate with the criticality of the process to the production of the desired grade of water (Note F). Monitoring microbial levels may also be important. 		

Table 2.2: Examples of Suggested Source Water and Equipment Testing and Frequencies (Note A) (continued)

Equipment Sample Location	Suggested Commissioning and Pre-validation Tests and Frequencies	Suggested Initial Phase Tests and Frequencies	Suggested Intermediary Phase Tests and Frequencies	Suggested Extended Tests and Frequencies (Note B)
Reverse Osmosis	<ul style="list-style-type: none"> Confirm conductivity and TOC reduction Confirm pH levels if pH is adjusted Monitor microbiological levels 	<ul style="list-style-type: none"> Quarterly or on-line for process control purposes, or at a frequency commensurate with the criticality of the process to the production of the desired grade of water (Note F). Monitoring microbial levels may also be important. 		
CEDI or other Deionization Process as a Final Treatment	<ul style="list-style-type: none"> Confirm conductivity reduction Confirm chemical reduction (Note D) Monitor TOC and microbiological levels 	<ul style="list-style-type: none"> Conductivity and TOC daily or on-line (Note C) Chemical testing daily (Note D) Microbiological testing daily (Note E, F) 	<ul style="list-style-type: none"> Conductivity and TOC at a frequency between daily and weekly or on-line (Note C, J) Chemical testing between daily and weekly (Note D, J) Microbiological testing between daily and weekly (Note E, F, J) 	<ul style="list-style-type: none"> Conductivity and TOC at regular intervals or on-line (Note C), typically at least once per week Chemical (Note D) and microbiological (Note E, F) testing at regular intervals, typically at least once per week
Ozone as part of the Purification System (Note F, G)	Monitor ozone and microbiological levels	<ul style="list-style-type: none"> Ozone levels on-line daily Microbiological testing daily (Note E, F) 	<ul style="list-style-type: none"> Ozone levels on-line Microbiological testing between daily and weekly (Note E, F, J) 	<ul style="list-style-type: none"> Ozone levels on-line Microbiological testing at regular intervals, typically at least once per week (Note E, F, J)
Ultraviolet Treatment for Microbiological Control or TOC Reduction (Note F, K)	Confirm microbio-logical reduction	Microbiological testing daily (Note E)	Microbiological testing between daily and weekly (Note E, F, J)	Microbiological testing at regular intervals (Note E, F), typically at least once per week
Ultraviolet Treatment for Ozone Destruction (Note F)	Monitor ozone levels	Quarterly or on-line for process control purposes, or at a frequency commensurate with the criticality of the process to the production of the desired grade of water.		
Ultrafiltration for Endotoxin Control (Note F)	Confirm absence of detectable endotoxin (Note L)	Endotoxin testing daily	Endotoxin testing between daily and weekly (Note J)	Endotoxin testing at regular intervals, typically at least once per week
Microbially Retentive Filtration (Note F)	Confirm acceptable microbiological levels	Microbiological testing daily (Note E)	Microbiological testing between daily and weekly (Note E, F, J)	Microbiological testing at regular intervals (Note E, F), typically at least once per week
Distillation	Confirm conductivity, TOC, endotoxin, microbiological, and chemical (Note D) content	<ul style="list-style-type: none"> Conductivity and TOC daily or on-line (Note C) Chemical testing daily (Note D) Microbiological testing daily (Note E, F) 	<ul style="list-style-type: none"> Conductivity and TOC at a frequency between daily and weekly or on-line (Note C, J) Chemical testing between daily and weekly (Note D, J) Microbiological testing between daily and weekly (Note E, F, J) 	<ul style="list-style-type: none"> Conductivity and TOC at regular intervals or on-line (Note C), typically at least once per week Chemical (Note D) and microbiological (Note E, F) testing at regular intervals, typically at least once per week

Table 2.2: Examples of Suggested Source Water and Equipment Testing and Frequencies (Note A) (continued)

