SPECIAL EDITION

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UTILITIES QUALIFICATION

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WATER SYSTEMS: THE BASICS

Part 1: Design as a Prelude to Validation

OVERVIEW

Water systems produce one of the most critical raw materials used in the manufacture of product. There is no system within a production facility that receives more focus in industrial journals and magazines or receives more attention during an FDA inspection than water systems. The impact of water on daily activities within the production facility is significant and therefore, the ability to receive and maintain high quality water on demand becomes essential.

The success (or failure) of products largely rests with the proper design, validation and continued maintenance of the selected and constructed water system. A successful design of a water system requires in-depth knowledge of the water quality requirements, determination of the critical operating parameters, identification of convenient delivery points, stringent maintenance procedures, and proper sampling and testing techniques. Part 1 of this two part series addresses the basics of water system design and identifies key information critical to the short and long term needs of a basic water system. Part 2 of the series will address the construction, validation, maintenance, and operation of a well-designed water system.

DEFINITIONS

There are a wide variety of systems available and creative ways in which to use these systems. Therefore, it is important that there is a clear understanding of the basic types of systems. The following definitions are generally accepted:

USP Purified Water: Water that is produced by distillation, reverse osmosis (RO), ion exchange or other means. The quality of water must result in conformance to USP specifications for purity.

Reverse Osmosis (RO) Water: Water that is produced by a reverse osmosis unit. This water passes through a system of membranes and is essentially demineralized.

Deionized (DI) Water: Water that is produced by passing treated water through a mixed bed or cation-anion exchange resin system.

Water for Injection (WFI): Water that is produced by RO or distillation, and conforms to the USP specifications for WFI.

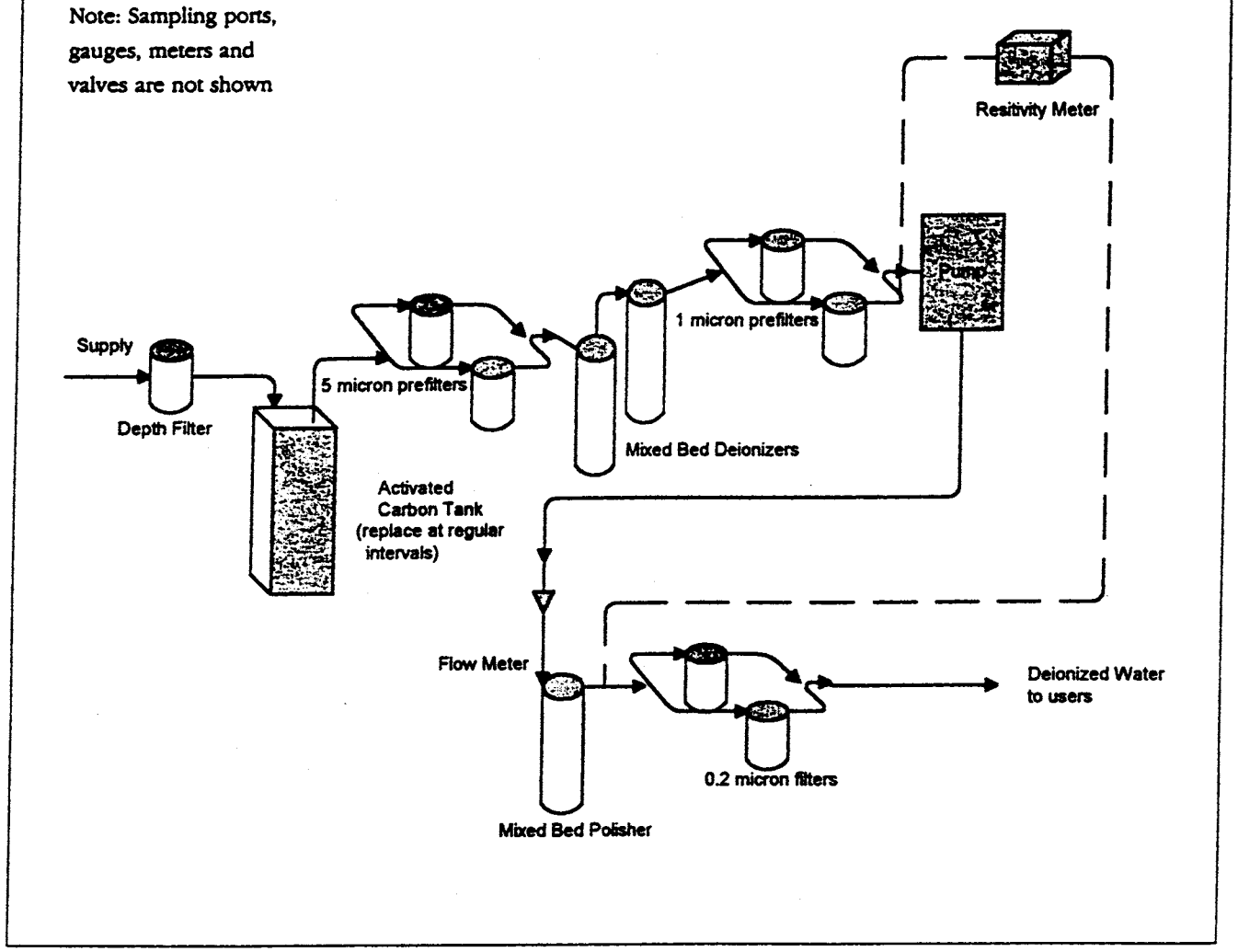
PRELIMINARY CONSIDERATIONS

Prior to the selection of the water system design, consideration must be given to the quality of the delivered water required for the current and proposed products to be manufactured. Over-design of the water system is not only initially expensive, but the ongoing maintenance can become unnecessarily burdensome with no return on the investment of time, money and personnel resources.

