Qualification of Purified Water Systems

David W. Vincent

Validation Technologies, Inc.

> **"This article discusses the basic steps in validating various water systems, and once they are validated, establishing a routine monitoring program to maintain them."**

There are various types of water used in the pharmaceutical industry. Their usage in the actual formulation, in processing operations, and as a final rinse of a product contact surface, enables them to truly be considered a product ingredient. Purified water can be produced many different ways and with various different designs and equipment. The usage of pharmaceutical grade water is very important in the production of pharmaceutical drug products. Therefore, the validation and routine monitoring of these systems are critical in maintaining the quality of the final product. This article discusses the basic steps in validating various water systems, and once they are validated, establishing a routine monitoring program to maintain them. In addition various types of water and their applications, design, validation requirements, steps for validating purified water systems, routine monitoring program, Preventative Maintenance (PM) and revalidation program.

Water is classified into many different groups, depending on its source, quality, treatment, or use. It is also necessary to define each classification by the minimum quality requirements, especially with regards to chemical and microbiological purity. The following is an example of the different types of water and their usage.

Water Usage in Pharmaceutical Production

- Water Requirements
  - Potable: Environmental Particulate Aggregates (EPA)
  - United States Pharmacopeia (USP) Purified
  - USP Water-For-Injection (WFI)

The following table lists the four basic water types and classification.[1]

Type I	Well water
Type II	Potable water
Type III	Purified water used for critical batch applications
Type IV	Food and Drug Administration (FDA) water for final rinse and formulation WFI

- *Type I Water*

Type I is untreated water used for utilities (fire protection, lawn sprinklers, etc.), and may be from a well or surface source.

- *Type II Water*

Type II is drinking water (potable) that must meet the Environmental Protection Agency (EPA) requirements for quality. Its source is from a private or city supply that has a variable degree of hardness and added chlorine for microbial control.

- *Type III Water*

Type III is purified water, which is the most difficult to control from a microbial standpoint, and 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.

• *Type IV Water*

Type IV water is the most critical quality level. It is commonly used in final formulation for parenteral applicants and as final rinse water for critical product contact surfaces. This water must satisfy the specifications for WFI as defined by USP compendia

Design Requirements for Water Systems

The first step in designing a water system is to define what the systems intended use will be. Once the system's use has been determined, it is important to test the incoming water source. This data will be used to determine what type water treatment is needed. The design, installation, and operation of water systems used to produce Purified and WFI include similar components, controls, and procedures. Usually WFI systems are designed to produce high quality water, and the most common methods employed are by distillation and Reverse Osmosis (RO). The design of these systems can vary from system to system. The following description is of a typical system, which only contains pretreatment and WFI. The pretreatment system is only used to create water to service the WFI distillation system.

Incoming City Water

The incoming source water is usually from the city municipal water treatment facility. The water quality must meet their own water quality standards (ERC-2), plus the EPA regulations on drinking water quality. The following table is a summary of the major contaminants found in some city water systems.

Contaminant	*City Feed Water Results*
Total Dissolve Solids (TDS)	125.74 mg/l
Total Hardness	77.71 mg/l
Total Organic Carbon (TOC)	10.45 ppm
pH	9.23
Microbial Limits	500 cfu/ml

It is also important to monitor the incoming city water flow rates or pressures.

Purified Water System

To maintain a high level of biological and chemical control, it is necessary to limit the load by pretreating 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 components found in a pretreatment system:

- Multimedia filter
- Duplex water softener with brine tank, and brine feed pump
- Hot water sanitizable carbon filter skid with circulation pump
- Heat exchanger
- Activated carbon filter
- Multi-cartridge filters
- RO feed tank with break tank and vent filter; RO feed pump
- Single pass RO unit
- Deionization bottles
- 0.5 micron filter
- Ultraviolet (UV) sterilizer
- 0.2 micron final filter

• *Multimedia Filter*

A multi-media filter is used to remove or reduce turbidity, suspended solids, and sediment from the feed water (incoming city water). The filtration also removes particles with a nominal size of 10 microns or greater.

