INTRODUCTION

There are various types of water used in the Pharmaceutical Industry. In their multiple uses, such as in actual product formulation, in processing operations, and as a final rinse of product contact surfaces, they can truly be considered product ingredients. Purified water can be produced many different ways and with a range of designs and equipment. The use of pharmaceutical grade water is crucial in the production of pharmaceutical drug products. Therefore, the validation and the routine monitoring of these systems are critical in maintaining the quality of the final product. This section of the article on critical utility systems will discuss the basic steps in validating water systems and, once validated, in establishing a routine monitoring program to maintain them.

Water is classified into several groups depending upon its source, quality, treatment, or use. It is also necessary to define each classification by its minimum quality requirements, especially with regard to expected chemical and microbiological purity.

Water Usage in Pharmaceutical Production

Water Requirements

- Potable – Environmental Protection Agency (EPA)
- United States Pharmacopoeia (USP) Purified Water (PW)
- USP Water-For-Injection (WFI)

The table in Figure 1 lists the four basic water types or categories.

Figure 1

Four Basic Types of Water Classification

<table>
<thead>
<tr>
<th>Level</th>
<th>Water Types</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Well water</td>
</tr>
<tr>
<td>II</td>
<td>Potable water</td>
</tr>
<tr>
<td>III</td>
<td>PW used for critical batch applications</td>
</tr>
<tr>
<td>IV</td>
<td>Food and Drug Administration (FDA) water for final rinse, formulation, and WFI</td>
</tr>
</tbody>
</table>

- Level I Water
  Level I is untreated water used for utilities (fire protection, lawn sprinklers, etc.) and may be from a well or surface source.
- Level II Water
  Level II (potable) is drinking water, which must meet
EPA requirements for quality. Its source can be a private or municipal supply that has a variable degree of hardness and added chlorine for microbial control.

- **Level III Water**
  Level III is purified water, which is the most difficult to control from a microbial standpoint. It is usually used for bulk batch application where there is no reasonable alternative and for non-parenteral product formulation. It is sometimes used as the initial cleaning agent for some processes.

- **Level IV Water**
  Level IV water is the most critical quality level. It is commonly used in final formulation for parenteral applications and it is also used as final rinse water for critical product contact surfaces. This water must satisfy the specifications for water for injection as defined by current USP requirements.

### Part C: Water Pre-Treatment System

To maintain a high level of biological and chemical control, it is necessary to limit the load by pre-treating the water source before it enters into the still. This is accomplished through several purification steps in the pretreatment sequence. The following components are typical of those found in a pretreatment system:

- Multi-media filter
- Duplex water softener with brine tank and brine feed pump
- Hot water sanitizable Carbon Filter Skid (CFS) with circulation pump
  - Heat exchanger
  - Activated carbon filter
- Multi-cartridge filters
- Water Pre-Treatment Component Detail
  - Multi-Media Filter
    - A multi-media filter is used to remove or reduce turbidity, suspended solids, and sediment from the feed water (incoming city water).
  - Duplex Water Softener
    - A duplex water softener, brine tank and feed pump system, produces a sodium cycle that will remove scaling and other trace minerals from the}

### Figure 2

**Major Contaminants in City Water Systems**

<table>
<thead>
<tr>
<th>Contaminant</th>
<th>City Feed Water Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Dissolved Solids (TDS)</td>
<td>125.74 mg/L</td>
</tr>
<tr>
<td>Total Hardness</td>
<td>77.71 mg/L</td>
</tr>
<tr>
<td>Total Organic Carbon (TOC)</td>
<td>10.45 ppm</td>
</tr>
<tr>
<td>pH</td>
<td>9.23</td>
</tr>
<tr>
<td>Microbial Limits</td>
<td>500 cfu/ml</td>
</tr>
</tbody>
</table>

**Incoming Municipal Water**

The incoming source water is usually from the local city water treatment facility. It is important to monitor the incoming water for quality, flow rates, and pressures. The water quality must meet water quality standards set by the Environmental Resource Council (ERC-2) plus the EPA regulations on drinking water quality. The data in Figure 2 is a summary of the major contaminants found in some municipal water systems.
water to improve RO operation and extend the life of the filter membrane.