In order to determine the product sensitivity to water quality, several key issues need to be investigated. The system design project can begin by asking the following questions:

- Is there any evidence, documented or anecdotal, which suggests that the product formulation has the potential for adverse effects due to the water quality?
- What quality of water is used in the production of competitive or similar products? Is there an

Diagram 1: Typical Deionized Water System



industry standard that has become expected for use in the production of the current or proposed products? Does the water system need to provide deionized, purified or Water for Injection (WFI)?

• Is the product regulated by the Center for Devices and Radiological Health (CDRH), the Center for Biologics Evaluation and Research (CBER) or the Center for Drug Evaluation and Research (CDER)? What is the product classification? Is it a drug or is it a device?

• Does the product have preservatives? Is the product sterile? Is the product required to be pyrogen-free? What is the level of purity required for the product?

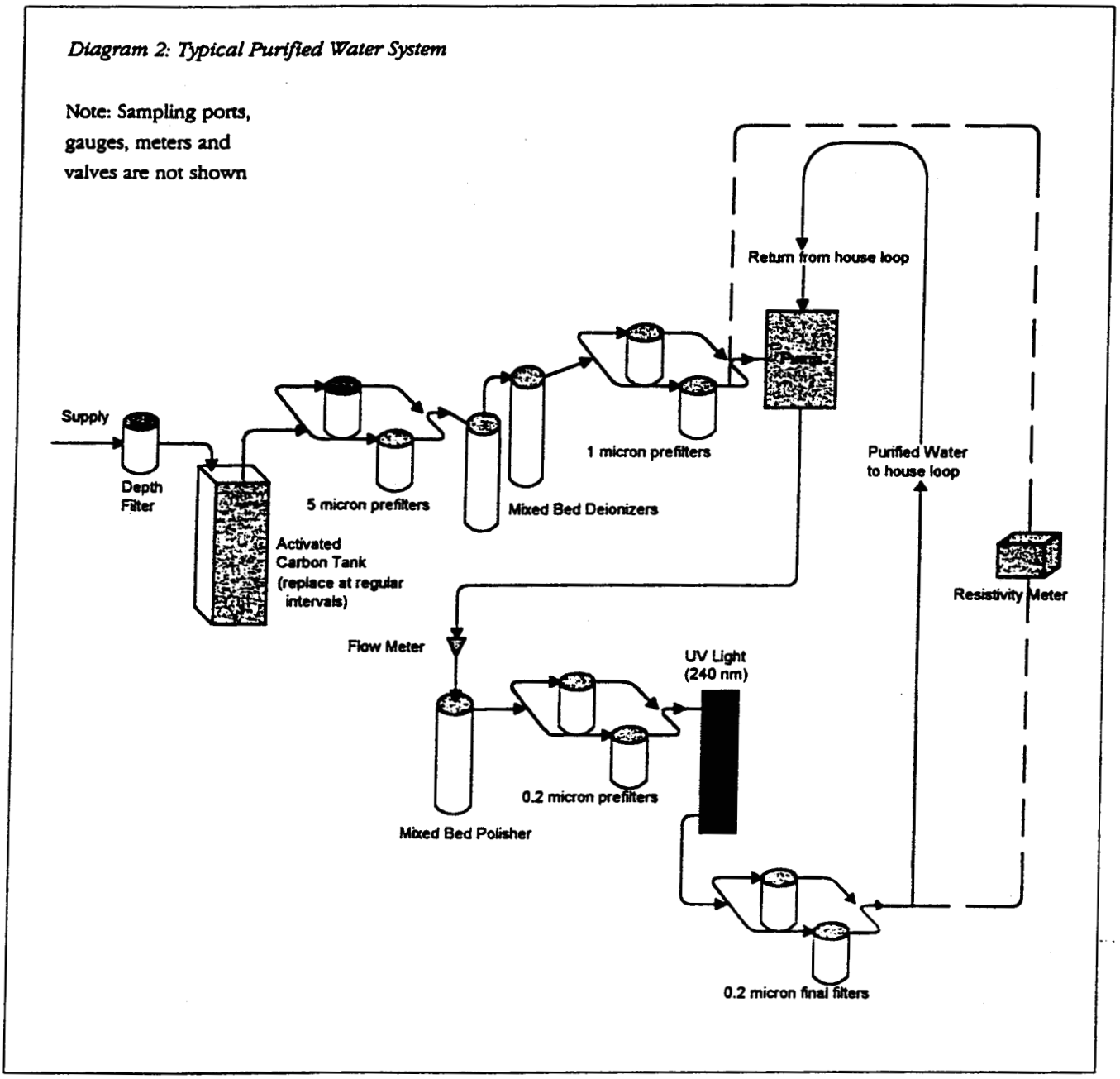
• Is water required as an ingredient in the product? Is water used in the processing? Is water only used for the cleaning of product contact vessels and equipment?

To address the capacity of the water system and the production needs, current and future, the following questions need to be addressed:

• What is the largest volume delivery currently needed? What is the largest volume needed for a distributed product during the first several years of market entry?

• What products are in development? What are the needs for these products?

Diagram 2: Typical Purified Water System



• Where will water be used in the facility? Do all points of use require the same quality of water? Do the volume needs vary between the use sites?

• Will the water be used directly from the use points or will it be stored in secondary containers? What is the length of time for storage and the expected volume to be stored?