• *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 water to improve RO operation and extend the life of the filter membrane.

• *Carbon Filter Skid*

The hot 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 loop are heated to 176ºF periodically to sanitize the carbon bed and associated components.

• *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 (RO)*

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 Deionization (DI) recirculation loop provides pressurized RO/DI water to the still feed system. The water in this system is flowing constantly through the DI recirculation pump, two deionization bottles in series, an UV 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 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.

• *Pretreatment Programmable Logic Controller (PLC)*

Some pretreatment systems are controlled by a PLC. 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 pretreatment system is designed to purify incoming city water from USP EPA drinking water standards to meet the following still feed water specification summarized in the table below.

Purified Water Specifications	
Conductivity	< 5 microsiemens/cm
Endotoxins	< 25 EU/ml
Microbial	< 200 CFU/ml
pH	5.5 to 7.0
Total Solids	< 5 mg/l
Chlorine	Non-detected

The previous specifications are those of the still manufacturer, and are not regulatory requirements. These still requirements can vary from system-to-system. It also depends 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 verse RO/DI) and the final quality output. The components that comprise the purified water system are skid mounted multimedia, water softener, carbon filter, dual pre-filters, UV sterilizer, RO unit, bioburden reduction filter, and storage tank. Below is a list of major components for a typical purified water system:

- Multimedia filter
- Duplex water softener with brine tank, and brine feed pump
- Hot water sanitizable carbon filter skid with circulation pump
- Heat exchanger
- Activated carbon filter
- Multi-cartridge filters
- RO feed tank with break tank and vent filter; RO feed pump
- Single pass RO unit
- Deionization bottles
- 0.5 micron filter
- Ultraviolet sterilizer
- 0.2-micron final filter
- Storage tank
- Tank vent filter

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 of 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 any incoming air 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 valves 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's tubing may be composed of stainless steel or plastic. The purification system is designed to purify water to meet USP 23 specifications. The following point of use specification is summarized in the following table.

Purified Water Specifications	
Conductivity	USP 24 Specification
Endotoxins	No Specifications
Bacteria	100 cfu/ml
pH	5.0 – 7.0
TOC	500 ppb

Water-for-Injection (WFI) Systems

The components that comprise the WFI system are four effect distillation unit, jacket storage tank, vent filter, cold, hot, and ambient WFI distribution loops with associated pumps, heat exchanger with cooling water, heat exchanger with chilled glycol, and a heat exchanger with chilled water.

Distillation System

USP 23 WFI is produced by a four-effect distillation unit. The WFI storage tank level transmitters control operation of the still. RO/DI treated water flows into the WFI still feed and produce 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 provides a three-log reduction in endotoxin and a five-log reduction in bacteria to meet USP 23 requirements.

WFI Storage System

WFI 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 80ºC. Temperature of the WFI within the storage system is maintained by a plant steam jacket on the WFI storage vessel. The temperature of the vessel contents is maintained above 80ºC.

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 pressurizing. 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, and 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.

Water-For-Injection (WFI) Specifications	
Conductivity	USP 24 specification
Endotoxins	0.25 EU/ml
Bacteria	10 cfu/100ml
pH	5.0 – 7.0
TOC	500 ppb

Validation Requirements for Purified Water Systems

The validation of water systems assures that the system will consistently produce water of predicable quality when operated in the prescribed manner. The validation of critical water systems involves a great deal of time and planning. The initial phase involves verifying that all related components, process monitors, and controls are installed and functioning as per design. The second phase is called the performance phase, which involves testing the systems for microbial and chemical qualities over certain periods of time. The final phase is the routine monitoring that is performed over the life of the system. At this stage, data is compiled and reviewed to determine trends, which will give a more accurate system profile. The data compiled includes seasonal variations, maintenance, and sanitation of the system.