✓ Carbon Filter Skid
The hot water sanitizable carbon filter is used to remove organic material and residual chlorine from the incoming softened water. The carbon bed is installed in a loop that consists of a recirculation pump, heat exchanger, and activated carbon filter. In order to minimize the risk of microbial contamination from the carbon bed, the contents of the CFS system and loop are periodically heated to 176°F to sanitize the carbon bed and its associated components.

➢ Heat Exchanger
The heat exchanger uses heated water up to 176°F to sanitize the carbon bed and its associated components.

• Pre-Treatment Programmable Logic Controller
A Programmable Logic Controller (PLC) controls some pre-treatment systems. The PLC is monitored by a Supervisory Control And Data Acquisition (SCADA) system. The SCADA system allows access to all visual and audible alarms for all equipment associated with the WFI system.

The pre-treatment system is designed to purify incoming city water from USP EPA drinking water standards to meet still feed water specifications summarized in Figure 3.

**Figure 3**

<table>
<thead>
<tr>
<th>Contaminant</th>
<th>Specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conductivity</td>
<td>&lt; 5 micro siemens/cm</td>
</tr>
<tr>
<td>Endotoxins</td>
<td>&lt; 25 EU/ml</td>
</tr>
<tr>
<td>Microbial</td>
<td>&lt; 500 cfu/ml</td>
</tr>
<tr>
<td>pH</td>
<td>5.5 to 7.0</td>
</tr>
<tr>
<td>Total Solids</td>
<td>&lt; 5 mg/L</td>
</tr>
<tr>
<td>Chlorine</td>
<td>Non-Detected</td>
</tr>
</tbody>
</table>

The pre-treatment water specifications are those of the still manufacturer and are not regulatory requirements. These still requirements can vary from system to system. Still requirements also depend on the quality of the feed water.

**Water Purification System**

Usually, the components associated with purification systems are similar to WFI systems with the exception of the method of water production (distillation versus RO/DI) and the final quality output. Along with the water pre-treatment system described above, these are the components that comprise a Purified Water System:

- **System Elements**
  - RO feed tank with break tank and vent filter; RO feed pump
  - Single pass reverse osmosis unit
  - Deionization (DI) bottles
    - Filter - 0.5 micron
  - Ultra-Violet (UV) sterilizer
    - Final filter - 0.2 micron
  - Storage tank (still)
    - Tank vent filter

- **System Details**
  - Pretreatment System (see "Part C: Water Pre-Treatment System" above)
  - Break Tank System
    A 100 gallon RO feed break tank provides an air break and reserve capacity for the RO system. The pump delivers feed water through two 1.0 micron multi-cartridge filters, which are used to remove carbon fines or other particulate matter from the water before it passes through the RO unit.

- **Reverse Osmosis**
  A single pass (RO unit is used to remove 99% of particulate matter, silica, bacteria, and endotoxins.) The operation of the RO unit is continuous in order to minimize bacterial load. When the still does not require feed water, the RO unit will
operate in a high recovery mode in order to minimize water consumption.

✓ Deionization System
The DI recirculation loop provides pressurized RO/DI water to the still feed system. The water in this system flows constantly through the DI recirculation pump, which consists of two deionization bottles in series, an ultra-violet sterilizer, and a 0.5 micron resin trap filter.

✓ UV Sterilizer and Final Filtration System
A 0.5 micron filter is used to decrease the bioburden levels and to prevent resin particles from the DI bottles from being deposited onto the surface in the UV sterilizer. A UV sterilizer and a 0.2 micron final filter are used to decrease the bioburden levels in the water before it enters into the still.

Purification Water Storage System
Purified water is supplied to a storage vessel from the purification system. Purified water quality is maintained within the storage system by constant recirculation within the storage system. The purified water is dumped after 24 hours to prevent proliferation of bacteria.

The purified water distribution loop returns to the storage vessel after being further polished and filtered. A 0.2 micron hydrophobic vent filter is usually employed on the purified water storage vessel to filter out any air coming into the storage vessel during purified water system draw down.