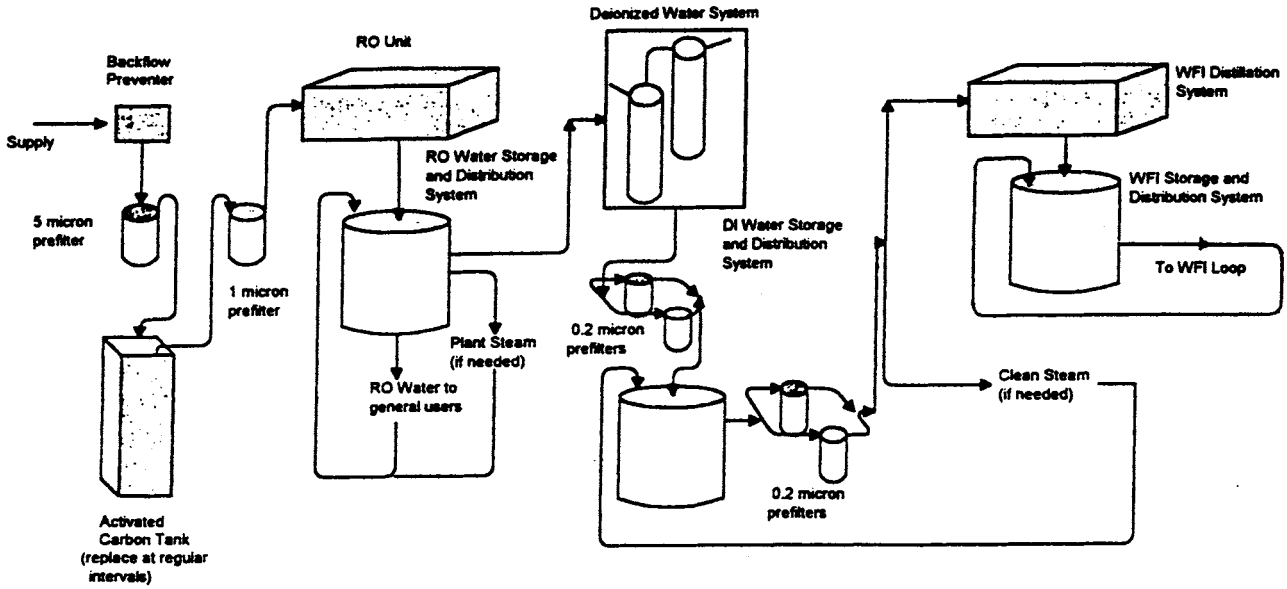
• Will the water be delivered to large volume use equipment, such as fermentation tanks or bulk reagent vessels? Will the water be used in the processing or cleaning of vials, large vessels, glassware and labware?

• Will the water be used for an autoclave, glass washer, or other equipment?

• What are the volume requirements for the equipment?

• Can water be collected and stored for "on demand use"? What is the regeneration time required to meet production needs?

Diagram 3: Overview of Production Sequence for Water for Injection



Considering the responses to the above questions, further evaluation must be made with respect to the material of construction. Materials used in the piping, storage tank, and on other water contact surfaces will depend on the quality of the water required. The expense of installing and documenting stainless steel versus plastic piping can be significant. In addition to the cost of construction, the required maintenance of the system over time should also be considered. The goal is to produce high quality water that consistently meets production requirements. If the system is expensive to maintain and resource demanding, a higher quality system design may be more cost effective in the long term. If the system design has the potential for contamination, it may also be more costly in the long term to install and maintain. The determination of the system cost versus the "product value" should be carefully evaluated in the final system design.

VENDOR SELECTION

The majority of newly founded companies do not have the benefit of having a facility engineer who is knowledgeable in water system design. It is therefore prudent for the design team to investigate the options that are available from vendors who specialize in the design and construction of water systems for FDA regulated industries. Much knowledge can be gained by having discussions with prospective designers and installers. With the basic needs identified, discussions will be significantly more beneficial and productive for both the company and the contractor. Identification of prospective vendors can be accomplished using several easy methods. First, and probably more effective, is to contact other similar industrial representatives. The network does work. Useful information may be gained by learning what worked (as well as what did not work) in the design and construction of other water systems used in other companies producing similar product types. Secondly, useful contacts can be made through conferences and meetings by visiting and discussing available services at the various vendor exhibits. In all cases, references should be obtained and investigated prior to serious discussions with prospective vendors. Vendor assessments should be made with respect to not only

their design input based on your projected needs, but also to the vendor's ability to meet expectations in the following areas:

- Final cost to original budget
- Timeliness and conformance to agreed upon time lines
- General responsiveness
- Knowledge of regulatory requirements
- Openness in discussion of the pros and cons of design options
- Agreement to provide justification for design preference
- Willingness to spend time in the plant with the users to assist in determining the system design needs
- Ease of start up and system operation
- Ability to provide required documentation timely
- Provision for maintenance contracts and troubleshooting support (Is there a local representative who will be on call in crisis situations?)
- Experience as a pharmaceutical vendor

Remember the contractor should be thoroughly familiar with the system operation. It is their primary business and they should be the experts. They should be able to easily address your questions and to provide the rationale for recommending one system over another.

SOURCE WATER CONSIDERATIONS

In the configuration of the system design, the source water quality must be considered. The local water company should be contacted by the design team and information obtained on the exact source of the water to be supplied to the facility. It should be determined if the water source has the potential to change depending on shortage or other factors. Seasonal variation should be discussed with respect to such things as algae blooms, increased silica during low reservoir states, etc. The water company should be able to provide periodic test reports and these should be compared to available water quality standards. Actual results should be reported and not a "pass or fail" qualifier. The water company should also be able to provide some in-sight as to what potential contaminants should be monitored and how often testing should be performed. The information gathered from the local water district should be added to the file and provided to the selected design and installation contractor. This information should also be reviewed during the development of the validation protocol, which will be addressed in Part 2.