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

Water Purification Systems

1. Pretreatment
    - Water softener
    - Depth filtration
    - Activated carbon and/or bisulfite injection
    - Demineralization
    - RO
2. Purification
    - Deionization
    - Distillation
    - RO
    - Ultrafiltration

A basic reference used for the validation of high purity water systems is the Parenteral Drug Association (PDA) Technical Report No. 4 titled, *Design Concepts for the Validation of a Water for Injection Systems*. The validation of water systems can be time consuming and very costly. In 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* in 1993.[3] The following are some points to consider from the FDA's perspective when validating critical water systems as per the above guidelines.

Phase 1

– All water systems should have documentation containing a system description and accurate drawing. The drawing needs to show all equipment in the systems from water input to points of use. It should also show all sampling points and their designations.

– 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.

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

– The sampling procedures for point of use should reflect how they are taken, e.g., use of hose, and time for flushing. At the end of two (2) or four (4) weeks, the firm should have developed its Standard Operating Procedures (SOPs) for operation and maintenance of the water system.

Phase 2

– The second phase of the water system validation is to demonstrating that the system will consistently produce the desired water quality when operated in conformance with SOPs. The 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 consistently produces the desired quality of water.

Phase 3

– 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 desired quality.

– 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.

– 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.

– 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 capa-

ble of consistently producing water that meets the desired specifications.

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

Once all regulatory concerns are addressed, it is important to consider microbiological and chemical requirements for each system. *Figure 1* contains limits for each level of water system.

Figure 1

Microbiological/Chemical Limits

Tests	Potable Water	Purified Water	Water-for injection
pH	N/A	5.0 - 7.0	5.0 - 7.0
TOC	N/A	500 ppb	500 ppb
Conductivity	N/A	4.7 to 5.8 µS/cm	USP 24 Specification/ Method
Bacteria	500 cfu/mL	100 cfu/mL	10 cfu/100mL
Endotoxins	N/A	Not Specified	0.25 EU/mL

cfu: Colony Forming Units

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 routine monitoring program. The USP-NF fifth supplement <1231>, *Water for Pharmaceutical Purposes*, defines a typical water system validation lifecycle which is shown in the graphical representation of *Figure 2*.

Steps for Validation of Water Systems

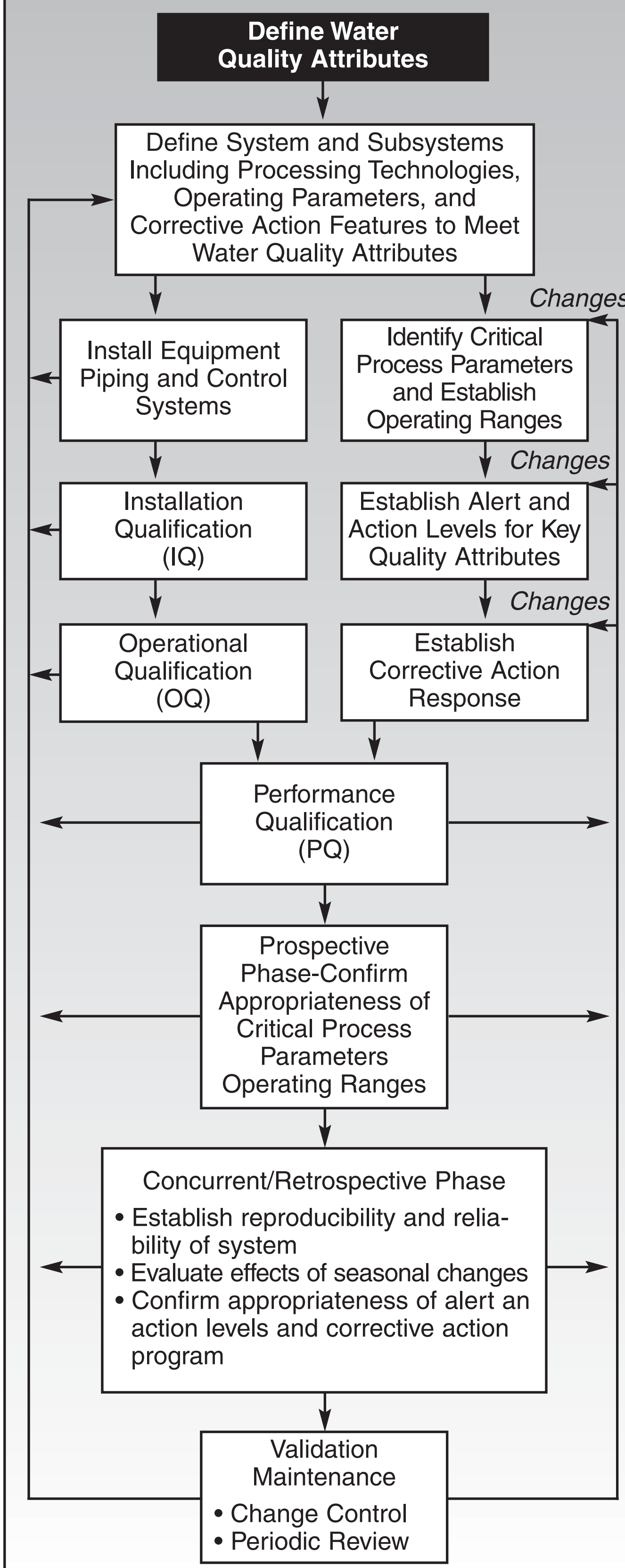
There are many ways of qualifying a water system. The following is one typical method:

Construction Qualification (CQ)

During the CQ phase of the validation, material certification on tubing and components should be collected. Welding logs should be inspected to insure that the welders are conforming to their own quality pro-

Figure 2

Water System Validation Lifecycle



gram. Certain test procedures, such as hydrostatic testing, should be witnessed and documented. Verification that piping is sloped to drain according to specifications and code should be completed.

Installation Qualification (IQ)

An IQ phase consists of field verifying that instruments, valves, heat exchangers, and major components are installed as per design specifications. The system should be inspected to verify that the drawings accurately depict the as-built configuration of the water system. The system should be checked to verify that there are no "dead legs." A dead leg is a length of piping that should be less than six inches of the pipe diameter's length. The data and reports for the cleaning and passivation activities should be reviewed, and the test results included in the final report. Passivation of the stainless steel piping and tank is important in removing various metal contaminates, which can cause oxidization of the surface areas. After the passivation process is complete, it is important to assure that there are no residues remaining in the system. Finally, check that distribution system and points of use valves are labeled and tagged. The water system should be fully commissioned before the OQ phase can start.[2]

Operational Qualification (OQ)

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

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

It is important to verify that all instrument and devices have been calibrated before starting the OQ. After all functions are verified, it is important to perform preliminary testing on the systems. This involves sampling the system for two weeks for microbial and chemical quality. It is also important to verify the efficiency of each major component to insure they perform according to their design specifications. For example, the carbon bed should be tested or monitored to insure it is capable of removing chlorides to an acceptable level. During the execution of the OQ protocol, it's important to verify that all valves function properly, and pumps are capable of meeting their appropriate pump curve requirements. It's also important to verify that all computerized control points are functioning per operational specifications. By performing this step, you will be able to determine if your system is ready for the PQ phase of the validation. This step will prevent unnecessary cost and time wasted on a system that may not be ready for the PQ study. All system SOPs should be developed and finalized during the OQ phase.

Testing the system before starting the PQ gives 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 PQ Study.

Performance Qualification (PQ)

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 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 recover. Sampling should be daily after each step in the purification process and at each point during the extent of the PQ. Again, it is important to monitor the incoming water source, in-between each major piece of equipment, and at the points of use. This is to insure each component is performing per design. By testing in between each major component, it will also be 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 rotate for each use point.