✓ Purified Distribution Loops
The generated purified water is distributed throughout in a continuous loop. In distribution systems, where the water circulates at a specified controlled temperature, dead legs and low flow should be avoided, and valve tie-in points should have length-to-diameter ratios of six or less. Components and distribution lines should be sloped and fitted with drain points. The distribution loop tubing may be composed of stainless steel or plastic. The purification system is designed to purify water to meet USP specifications. Point of use specifications are summarized in Figure 4:

Water-for-Injection System
The components that comprise the WFI system include:

- Four-effect distillation unit
- Jacket storage tank
- Cold, hot, and ambient WFI distribution loops with associated pumps
- Heat exchanger with cooling water
- Heat exchanger with chilled glycol
- Heat exchanger with chilled water

System Details

Distillation System
A four-effect distillation unit produces USP water for injection. The WFI storage tank level transmitters control the operation of the still. RO/DI treated water flows into the WFI still feed and produces WFI quality distillate.

The multi-effect still is capable of producing clean steam for periodic clean steam sterilization of the WFI storage and distribution systems. The distillation process will provide a three-log reduction in endotoxin and a five-log reduction in bacteria to meet the requirements of USP testing results.

WFI Storage System
Water for injection is supplied to a storage vessel from the multi-effect still. WFI quality water is maintained within the storage system by constant recirculation of the storage system contents at greater than 80˚C. A plant steam jacket on the WFI storage vessel maintains the temperature of the WFI within the storage system. The temperature of the vessel contents is maintained above 80˚C.

---

**Figure 4**

**Purified Water Specifications**

<table>
<thead>
<tr>
<th>Contaminant</th>
<th>Specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conductivity</td>
<td>USP Specifications</td>
</tr>
<tr>
<td>Endotoxins</td>
<td>No Specifications</td>
</tr>
<tr>
<td>Bacteria</td>
<td>100 cfu/ml</td>
</tr>
<tr>
<td>pH</td>
<td>5.0 - 7.0</td>
</tr>
<tr>
<td>TOC</td>
<td>500 ppb</td>
</tr>
</tbody>
</table>

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Contaminant Specification

- Conductivity USP Specifications
- Endotoxins No Specifications
- Bacteria 100 cfu/ml
- pH 5.0 - 7.0
- TOC 500 ppb
The hot WFI distribution loop returns to the WFI storage vessel through a spray ball. The spray ball constantly rinses the dome and sidewalls of the storage vessel with hot WFI to maintain cleanliness within the storage tank.

A 0.2 micron hydrophobic vent filter is usually employed on the WFI storage vessel to filter any incoming air into the storage vessel during WFI system draw down. The filter is provided with a low-pressure plant steam jacket to prevent filter plugging. Valves and ports are provided on the vent filter for clean steam sanitization of the vent filter after cartridge replacement. A rupture disk on the storage vessel protects it from over-pressure. A burst monitor indicates rupture disk over-pressure and activates an alarm. The WFI storage tank temperature is continuously monitored.

- **WFI Distribution Loops**
  The generated WFI distributed throughout the facility can be in three different loops: hot distribution, ambient distribution, or cold distribution. In distribution systems where the water circulates at high temperature, dead legs and low flow should be avoided, and valve tie-in points should have length-to-diameter ratios of six or less. Components and distribution lines should be sloped and fitted with drain points. WFI specifications are summarized in Figure 5.

### Figure 5

<table>
<thead>
<tr>
<th>Water-For-Injection Specifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contaminant</td>
</tr>
<tr>
<td>Conductivity</td>
</tr>
<tr>
<td>Endotoxins</td>
</tr>
<tr>
<td>Bacteria</td>
</tr>
<tr>
<td>pH</td>
</tr>
<tr>
<td>TOC</td>
</tr>
</tbody>
</table>

### Water Purification System Functions

- Deionization
- Distillation
- Reverse osmosis filtration
- Ultra filtration

### Water Validation Phases

A basic reference used for the validation of high purity water systems is the Parenteral Drug Association Technical Report Number 4, entitled: *Design Concepts for the Validation of Water for Injection Systems*. The validation of water systems can be time consuming and very costly. In 1993, realizing that the Pharmaceutical Industry needed some guidance in the validation of critical water systems, the FDA published the *Guide to Inspections of High Purity Water Systems*. The following are some points to consider from the FDA's perspective when validating critical water systems according to their guidelines:

- The initial phase involves verifying that all related components, process monitors, and controls have been installed and are functioning as designed.
- The second phase is called the performance phase and involves testing the systems for microbial and chemical qualities over certain periods of time.
- The final phase is the routine monitoring performed over the life of the system. At this stage, data is compiled and reviewed to determine trends that will give a more accurate system profile. The data compiled includes seasonal variations, maintenance, and sanitation of the system.