Equipment Sample Location	Suggested Commissioning and Pre-validation Tests and Frequencies	Suggested Initial Phase Tests and Frequencies	Suggested Intermediary Phase Tests and Frequencies	Suggested Extended Tests and Frequencies (Note B)
Finished Water leaving Purification System	Confirm conductivity, chemical (Note D), TOC, microbiological, and endotoxin levels, if applicable	<ul style="list-style-type: none"> Conductivity and TOC daily or on-line (Note C) Chemical testing daily (Note D) Microbiological testing daily (Note E) Endotoxin testing, if applicable, daily 	<ul style="list-style-type: none"> Conductivity and TOC at a frequency between daily and weekly or on-line (Note C) Chemical testing at a frequency between daily and weekly (Note D) Microbiological testing at a frequency between daily and weekly (Note E) Endotoxin testing, if applicable at a frequency between daily and weekly 	<ul style="list-style-type: none"> Conductivity and TOC at regular intervals or on-line (Note C), typically at least once per week Chemical (Note D), microbiological (Note E) and endotoxin (if applicable) testing at regular intervals, typically at least once per week

Note A: This table lists several of the most commonly used treatment processes and may contain treatment steps that are not present in all systems. There may also be treatment processes in use that are not listed in this table. In all cases, the extent and frequency of sampling should be commensurate with the criticality of the process to the production of the desired grade of water.

Note B: The frequency and extent of sampling during the extended phase of the performance qualification typically serves as the initial frequency and extent for future validation maintenance testing, but is subject to adjustment based on a review of accumulated data and the use of risk analysis tools.

Note C: Verification of the equivalency of on-line readings to those obtained from sampling should be established in order to utilize on-line readings as suitable for quality control release.

Note D: Chemical testing may or may not be required as determined by applicable pharmacopoeias.

Note E: Microbiological identification testing may be performed to provide a profile of the resident micro flora within the water system.

Note F: Depending on the criticality of the process to the desired impurity/contaminant content of the water, less frequent sampling and testing may be performed for processes determined to be less critical.

Note G: Refer to the *ISPE Good Practice Guide: Ozone Sanitization of Pharmaceutical Water Systems* [16] for a more complete review of ozone and its use in the pharmaceutical industry.

Note H: A slight excess is desirable, but overdosing may create undesirable and unintended side effects.

Note I: In the event that ultrafiltration is used for microbial reduction, testing should reflect the impurity/contaminant reflects process operation.

Note J: Testing frequency dependent on criticality.

Note K: When an ultraviolet treatment unit is used for TOC reduction, organic molecules are oxidized and converted into molecules that actually increase the conductivity of the water. Typically, the increase in conductivity is not monitored because there is an ion exchange process immediately downstream of the ultraviolet treatment unit that removes the oxidized organic material, reducing both the conductivity and the TOC.

Note L: The limit of detection shall be commensurate with the level of endotoxin appropriate for the process.

Table 2.3: Examples of Purified Water Distribution System Water Testing and Frequencies (Note A)

Purified Water Distribution System (Sample Location)	Commissioning Tests and Frequencies	Initial Phase Tests and Frequencies	Intermediary Phase Tests and Frequencies	Extended Phase Tests and Frequencies (Note B)
Downstream of Distribution Pump discharge prior to beginning in loop unit operations	Confirm conductivity, chemical (Note E), TOC and micro-biological levels	<ul style="list-style-type: none"> Conductivity and TOC daily or on-line (Note D) Chemical testing daily (Note E) Microbiological testing daily (Note F) 	<ul style="list-style-type: none"> Conductivity and TOC at a frequency between daily and weekly or on-line (Note D) Chemical testing at a frequency between daily and weekly (Note E) Microbiological testing at a frequency between daily and weekly (Note F) 	<ul style="list-style-type: none"> Conductivity and TOC at regular intervals or on-line (Note D), typically at least once per week Chemical (Note E) and microbiological (Note F) testing at regular intervals, typically at least once per week
Sample Port following the beginning in loop operations or the first use point	Confirm conductivity, chemical (Note E), TOC and microbiological levels	<ul style="list-style-type: none"> Conductivity and TOC daily or on-line (Note D) Chemical testing daily (Note E) Microbiological testing daily (Note F) 	<ul style="list-style-type: none"> Conductivity and TOC at a frequency between daily and weekly or on-line (Note D) Chemical testing at a frequency between daily and weekly (Note E) Microbiological testing at a frequency between daily and weekly (Notes F) 	<ul style="list-style-type: none"> Conductivity and TOC at regular intervals or on-line (Note D), typically at least once per week Chemical (Note E) and microbiological (Note F) testing at regular intervals, typically at least once per week
Critical Use Point (Note G)	Confirm conductivity, chemical (Note E), TOC and microbiological levels	<ul style="list-style-type: none"> Conductivity and TOC daily or on-line (Note D) Chemical testing daily (Note E) Microbiological testing daily (Note F) 	<ul style="list-style-type: none"> Conductivity and TOC at a frequency between daily and weekly or on-line (Note D) Chemical testing at a frequency between daily and weekly (Note E) Microbiological testing at a frequency between daily and weekly (Note F) 	<ul style="list-style-type: none"> Conductivity and TOC at regular intervals or on-line (Note D), typically at least once per week Chemical (Note E) and microbiological (Note F) testing at regular intervals, typically at least once per week
Non-critical Use Point (Note H)	Confirm conductivity, chemical (Note E), TOC and micro-biological levels	<ul style="list-style-type: none"> Conductivity and TOC daily or on-line (Note D) Chemical testing daily (Note E) Microbiological testing daily (Note F) 	<ul style="list-style-type: none"> Conductivity and TOC at a frequency between daily and monthly or on-line (Note D) Chemical testing at a frequency between daily and monthly (Note E) Microbiological testing at a frequency between daily and monthly (Note F) 	<ul style="list-style-type: none"> Conductivity and TOC at regular intervals or on-line (Note D), typically at least once per month Chemical (Note E) and microbiological (Note F) testing at regular intervals, typically at least once per month