Test Methods and Materials Used During PQ Study

The use of proper test methods and materials are critical to any validation project. That is why it is important to qualify them before the actual PQ study. The USP fifth supplements, 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, DC 20005.[4] These methodologies are considered appropriate for establishing trends in the number 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 higher number of CFUs being observed. The following are some of the recommended methods that are generally satisfactory for monitoring pharmaceutical water systems:[5]

Drinking Water:	Pour Plate Method
	Minimum sample – 1.0 ml
	Plate count agar
	42 to 72 hours at 30º to 35ºC
Purified Water:	Pour Plate Method
	Minimum sample – 1.0 ml
	Plate count agar
	42 to 72 hours at 30º to 35ºC
Water-For-Injection:	Pour Plate Method
	Minimum sample – 1.0 ml
	Plate count agar
	42 to 72 hours at 30º to 35ºC

While the above methodology may be considered acceptable, it is also important to consider other alternative methodologies. For example, low nutrient media may be compared with high nutrient media, especially during the validation of a water system. The use of high (enriched) nutrient media is normally used for the isolation and enumeration of hetetrophic bacteria. It is also important to consider slow growth bacteria that are living in an environment with very little 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 requires a higher temperature and shorter incubation period; whereas low nutrient media requires lower temperature and a longer incubation period. Since the amount of bacteria detected in a 100 ml sample may be very low, a larger sample volume (250 – 300 ml) should especially be considered 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. By not doing so, one may not get an accurate count because of the bactericidal affect the chlorine will have on the microbial results.

Routine Monitoring Program for Purified Water Systems

Once the PQ is completed, the "real time" validation of the critical utilities begins. Usually the PQ study is performed over a short period of time, and with intensive sampling. But the routine Environmental Monitoring (EM) is performed during the life of the facility, and usually involves less intense sampling. The data collected from routine EM programs includes seasonal variations, and manufacturing activities, along with maintenance and cleaning activities. The most effective EM programs are the ones with clear and precise procedures.

Routine Environmental Monitoring Program

When establishing a routine EM program, the data for the PQ study should have the starting point for determining the sampling sites and frequencies of testing. It is also important to have an accurate drawing indicating the sampling sites. The program should also include environmental worksheets to record test results. The worksheet data can be entered into a computer-aided software program that can be used to trend and perform queries on environmental data.

Establishment of Alert and Action Limits

Alert Limits – The concentration of viable and non-viable particulate in a controlled environment that, when exceeded, signal a potential drift from normal operating conditions.

Action Limits – The concentration of viable and non-viable particulate in a controlled environment that, when exceeded, signal a potential drift from normal operating conditions, and which require an investigation and corrective action.

Alert and action limits are usually derived statistically from historical data. These "limits" are conservative measures designed to signal potential drift from historical or design performance characteristics.

The establishment of the alert action limits should be written and utilized in a consistent, non-arbitrary manner. It is important to remember that alert/action levels should not be extensions of product specifications. If an alert level is exceeded, correct action may not be required, but records should show that the excursion was recognized. But if alert levels are consistently exceeding their limits, an investigative action should be taken.

If an excursion occurs above an action level, as a minimum, one should review the data. An investigation should be undertaken, and corrective and alert notices to responsible parties and departments.

When an action limit is exceeded, an investigation and corrective action should be performed. The following actions may be taken, but are not limited to the following:

- Generate an Environmental Deviation Report (EDR) form
- Issue an alert notice
- Investigate the environmental deviation
- Perform corrective action
- Resample Out-of Limit (OOL) locations
- Review maintenance and cleaning logs
- Perform gram stain/identification of isolated organism(s)
- Determine sensitivity of isolate to disinfectant being used
- Review risk of product contact

No further action is usually required when acceptable levels are re-attained. The results from the retest are recorded on the EDR form, disposition as pass and file future for reference.

If the retest indicates that acceptable levels have not been met, the Quality Control (QC) department will initiate an investigation report with the description of the deviation to directors of Quality Assurance (QA) and manufacturing. It is the responsibility of manufacturing and/or facility department to conduct an immediate investigation, and initiate corrective actions to restore the area to normal operating conditions. QA is responsible for evaluating the impact of the conditions on product quality.