Each water system is design differently and therefore, must be validated according to its intended design and use. This section of the article will cover water systems at levels II, III, and IV only, since these are the most commonly used in pharmaceutical applications.
Phase 1

1. All water systems should have documentation containing a system description along with accurate drawings. The drawings must show all equipment in the system from water input to points of use. They should also show all sampling points and their designations.

2. After all the equipment and piping has been verified as installed correctly and working as specified, the initial phase of the water system validation can begin.

3. During the initial phase, the operational parameters and cleaning or sanitation procedures and frequencies will be developed. Sampling should be completed daily after each step in the purification process and at each point of use for two to four weeks.

4. The sampling procedures for points of use should detail how the samples are to be taken, e.g.: use of hose and time for flushing. At the end of the dedicated two- or four-week period, the firm should have developed its Standard Operating Procedures (SOPs) for the operation and maintenance of the water system.

Phase 2

The second phase of the water system validation must demonstrate that the system will consistently produce the desired water quality when operated in conformance with the SOPs. Sampling is performed as in the initial phase and for the same period. At the end of this phase, the data should demonstrate that the system would consistently produce the desired quality of water.

Phase 3

1. The third phase of validation is designed to demonstrate that, when the water system is operated in accordance with the SOPs over a long period of time, it will consistently produce water of the desired quality.

2. Any variations in the quality of the feed water that could affect the operation, and ultimately the water quality, will be noticed during this phase of the validation.

3. Sampling is performed according to routine procedures and frequencies. For WFI systems, samples should be taken daily from a minimum of one point of use, with all points of use tested weekly.

4. The validation of the water system is completed when the firm has collected data for a full year.

The FDA states that, "while the above validation scheme is not the only way a system can be validated, it contains the necessary elements for validation of a water system."

- First, there must be data to support the SOPs.

- Second, there must be data demonstrating that the SOPs are valid and that the system is capable of consistently producing water that meets the desired specifications.

- Third, there must be data to demonstrate that seasonal variations in the feed water do not adversely affect the operation of the system or the water quality. This last part of the validation involves the compilation of the data, with any conclusions, into a final report.

Figure 6

Microbiological and Chemical Limits

<table>
<thead>
<tr>
<th>Test</th>
<th>Potable Water</th>
<th>Purified</th>
<th>Water-For-Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>N/A</td>
<td>5.0 - 7.0</td>
<td>5.0 - 7.0</td>
</tr>
<tr>
<td>TOC</td>
<td>N/A</td>
<td>500 ppb</td>
<td>500 ppb</td>
</tr>
<tr>
<td>Conductivity</td>
<td>N/A</td>
<td>4.7 to 5.8 μS/cm</td>
<td>Current USP specifications or method</td>
</tr>
<tr>
<td>Bacteria</td>
<td>500 cfu/mL</td>
<td>100 cfu/mL</td>
<td>10 cfu/100 mL</td>
</tr>
<tr>
<td>Endotoxins</td>
<td>N/A</td>
<td>Not specified</td>
<td>0.25 EU/mL</td>
</tr>
</tbody>
</table>

cfu: Colony Forming Units
Once all regulatory concerns are addressed, it is important to consider microbiological and chemical requirements for each system. Figure 6 contains limits for each level of water system.

A validation program qualifies the design, installation, operation, and performance of the system. It begins when the system design moves through different phases: Construction Qualification (CQ), Installation Qualification (IQ), Operational Qualification (OQ), Performance Qualification (PQ), and the routine monitoring program. The USP-NF Fifth Supplement (1231), Water for Pharmaceutical Purposes, defines a typical water system validation lifecycle in the graphical representation of Figure 7.

**Validation Requirements for Purified Water Systems**

There are numerous methods of qualifying a water system; the following is one typical method:

**Construction Qualification**

During the CQ phase of the validation, material certification on tubing and components should be collected. Welding logs should be inspected to ensure that the welders are conforming to their own quality program. Certain test procedures such as hydrostatic testing should be witnessed and documented. Verification that piping is sloped to drain according to specification and code should be completed.