Table 2.3: Examples of Purified Water Distribution System Water Testing and Frequencies (Note A) (continued)

Purified Water Distribution System (Sample Location)	Commissioning Tests and Frequencies	Initial Phase Tests and Frequencies	Intermediary Phase Tests and Frequencies	Extended Phase Tests and Frequencies (Note B)
Last POU or end of loop sample port (Note I)	<p>Confirm conductivity, chemical (Note E), TOC, and microbiological levels</p> <p>Confirm any other physical attributes such as flow rate, temperature, pressure, etc. at minimum and maximum water use scenarios as defined in a User Requirement Specification</p>	<ul style="list-style-type: none"> Conductivity and TOC daily or on-line (Note D) Chemical testing daily (Note E) Microbiological testing daily (Note F) 	<ul style="list-style-type: none"> Conductivity and TOC at a frequency between daily and weekly or on-line (Note D) Chemical testing at a frequency between daily and weekly (Note E) Microbiological testing at a frequency between daily and weekly (Note F) 	<ul style="list-style-type: none"> Conductivity and TOC at regular intervals or online (Note D), typically at least once per week Chemical (Note E) and microbiological (Note F) and other physical attribute testing at regular intervals, typically at least once per week

Note A: For any equipment that may be present as part of the PW distribution system, refer to Table 2.2.

Note B: The frequency and extent of sampling during the extended phase of the performance qualification typically serves as the initial frequency and extent for future validation maintenance testing, but is subject to adjustment based on a review of accumulated data and the use of risk analysis tools.

Note C: There are many variations on distribution system designs. This portion of the table is intended to capture considerations in “chase the tail” system configurations having no storage tank. In these instances, the incoming water to this system should be verified as suitable.

Note D: Verification of the equivalency of on-line readings to those obtained from sampling should be established in order to utilize on-line readings as suitable for quality control release.

Note E: Chemical testing may or may not be required as determined by applicable pharmacopoeias.

Note F: Microbiological identification testing is performed to provide a profile of the resident micro flora within the water system. Only those isolated from the microbiological samples taken at POU that are visually distinct (i.e., physical colony characteristics) should be identified to minimize redundancy. Microbial identification is not required where microorganisms with identical colony characteristics have been previously identified

Note G: A critical use point is defined as a point providing water that is either an ingredient or has direct product contact or one that is used for final rinse

Note H: A non-critical use point could be a point providing water that does not directly contact the product or process, such as pre-rinse or non-product contact use, or a use point that has been taken out of service and is no longer used for manufacturing but has not been removed from the system.

Note I: There may be additional equipment such as heat exchangers, ultraviolet units, etc., between the last POU and the storage tank. In these cases, it may also be appropriate to monitor each of these unit operations before the water is returned to the storage tank.