After corrective actions have been taken, the affected location(s) should be retested at least three times. Acceptable levels are reattained if three consecutive retests meet acceptable levels. Once the system is operating in a compliant state, QA is responsible for releasing the system to manufacturing

“The most effective EM [Environmental Monitoring] programs are the ones with clear and precise procedures.”

Corrective Action Program for Purified Water Systems

The purpose of a corrective action program is to investigate critical system failures, and reporting and documenting these failures, and making the necessary corrective action to bring the system into a compliance state.

The following program is applicable to purified water, and WFI, systems.

Program Procedures

An environmental investigation applies to any situations not considered an immediate threat to a critical system, but which, if allowed to continue, may become serious. An EDR must be filled out under the following or similar circumstances.

Water Systems

- When QC sample consistently exceeds alert limits for all QC test results.
- When a QC sample of water exceeds the action level for bacterial count.
- When a QC sample of water exceeds the action level for endotoxins limits.
- When a QC sample of water exceeds the limit for USP 24 chemistry.
- When a possible minor malfunction in the water system is observed.

Investigation and Corrective Action

The following steps should be taken:

- QA and the responsible facility (facility related) and/or production (process or equipment related) department will investigate the system and recommend corrective action.
- Document the proposed corrective action on the

EDR form

- The facilities and/or production manager will sign the EDR form, and return it to QA for review and approval of corrective action.
- Perform the corrective action immediately, if possible. If the action requires planning, materials, or time to implement, perform it as soon as possible.
- QA will review the proposed corrective action and any subsequent QC retesting data. If the investigation or the data shows that the system is in control, QA will sign the form, distribute copies, and file the QA copy of the form.
- Distribute copies to QA, facility manager, production, and the system and/or product file.

Manufacturing Alert Notice For Action Limit Failures

A manufacturing alert notice applies to any situation that is considered an immediate threat to a critical system or process equipment, and which may have a direct impact on the quality of the product. A manufacturing alert notice is issued to the manufacturing department notifying them that a system may or may not be used (depending on the circumstance and severity of the problem) until corrective action has been taken to bring it back into compliance. A manufacturing alert notice form must be filled out under the following or similar circumstances:

- When two or more retest samples exceed the action limits
- When you observe a questionable condition (sanitation, potential contamination)
- When you observe a possible minor or major malfunction in the utility system, which could possibly compromise the integrity of the production area
- When a QC test sample exceeds the action limits
- If a system is still not in compliance after the first environmental corrective action or investigation was taken

Corrective Action Program

An EDR form is initiated immediately when action levels are exceeded. A number is assigned to the deviation for traceability. The number consists of four groups of digits; the first group represents the system, the second group represents the year, and the third group a sequential number (i.e., Water-For-Injection; WF-96-01, and USP purified water).

The manufacturing manager and/or appropriate individual(s), are notified immediately of the type of deviation, and their signature/date obtained, along with the appropriate corrective actions are taken.

An EDR form will usually include the following section:

Section 1
1. The EDR number
2. System affected
3. Location where levels have been exceed
4. Room number

Section 2
1. Sample location, (i.e., point of use)
2. System sampled (WFI, USP purifed)

Section 3
1. Initial sample data
2. QC test results (collection data, site, sample data action levels)
3. Recommended corrective actions (if applicable)

Section 4
1. Corrective actions taken (requires a description of the action taken)

Section 5
1. Retest sample data
2. QC test results (collection data, site, sample data action levels)
3. EDR disposition (resampling results pass/fail)

Section 6
1. Other action taken (if applicable)
2. Results acceptable (no further steps required)
3. Not acceptable (investigation continues

After the investigation is completed, include any supporting documentation with the report. Also maintain a history file on each system to determine if there are any reoccurring failures, which may require modification or redesign of the system.