The source water quality will have a definite effect on the design, selection and maintenance of the system components. The cost considerations for the maintenance of the components need to be factored into the system selection. In the event the source water is of particularly low quality, additional components may be needed or the preventative maintenance (for example, system component replacement and/or deionization resin regeneration) may need to be significantly increased.

PRELIMINARY DESIGN

Once some of the preliminary questions have been addressed and several prospective vendors have been identified, meetings should be held with each vendor to begin the process of designing the required system. There are numerous options and it is essential that system requirements are understood in order to provide specifications to the vendors. It is not unusual, however, for the details of the specifications to be incomplete at this stage, but it is important to work with the vendors and complete the design specifications through your discussions. The vendors will come prepared with a series of questions that will enable the design team to more accurately draft the design that will meet your requirements. Obviously, the more answers you have to their questions, the better suited the design will be. When dealing with several vendors it is extremely important to maintain the information shared with you during your discussions as confidential. It is

not acceptable to play one vendor against the other with the bidding process or design development. Each vendor should develop their own independent cost estimates with their own proposed system design.

Some of the potential vendors may be able to provide the piping for the loop and have the capability of installing the piping. If this is the case, discussions should be held at this same time to specify the required piping materials needed for construction as well as location of the points of use. If the vendor is not able to provide support for the loop, it will be beneficial to have separate meetings with the prospective piping vendors. Once the piping and water system contractors are identified, joint meetings with both groups should be held to coordinate the project. Consideration should be given to companies who have worked together successfully on other projects.

QUOTATIONS AND FINAL VENDOR SELECTION

Once the specifications have been developed for both the piping and the water system components, official bids should be provided to a minimum of three prospective contractors. The same information must be provided to all companies who are being asked to quote on the project. Upon receipt of the quotations, they need to be reviewed carefully for completeness and accuracy. The described options should be compared to the specifications and all components required should be listed with full descriptions and individual pricing.

In addition to the accuracy and completeness of the quotation, several other parameters should be considered along with the price for vendor selection. The questions that should be asked include:

- How soon did the vendor respond to the quotation?
- Was the sales person helpful and responsive?
- Did the sales person try to sell you a system that was different from the one you thought you needed?
- Were the questions asked during the design phase of the system meaningful?
- What is the service record for the system (obtain this information from the provided references)?
- Is there a local representative who can respond on 24 hours notice?
- What is the lead time for the system?
- Does the vendor have a reputation for "on time" installation and being responsive to system problems?

PLACING THE ORDER

Considering the specifications and agreed upon quotation, the purchase order can be prepared. It should be made very clear what you are getting for the quoted price, so it will be important to once again list the services and support items you anticipate receiving with the system. The following items need to be included:

- A complete drawing of the system that has been designed. Each component should be clearly identified with the manufacturer, model number and price along with other descriptive terms for clarity. This should include such items as deionization tanks, filters and housings, valves, sampling ports, gauges, UV lights, pumps, relief values and storage tanks.
- A full description of each component that will be included with the selected system. This should include material identification and a tracking record for all product contact surfaces.
- Written procedures on the vendor's preferred sanitization and start up procedures.
- Written procedures for calibration of the equipment.
- Written procedures for the service on the equipment and recommendations for a preferred service provider.
- Written operation procedures for the system along with specifications for such variables as pressure differentials between gauges, and resisitivity.
- Recommendations for corrective action when the actual readings do not meet the established specifications.
- Written procedures for the installation of

new filters into existing housings, and regeneration of the deionization beds.

• Other supporting documentation, such as validation guidelines or recommendations, as well as other operational procedures.

• Spare parts list and recommended spare parts to stock.

It is important to negotiate for this documentation when the order is placed so the expectations are clearly understood by both parties. The vendor is the expert and has access to a significant quantity of reference documents as well as resource information based on historical experience.

If an arrangement can be made to have the drawings and component information provided early, a draft of the installation qualification section of the Water System Validation can be generated. With this section completed, it can be used when the technicians are actually installing the system components. This saves time, money and resources.

POTENTIAL PROBLEMS IN DESIGN SELECTION

When the time is not spent to properly plan, there can be significant problems which result. These include some of the following potential frustrations:

- The system is incapable of operating with extreme source water variation.
- The flow is inadequate to support the needs.
- The sampling ports are not adequate to provide a "clean" sample.
- The valves selected are not easily sanitized and allow contamination to occur.
- The sampling ports are not located to provide for ease of access and are not properly placed to appropriately monitor the system performance.
- There are not enough use points or too many use points.
- There are dead legs. Note: Dead legs should not exceed six pipe diameters in piping length.
- There is no flow during non-use periods.
- The system is not designed or constructed to provide the quality of water required for the particular product type.
- The carbon beds are not designed to provide for proper sanitization and to minimize bacterial growth.

CONCLUSION

Although time consuming and frustrating, the design planning for a water system will result in a high return for the time invested. Investigating what is actually needed, evaluating the pros and cons for the various options, talking to other users, and gaining in-depth knowledge of how water systems operate will have significant benefit. A well-designed system that meets the production needs, is well maintained by trained staff members, and monitored regularly (and correctly) will result in high quality and consistent water. Down time, troubleshooting and potential product problems will decrease cost and inefficiency plant wide. Spend the time upfront and design the system based on facts, not speculation.