**Commissioning and Startup**

The commissioning and startup of a water system is one of the most important phases of any critical utility system. Commissioning is a method of determining major problems with a water system before the qualification phase is executed. The commissioning phase allows major problems to be corrected immediately, therefore minimizing the deviations that would have to be addressed during the execution of the qualification phase.

**Installation Qualification**

An IQ phase consists of verifying that instruments, valves, heat exchangers, and major components are installed according to design specifications. The system should be inspected to verify that the drawings accurately depict the as-built configuration of the water system. The validation engineer should review the data on cleaning and passivation as well as the test results included in the final report. Passivation of the stainless steel piping and tank is important in removing various metal contaminants that can cause oxidation of surface areas. After the passivation process is complete, it is important to ensure that no residues remain in the system. Last of all, it is important to verify that the distribution system and the point of use valves are labeled and tagged.

**Operational Qualification**

During the OQ phase it is important to test and verify the following functions:

- Flow and pressure rates
- Temperature and conductivity
- Sanitization or Steam-In-Place (SIP) procedures
- Computer control functions
- Alarms
- Pumps
- Major components function according to design specifications
- Filter integrity

It is imperative to verify that all instruments and devices have been calibrated before starting the OQ. After all functions are verified, it is essential to perform preliminary testing on the system. This involves sampling the system during a two-week period for microbial and chemical quality. It is also important to verify the efficiency of each major component to ensure it performs according to the design specifications. For example, the carbon bed should be tested or monitored to ensure it is capable of removing chlorides to an acceptable level. By performing this step, you will be able to determine whether the system is ready for the PQ phase of the validation. This step will prevent the waste of financial resources and time spent unnecessarily on a system that may not be ready for the PQ study. All system SOPs should be developed and finalized during the OQ phase.

Performing a baseline test of the system before starting the PQ should capture valuable information on the system’s ability to produce high quality water. It is important to qualify the microbiological and chemical test methods before starting the Performance Qualification Study.

**Performance Qualification**

The PQ phase involves monitoring the system for microbial and chemical quality over a specified period of time. Most companies perform this study for 30 to 60 consecutive days. After 30 days, the system is shut down for 24 hours (stagnation test). After 24 hours, testing continues for another 30 days to determine how long it takes for the system to...
Figure 7

Typical Water System Validation Lifecycle

1. Define Water Quality Attributes
   - Define systems and subsystems including Processing Technologies, Operating Parameters, and Corrective Action features to meet water quality attributes

2. Install Equipment Piping and Control Systems

3. Installation Qualification (IQ)

4. Operational Qualification (OQ)

5. Performance Qualification (PQ)

6. Prospective Phase—Confirm Appropriateness of Critical Process Parameter Operating Ranges

7. Concurrent/Retrospective Phase
   - Establish reproducibility and reliability system
   - Evaluate effects of seasonal changes
   - Confirm appropriateness of alert and action levels and corrective action program

8. Establish Corrective Action Response

9. Establish Alert and Action Levels for Key Quality Attributes

10. Define Alert and Action Levels for Key Quality Attributes

11. Validation Maintenance
    - Change Control
    - Periodic Review
to recover. Sampling should be performed daily after each step in the purification process and at each point during the period of the PQ. Again, it is important to monitor the incoming water source between each major piece of equipment and at the points of use. This is done to ensure that each component is performing according to design. Testing between each major component makes it easier to detect the source of any problems, should they occur. Sampling for microbial and endotoxin levels should be performed on a daily basis, whereas chemical analysis can be performed for each use point.

**Test Methods and Materials Used During PQ Study**

The use of proper test methods and materials is critical to any validation project. That is why it is important to qualify them before the actual PQ study. The USP Fifth Supplement’s, USP-NF, (1231) *Water for Pharmaceutical Purposes*, recommended methodologies are derived from the *Standard Methods for the Examination of Water and Wastewater*, 18th Edition, American Public Health Association, Washington, D.C., 2005. Although these methodologies are considered appropriate for establishing trends in the number of Colony Forming Units (CFUs) observed in the routine microbiological monitoring of ingredient water, they do however, recognize that other combinations of media, time, and temperature of incubation, may occasionally, or even consistently, result in a higher number of CFUs being observed. The following is the recommended method generally satisfactory for monitoring pharmaceutical drinking water, purified water, and water for injection systems:

**Pour Plate Method**

- Minimum sample - 1.0 ml
- Plate count agar
- 42 to 72 hours at 30˚ to 35˚C

While the above methodology may be considered acceptable, it is also important to consider alternative methodologies. For example, low nutrient media may be compared with high nutrient media, especially during the validation of water systems. The use of high (enriched) nutrient media is normally used for the isolation and enumeration of heterotrophic bacteria. It is also important to consider slow growth bacteria that are living in an environment with minimal nutritional supplements or that are under stress from chemical agents. Therefore, it may be important to consider the use of a low nutrient media. High nutrient media require a higher temperature and a shorter incubation period. Whereas most low nutrient media require lower temperatures and longer incubation periods. Since the amount of bacteria detected in a 100 ml sample may be very low, a larger sample volume (250 - 300 ml) should be considered especially for WFI systems.

When testing drinking water for microbial quality, it is also important to inactivate the chlorine that is normally used to treat the water. Failing to do so may cause an inaccurate count because of the bactericidal affect the chlorine will have on the microorganisms.

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**Clean Steam Systems**

**INTRODUCTION**

The purpose of a clean steam generator system is to produce high quality clean steam that will meet certain chemical, endotoxin, and microbial specifications. Clean steam systems are normally constructed of high quality stainless steel that will not rust. Also, the steam is produced without the use of boiler additives, because the steam will be used for product contact surfaces. Clean steam systems are usually used in the sterilization of critical components. Clean steam systems are designed to produce high purity steam that is free from chemical contaminates and is low in endotoxins. The sampling of clean stream is usually performed with a clean steam condenser. The condenser is usually connected to a water source to cool the steam to a liquid state. It is essential to perform a hydrostatic test on the condensing unit before using it for sampling. The test will ensure that there are no leaks in the unit that may contaminate the sample.

**Design Requirements for Clean Steam Systems**

Before a clean steam system can be designed, the system’s intended use must be defined. The design, installation, and operation of water systems used to produce high purity clean steam usually involve various types of systems. There are many varieties of clean steam systems. A typical system, which is commonly used in the Pharmaceutical Industry, is multi-effect columns.

The clean steam system requires various sorts of supporting water systems for the production of clean steam. These include, purified water and water for injection systems. Usually, the clean steam system supports certain critical equipment and utilities such as the following:
Clean Steam System Construction

The components that comprise various clean steam systems are as follows:

- Multi-Effect Columns
- Condenser
- Heat Exchanger

Construction Qualification

During the CQ phase of the validation, material certification of tubing and components should be collected. Welding logs should be inspected to ensure that the welders are conforming to their own quality program. Certain test procedures, such as hydrostatic testing, should be witnessed and documented. At the same time, verification that piping is sloped to drain as specified and according to code should be completed.

Commissioning and Startup

During the commissioning phase, all major components are checked to ensure they function properly and all critical operating parameters have been set and verified according to function specifications. A final walk down of the system is performed to verify that the system is ready for the qualification phase.

Installation Qualification

An IQ phase consists of verifying that instruments, valves, heat exchangers, and major components are installed as specified in the design. Another key element is the verification of critical utility support such as high quality water, plant steam, and electrical power. The system should be inspected to verify that the drawings accurately depict the as-built configuration of the water system. The data on cleaning and passivation should be reviewed. The distribution system and point of use valves should also be labeled and tagged.

Operational Qualification

During the OQ phase, it is important to test and verify the following functions:

- Flow and pressure rates
- Temperature and conductivity
- Computer control functions
- Alarms

- Pumps
- Major components functions
- Plant steam

It is critical to verify that all instruments and devices have been calibrated before starting the OQ. After all functions are verified, perform the crucial preliminary testing on the systems. This involves sampling the system for microbial and chemical quality for a period of two-weeks. All system SOPs must be developed and finalized during the OQ phase.

Testing the system before starting the performance qualification gives valuable information on the system’s ability to produce high quality clean steam. Once again, it is critical to qualify the microbiological and chemical test methods before starting the Performance Qualification Study.

Performance Qualification

The PQ phase involves monitoring the system for microbial and chemical quality over a specific period of time. Most companies perform this study for 30 consecutive days. Sampling should be performed daily at each point for the duration of the PQ.