Water Systems Corrective Action

Corrective actions for pretreatment water, purified water and WFI systems may be included, but are not limited to, the following:

- Additional sampling and testing
- Review/repeat sanitization procedures
- Review sampling/testing technique

- Review validation data
- Check on possible unusual events during sampling and/or testing
- Review 0.2µm filter and tank vent filter integrity test results
- Review maintenance and sanitization logs
- Perform gram stain/identification of isolated organism(s)
- SIP the entire system
- Inspect all major components on the pretreatment, purified, and WFI system
- Review risk of product contact

No further action is required when acceptable levels are reattained. Record retest results on the EDR form, disposition as Pass, and file future for reference.

If the retest indicates that acceptable levels have not been met, initiate another investigation report to directors of QA and manufacturing with the description of the deviation. It is the responsibility of manufacturing to conduct an immediate investigation, and to initiate corrective actions to restore the area to normal operating conditions. QA should be responsible for evaluating the impact of the conditions on product quality.

After corrective actions have been taken, the affected location(s) will be retested at least three times. Acceptable levels are reattained if three consecutive retests meet acceptable levels.

Preventative Maintenance (PM) Program

Once the purified systems is qualified, it's important to place the system and its components in the PM program. This requires placing the system under a routine maintenance schedule. Normal PM may require filters being replaced, gauges and devices calibrated, loop being sanitized, pumps being inspected, and softener or carbon beds replaced. For WFI systems, a routine passivation schedule must be implemented as part of the PM. The purified water systems with stainless steel piping may require passivation every two to three years, depending on the age of the system. If the system is shut down for PM or emergency repairs, a procedure should be developed to determine if the system is still in a validated state. This may require sample testing the water for two – three days. The water may be used at risk for GMP activities if one-day results for chemistry is acceptable.

Revalidation of Critical Systems

Revalidation will occur when any significant changes or alterations occur to any above systems. (i.e., modification of purified water system major components). The extent of the testing will be determined on a case-by-case basis, and will be properly documented and filed. Revalidation for a critical utility should be performed annually or semi-annually, depending on the criticality of the system. The revalidation SOP should be written, which includes the extent of testing and the system under the program. Once the water system IQ is completed, it's important to place the system in the change control program. Changes to the system and drawings should be reviewed annually to determine if some degree of requalification is required. An annual summary report should be written that includes yearly trended QC data, changes or modifications made to the system, or any major maintenance issues. The final report should include a statement that the system is still in state of control and fully qualified for manufacturing use. ❑

References

1. Center for Drugs and Biologics, Center for Devices and Radiographic Health. "Guidelines on General Principles of Process Validation." FDA Rockville, Maryland. 1987.
2. "cGMP Compliance in Architecture and Construction of Biopharmaceutical Manufacturing Facilities." *BioPharm*. Prepared January-February. 1993.
3. FDA. "Guide to Inspections of High Purity Water Systems." (1993).
4. Standard Methods for the Examination of Water and Wastewater, 18th Edition. American Public Health Association. Washington, DC 20005.
5. PDA Environmental Task Force. "Fundamentals of a Microbiological Environmental Monitoring Program." Vol. 44. Supplement 1990.

Article Acronym Listing

CFU:	Colony Forming Unit
CQ:	Construction Qualification
DI:	Deionization
EDR:	Environmental Deviation Report
EM:	Environmental Monitoring
EPA:	Environmental Particulate Aggregates
EPA:	Environmental Protection Agency
FDA:	Food and Drug Administration
IQ:	Installation Qualification
TDS:	Total Dissolve Solids
OOL:	Out-of Limit
OQ:	Operational Qualification
PDA:	Perenteral Drug Association
PLC:	Programmable Logic Controllers
PM:	Preventative Maintenance
PQ:	Performance Qualification
QA:	Quality Assurance
QC:	Quality Control
RO:	Reverse Osmosis
SCADA:	Supervisory Control And Data Acquisition
SIP:	Steam-In-Place
SOP:	Standard Operating Procedure
TOC:	Total Organic Carbon
USP:	United States Pharmacopeia
UV:	Ultraviolet
WFI:	Water-For-Injection