In Part 2 or this two part series on "Water Systems: The Basics", the second article will address installation, start up, validation, sanitization, monitoring, sampling, testing, and maintenance of water systems. ■

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WATER SYSTEMS: THE BASICS

Part 2: Validation and Maintenance

Part 1 of this article, which appeared in the February issue of the Journal, discussed preliminary considerations for the selection of a water system design and vendors for installation and maintenance. This part will examine the installation, start-up, validation, operation, and maintenance of water systems.

PRE-INSTALLATION CONSIDERATIONS

Following the placement of an order, the first step a company should take is to request documentation on each component of the system. (It is not uncommon to ask a vendor for multiple copies.) This documentation should be reviewed carefully, prior to the delivery of these materials, for discrepancies between the original order and components scheduled for shipment. If inconsistencies exist, resolve them as quickly as possible.

You also should review all drawings and weld inspection reports before installation. The documentation received should be complete enough to allow for the preparation of the first draft of the validation Installation Qualification protocol. In turn, you can schedule the delivery of materials to ensure that the individuals involved in the validation are present at the time of receipt.

DELIVERY INSPECTION

When materials are delivered, the shipment should be inspected for damage. Bring any visible damage to the attention of the shipping company and the vendor. Remember to compare the shipment to the packing list and the components listed on the original order. If changes to the system occur, such as a substitution of materials or components that do not meet specifications, record these carefully.

All items, such as piping and fittings, should be verified for proper length, diameter, and quantity. Be sure to resolve any discrepancies prior to the start of construction. The review and verification of the delivery, as well as any deviations, should be documented and maintained in the water system files.

Store delivered materials in a clean area, keeping all protective packaging intact. For example, end caps should remain on piping. Taking such precautions also will minimize potential damage and contamination. To avoid the relocating and additional handling of materials, prepare the storage area prior to delivery.

INSTALLATION OF HOUSE LOOP

The installation of the house loop should be coordinated with the validation team, which is responsible for monitoring, inspecting, and documenting the loop. Dead legs, of any length, should be minimized. Inspection should include verification that dead legs do not exist in the loop's main body or at sampling valves and ports, which exceed six internal pipe diameters.

If the system is constructed with stainless steel piping, you will need to inspect the welds, all of which should be made using orbital automatic welding equipment. If manual welds are used, they should be inspected according to strict welding standards. Include the weld map and log, as well as the boroscope inspection report, in the water system files. After the piping is installed, inspect it for leaks using clean air or filtered nitrogen. All piping should be labeled with the flow

direction and type of water, deionized or Water for Injection (WFI), in the loop.

INSTALLATION OF SYSTEM COMPONENTS

Installation should be verified using assembly drawings and specifications. At the very least, indicate any deviations on the blueprints, which you should use to finish the "as built" drawings. After installation is complete, a final review should be made to ensure the documentation accurately reflects the system and meets all specifications and minimum quality requirements.

PASSIVATION AND SANITIZATION AFTER INSTALLATION

Following the installation, the system should be cleaned and prepared for use. If the system is stainless steel, piping will require passivation in order to make the system more resistant to corrosion. Some of the most common solutions used for passivation of stainless steel are non-toxic chelants. Before planning the passivation, it is advisable to obtain professional advice from specialists in the field.

Once passivated, the system should be sanitized to remove undesirable elements and to decrease bacterial load. If the system is constructed from materials other than stainless steel, flush it well prior to sanitization. The method chosen for sanitization is dependent on the specific materials used in the system construction.

START-UP

Time should be allocated for start-up and commissioning before Operational Qualification validation testing is scheduled. The commission of a water system should include representatives from the water system vendor, design company, and your firm. Most water systems are custom designed with respect to the in-house piping, which can cause unique problems during the initial start-up. However, with the appropriate personnel on hand, the rest of the commissioning should proceed smoothly. The documentation of changes made to the design during start-up is essential for the validation package.

INSTALLATION QUALIFICATION

Identify and document utility requirements, as well as each piece of equipment and piping, during IQ. This documentation should include the surface area of the ion-exchange resins and the specification for regenerant chemicals.

The format of the IQ varies from one company to the next. However, the following sections should be included:

- *Equipment Description and Overview* – Provides background design information, a description of the quality of water the system is intended to supply, and a functional description including each process step.
- *Equipment* – Provides specific identification for each component and piece of equipment in the system. This should include information on valves, monitoring devices, filters, filter housings, storage tanks, ports, as well as materials of construction, the chosen vendor, and specifications.
- *Electrical Equipment* – Provides specific information on electrical equipment. This should include details on the panel locations, as well as safety information.
- *Other Utility Equipment* – Identifies other utilities which may be required by the system equipment.
- *Drawing Location* – Provides the storage location for drawings, manuals, and technical information supplied by vendors and installers.
- *Calibration Records* – Provides identification of the equipment which requires calibration, the actual calibration records, and the due date for the next calibration. Additional information should include traceability to the National Institute of Science and Technology (NIST) standards. Instrumentation generally is calibrated prior to OQ, which should include calibration status.
- *Installation Qualification Protocol* – Provides an outline for the verification of each piece of equipment for installation, labeling, and location. The IQ protocol must be very detailed and specific to the system being validated. It also must document that the system has been installed according to manufacturer instructions and specifications.

• *Standard Operating Procedures* – Provides a list of all applicable procedures and should include current revisions at the time of validation. Typically, these are drafted during OQ and refined during Performance Qualification.

• *Preventative Maintenance Procedures* – Provides a list of all applicable maintenance procedures and should include current revisions at the time of validation. Typically, these are drafted during OQ and refined during PQ.