At this point, monitoring the incoming water source is key because doing so will make it easier to detect the source of any problems, should they occur. Since plant steam is used to heat up the water source via a heat exchanger, it is important to also test for hydrazine. This test will ensure that there are no leaks from the heat exchanger that may introduce hydrazine into the clean steam system.

Acceptance Criteria

The performance qualification test period usually extends for 30 days. Clean steam condensate samples taken at the clean steam sampling valve shall meet the criteria indicated in Figure 8.
Test Equipment and Materials
- Equipment and materials necessary to collect water samples as indicated in the SOP
- Equipment and materials necessary to perform USP chemical analysis for the clean steam system
- Equipment and materials necessary to perform conductivity and pH tests for clean steam systems
- Equipment and materials necessary to perform microbial testing for clean steam systems, according to the appropriate SOPs
- Equipment and materials necessary to perform Limulus Amebocyte Lysate (LAL) testing for clean steam system as indicated by the SOPs
- Equipment and materials necessary to perform TOC testing for clean steam systems as indicated in the SOPs
- Equipment and materials necessary to perform hydrazine testing for clean steam systems

Procedure
The following is one procedure that can be used during the intensive monitoring phase of the clean steam system:

1. Collect samples as indicated in applicable SOPs.
2. Test samples in accordance with applicable SOPs.
3. Connect hose to condensate sampler.
4. Flush all sample lines for three minutes before using or as suggested by the manufacturer.
5. Record test results as specified in the applicable SOP forms or on applicable data collection forms.
6. Samples should be taken on a daily basis for 30 days to monitor endotoxin and microbial activity.

Data Analysis
Where applicable, calculate the arithmetic mean and identify minimum and maximum readings for each sample port. Summarize data in tables and correlate maintenance activities to test data where applicable. Identify microbial organisms to species level.

At the end of the PQ test period, assemble all documentation and tabulate the results into spreadsheets that are capable of trending the data. Collect copies of all applicable collection data forms and validation notebook pages. Once the data has been reviewed and a final report has been written, the system is ready for the routine monitoring program.

(This completes Part II of "Design, Construction, Commission, and Qualification of Critical Utility Systems." The final and third part of this article covering HVAC and Gas Systems will appear in the November 2005 issue of this Journal. The first part of this article, an overview of critical utility systems, appeared in the May 2005 issue of the JVT.)

About the Author
David W. Vincent has over 25 years experience in the Biopharmaceutical Industry with 19 years dedicated to the fields of validation and engineering. He has a B.S. degree in Microbiology and Mechanical Engineering Technology; Mr. Vincent has consulted for many companies both nationally and internationally. He has presented many training seminars and has written numerous articles and technical guides regarding validation topics. Mr. Vincent teaches "Validation Program for the Pharmaceutical, Biotechnology, and Medical Device Industries" at San Diego State University (SDSU) for their Regulatory Affairs Master Degree program.
Currently, Dave is the Chief Executive Office (CEO) for Validation Technologies Incorporated (VTI), a worldwide validation and technical services company. VTI is also a certified commissioning company that offers commissioning and startup functions for the Healthcare Industry. Dave can be reached by phone at 800-930-9222, by fax at 858-638-5532, or by e-mail at david@validation.org. (Web site is located at www.validation.org)

REFERENCES


**Article Acronym Listing**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>CFS</td>
<td>Carbon Filter Skid</td>
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<td>CFU</td>
<td>Colony Forming Unit</td>
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<tr>
<td>CQ</td>
<td>Construction Qualification</td>
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<td>Deionization</td>
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<td>Environmental Resource Council</td>
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<td>Food and Drug Administration</td>
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<td>IQ</td>
<td>Installation Qualification</td>
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<td>LAL</td>
<td>Limulus Amebocyte Lysate</td>
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<tr>
<td>OQ</td>
<td>Operational Qualification</td>
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<td>PLC</td>
<td>Programmable Logic Controller</td>
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<td>Performance Qualification</td>
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<td>RO</td>
<td>Reverse Osmosis</td>
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<td>SCADA</td>
<td>Supervisory Control And Data Acquisition</td>
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<td>Steam-In-Place</td>
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<td>SOP</td>
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<td>Ultra Violet</td>
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