OPERATIONAL QUALIFICATION

OQ should provide the protocol with the test functions and describe specifically the items to be inspected and tested. The protocol should describe clearly how many replicate tests should be done in order to verify each parameter being evaluated. It also should include an introduction outlining the purpose of the inspection and a list of materials, methods, and test functions to be used.

Test functions should explain the parameter to be tested, the purpose of the testing, acceptance criteria, and the procedure to be followed. Make sure to include tests that verify the following:

- Adequate flow
- Low volume of supply water
- Excessive pressure drop between pressure valves
- Resistivity drop below set points
- Temperature drop or increase beyond set levels (for hot WFI systems)
- Operational range of flow rates
- Recirculation to minimize intermittent use and low flow

Your first OQ step should be to verify that the operation of the system is properly described in the draft SOP. The protocol for system operation should be developed using the vendor manual, as well as other published references for water system validation. Following verification of the system, you should test for the following:

• Check the system to determine whether it's operating according to the written procedure.

• Determine whether critical parameters, such as the minimum circulating pressure and return pressure, are maintained.

• Verify the alarm settings, including low water level, resistivity changes, and excessive pressure differentials. (Because of safety issues involving testers and equipment, the simulation of some alarms may be advisable.)

PERFORMANCE QUALIFICATION

During the PQ phase, you should develop a sampling plan which helps verify the water quality being supplied by the system. The format of the protocol is the same as the OQ. It should clearly describe the number and location of samples to be taken and how they should be tested. Each test function should outline the purpose, acceptance criteria, and procedure for testing the parameter of interest. These PQ functions should include testing samples for microbial, endotoxin, and chemical contamination. The sampling plan for evaluating performance should be defined in the PQ.

TEST REPORTS

At the completion of each qualification phase (IQ, OQ, and PQ), you should write a comprehensive report to summarize validation findings. It is becoming common practice to validate water systems for an entire year. (It should be noted, however, that chemical, microbial, and endotoxin monitoring and trending never ends completely.) Since this interval is extensive, interim reports should be prepared reviewing available data to date. (You should compile a comprehensive report at the end of the study.) Data obtained during validation must support your summaries. It is advisable to include all raw data in the appendix of the report. This data should be accurate, complete, and well-labeled, specifying when it was finished, who performed the testing, and the samples or sites tested and inspected.

RE-VALIDATION

The period or conditions for re-validating the system should be defined and documented early in

the validation cycle. Circumstances requiring re-validation include:

- A change in system design which potentially could effect flow rates, temperature, storage, delivery, sampling, or water quality
- The consistent surpassing of alert and action levels
- Product failure or performance problems, which may be caused by water
- A change in sanitizing agents or procedures

While re-validation does not necessarily require a complete repeat of IQ, OQ, and PQ, it is a good idea to use previously written protocols as models for the development of the re-validation protocol. The new protocol should contain the key inspections and tests that will enable a thorough evaluation of system capabilities. For example, re-validation may include increased sampling and/or testing for chemical, endotoxin, and microbial contamination.

SANITIZATION

The primary method of controlling microbial contamination in water systems is through the execution of sanitization procedures. Properly performed sanitization removes potentially hazardous elements, reduces the microbial load, and results in water quality which meets the USP requirements for purified water.

Water systems can be sanitized using either chemical or thermal methods. In either case, design considerations are essential in choosing a method. You cannot sanitize a water system if the design has not taken into account the method to be used and how sanitization will be performed.

One of the primary concerns in a water system is the build-up of biofilm generated from common water-borne micro-organisms, such as Pseudomonas aeruginosa. This biofilm may prevent effective sanitization when using in-line ultraviolet lights at wavelength 254 nm. Ultraviolet lights may require combined use with either chemical or thermal sanitization methods.

Thermal methods used for sanitization may require periodic or continuous circulation (8 to 12 hours) of hot water (65-80°C) or the use of steam. (Other combinations of time and water temperature also may work.) Obviously, up-front planning at the design stage is necessary to utilize these methods, which call for the compatibility of components, such as stainless steel and selected polymers, with elevated temperatures.

Chemical sanitization may be used on a wide variety of materials, but it is necessary to verify the compatibility of the chosen chemicals with the materials of construction prior to their use on the water system. Remember also that vendors may recommend sanitizers for a system. Chemicals commonly used include:

- 0.2-10% Hydrogen Peroxide
- Ozone
- 0.5-1.0% Peracetic Acid
- 0.5% Sodium Hydroxide
- 0.25% Hydrogen Peroxide in a 1% solution of Sodium Hydroxide
- 10ppm Hypochlorite

Any sanitization method will require validation to demonstrate and document its effectiveness, as well as its removal of sanitization chemicals. This validation should include temperature distribution for the thermal methods. The validation for the chemical methods should verify that an appropriate concentration of chemicals was distributed throughout the system.

The schedule for sanitization is determined by system performance. You can chart the frequency of the sanitization by appropriately monitoring for micro-organisms at various sampling points in the system. When used with proper alert and action levels, this procedure will ensure the sanitization schedule chosen is adequate to maintain a consistent supply of high quality water.

SAMPLING

All samples must be labeled properly with date, time, and location. You also may include the system description and technician who took the sample. In addition, you must document the method

Table 1. Potential Problems In Sampling, Testing, and Maintenance

❑ SAMPLES NOT TESTED FOR THE PRESENCE OF TOTAL AND FREE CHLORINE.
❑ FILTERS, NOT CHANGED ON A REGULAR BASIS, BECOME OVERGROWN WITH MICROBES.
❑ SYSTEM NOT MONITORED FREQUENTLY ENOUGH TO PROVIDE EARLY WARNING FOR UPSTREAM CONTAMINATION PROBLEMS, WHICH RESULTS IN CONTAMINATED WATER AT USE POINTS.
❑ INDIVIDUALS TAKING SAMPLES ARE TRAINED IMPROPERLY AND SAMPLES BECOME CONTAMINATED, WHICH RESULTS IN EXCESSIVE OVER SANITIZATION, DOWN-TIME, AND INCONSISTENT/INACCURATE DATA.
❑ SAMPLES NOT HELD LONG ENOUGH TO ALLOW SLOW-GROWING BACTERIA TO DEVELOP. (COMMON PRACTICE IS TO HOLD CULTURES FOR TWO DAYS, THEN COUNT AND DISCARD THEM. A MINIMUM FIVE TO SEVEN DAY READ IS STRONGLY RECOMMENDED.)
❑ SANITIZATION METHOD AND/OR AGENT IS INEFFECTIVE.
❑ CHECKS NOT PERFORMED TO ENSURE THE SANITIZING AGENT HAS BEEN REMOVED.
❑ SYSTEM HAS NOT BEEN VALIDATED AND ITS OPERATING CHARACTERISTICS ARE NOT KNOWN OR DEFINED.
❑ PROPOSED ACTIONS ARE NOT TAKEN IN A TIMELY MANNER TO PREVENT EXCESSIVE SYSTEM CONTAMINATION ONCE ALERT AND ACTION LIMITS ARE ESTABLISHED.
❑ UNRELIABLE VENDORS ARE CHOSEN FOR THE REGENERATION OF THE DEIONIZER BEDS, WHICH RESULTS IN CHANNELING OR INADEQUATE PROCESSING.
❑ MONITORING DEVICES NOT PROPERLY CALIBRATED OR NOT APPROPRIATELY PLACED IN THE SYSTEM.
❑ STAINLESS STEEL PIPING AND TANK NOT PASSIVATED TO MINIMIZE CORROSION FOR A WFI SYSTEM.
❑ MULTIMEDIA BED IS HEAVILY CONTAMINATED WITH MICROBIAL BIOBURDEN, WHICH RESULTS IN CONTAMINATION OF THE ENTIRE SYSTEM.
❑ WATER SOFTENER COMPONENT IS NOT ADEQUATELY MAINTAINED AND BECOMES A SOURCE OF CHEMICAL AND MICROBIAL CONTAMINATION FOR THE ENTIRE SYSTEM.
❑ DATA IS NOT ROUTINELY REVIEWED AND CHARTED FOR TRENDS.

of sampling exactly. For example, will hoses and flushing be part of the sampling procedure? All individuals involved with the sampling must be trained to follow the written procedures precisely. (See Table 1.)

Microbial Sampling

Since sampling and frequent monitoring is required to ensure a water system is operating in a state of control and consistently provides high quality water which meets specification, it is important to take samples from points in the system that accurately reflect its operating state. In addition, samples of the source water should be taken periodically to check the quality of the system's feed water. Initial sampling should be performed frequently. Completion of the final sampling plan is dependent on the results from the validation. Other considerations for determining the frequency of the sampling include the location of sample ports and the type of water being sampled.

In all cases, samples must be representative of the water being tested and not influenced by either the sampling technique or the sample port design. This requires sanitization and pre-flushing of sample ports, as well as extreme care in the collection of the sample. It is not uncommon to have samples contaminated due to the manner in which

they are collected, leading to test results which require follow up, repeat work, and explanation. All of this type of work can and should be avoided. In the event of high and unexpected results, it is important to review the data with the sample location to determine whether the results are suspect or elevated due to technique.

Sterile glass bottles often are used for the collection of microbial test samples. However, sterile disposable polypropylene tubes and other sterile containers also can be employed. You may use collection containers more than once, provided the cleaning procedure is validated.

The sample volume for membrane filtration used by many manufacturers is 50-100 mL from each sample port. For WFI, some manufacturers employ 100-300 mL samples for increased sensitivity. These larger sample volumes are necessary for precise determination of low level contaminates. Use of volumes less than 50 mL per sample port is not recommended due to the inaccuracy of low level contamination.

Samples collected should be stored and tested promptly in a manner that minimizes potential for microbial growth. It is not advisable to store samples for periods longer than 24 hours prior to testing. (Remember that temperature is critical to storage duration.) Adding stabilizing agents to a sample, which will be tested for microbial contamination, is not recommended.

Chemical Samples

Sample containers for water testing of chemical contaminants must be extremely clean and made of high quality glass or plastic. If you have not demonstrated that container materials are free of leachables and extractibles (e.g., residual monomers, residual solvents, byproducts from irradiation, etc.), then do not use them for sample collection.

If low quality containers are used for sample collection, erroneous results may result. Today, during the first phase of water testing, many companies are employing analytical methods, which are more sensitive than USP methods, in order to "fingerprint" water quality. High quality containers are essential when using such analytical methods.

Endotoxin Samples

Samples of endotoxin require extreme care to avoid pyrogen contamination. For this reason, test samples should be taken in depyrogenated glassware. Do not add preservatives to the sample unless specified by the vendor's approved testing procedure. Samples should be tested promptly. Our recommendation is to not store them.

TESTING

All test results should be recorded, dated, and signed by the individual performing the tests. A second individual, knowledgeable in the testing methods used, should review and sign the individual test reports, as well as a final summary report.

Microbial Testing

The method chosen for microbial testing needs careful consideration in regard to sensitivity, recovery, selectivity, incubation time/temperature, costs, ease of testing, and reproducibility. Test method options include:

- Pour plates
- Spread plates
- Membrane filtration
- A variety of instrumental approaches, such as direct microscopic counting

Usually, our method of choice is membrane filtration, which utilizes a 0.45 micron filter, 100 mL sample size, Plate Count Agar, and an incubation of 48-72 hours at 30-35°C. Preference to this method is due to its increased sensitivity. An alternate, commonly-employed method is the Pour Plate technique, which utilizes a 1.0 mL sample volume, Plate Count Agar, and an incubation of 48-72 hours at 30-35°C.

Although the minimum incubation time and temperature is listed in many references as 48 hours at 30-35°C, it is a good practice to incubate the media an additional 5-7 days at 20-25°C. This additional incubation time at room temperature allows slower growing organisms to develop visible colonies.

The standard media used is Plate Count Agar. A "low" nutrient agar, it is beneficial for isolating slow growing bacteria, which either have been injured by exposure to disinfectants or prefer by nature to grow in less nutrient-rich media, such as Pseudomonas (one of the most commonly found water contaminants).

During the validation of a new system and then periodically afterwards, you should identify recovered organisms according to species or genus. A limited number of contaminating organisms typically are found in high purity water. Once the preliminary identifications are made and the cultural and growth characteristics are known, it is adequate to monitor the type of organism without characterization. Organisms may be identified by colonial morphology and staining characteristics. Colonial morphology refers to the organism's shape (spreading, convex, flat, or heaped), texture (smooth, rough, firm, or mucoid) and color (transparent or opaque.) Staining characteristics refer to whether its gram positive or negative and spore or non-spore forming.

Endotoxin Testing

Gram negative organisms, commonly found in water, are known to form biofilm. These bacteria contain endotoxin, a lipopolysaccharide component, in the cell envelope. Endotoxin is problematic because it causes pyrogenic reactions (fevers) in humans and animals and may lead to performance problems with device and diagnostic products.

Testing for endotoxin is performed most commonly using the Limulus Amebocyte Lysate (LAL) System rather than the rabbit test (direct injection) for pyrogens. Endotoxin testing methods include:

- Gel-clot
- Chromogenic
- Endpoint- or kinetic-turbidimetric techniques

These methods require validation according to the "Guideline on Validation of the Limulus Amebocyte Lysate Test as an End-Product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products and Medical Devices."

Endotoxin tests, which are sensitive to contamination, call for great care to avoid inaccurate results. The testing procedure for the chosen method should be read and followed carefully.

Chemical Testing

Tests are performed for many attributes, including:

- Appearance
- pH
- Odor
- Specific resistance
- Non-viable particulate matter
- Chloride
- Sulfate
- Heavy metals
- Ammonia
- Calcium
- Carbon dioxide
- Oxidizable substances

Test methods, along with the procedures for preparing the various test solutions, are described fully in the USP. Though they are respected standards, questions have arisen regarding their sensitivity and reproducibility. Therefore, some companies are moving toward automated analytical methods that offer added detection capability.

ALERT AND ACTION PROGRAM

Water systems must be monitored to confirm that they operate within their specified parameters and produce water of consistently high quality. You may set specifications for testing using either published ranges or levels tightened internally. Acceptance criteria may be different for specific sampling ports. Usually specifications are less stringent for "upstream" sampling ports and more stringent at the point of use, where the water is most pure.

By carefully selecting sampling points and the operating specifications at those points, you can monitor the system very successfully with the use of alert and action levels. An alert level is defined as the range that, when exceeded, indicates a

process may have drifted from its acceptable operating level. When this range is exceeded, corrective action is not required, but an investigation is necessary to determine the cause. Reaching the alert level should serve as a warning. Once water enters this stage, it is necessary to consistently check and maintain the system to avoid the occurrence of this problem.

When specifications exceed accepted USP limits, the process moves into the action level, a range that indicates a process actually has drifted from its normal operating range. This stage requires investigation and corrective action to bring the system back to an acceptable operating state.

In the event the system enters the action level, consideration of the product manufactured during the alert and action intervals is required. To ensure that the product has not been compromised, additional testing of the product may be necessary. Because such extensive testing is required for some products to demonstrate that they have not been effected by water used during an action level, some manufacturers have chosen to shut down production once the water reaches this critical range. Remember that, since products are regulated very tightly by the FDA, restrictions may preclude the use of water while it is at an action level.

As part of the Alert and Action Program, periodic reviews should be performed on the data collected. (Conduct the first as soon as possible.) Evaluate data for possible trends and any potential correlations between system performance and maintenance. A written evaluation and summary of the trend analysis should be prepared, distributed, and reviewed.

Microbial Limits

Current literature dealing with pharmaceutical grade water lists generally accepted microbial action levels at 100 colony forming units/mL for purified water and 10 colony forming units/mL for WFI. These levels are based on the membrane and pour plate methods described earlier. If other methods are used, new limits should be established and validated.

Endotoxin Limits

Limits for endotoxin in USP purified water are not required. However, testing should be done for endotoxin if the USP purified water is source water for a WFI system. Still, many manufacturers only guarantee a 2.5 to 3.0 log reduction in endotoxin levels, which means a purified system at 250 EU/mL is not acceptable as feedwater. The specification for endotoxin in WFI is not more than 0.25 EU/mL.

MONITORING

Routine monitoring is required in order to ensure the system is operating in a state of control. The data collected from mechanical rounds, as well as microbial and chemical testing, should be reviewed and entered in a trend analysis program. This allows for an efficient method of evaluating process performance. Furthermore, this information may be used to predict when and where the system may drift from normal operating parameters.

The validation test report is a key link between information found during qualification testing and requirements for monitoring system operation. SOPs are required to document each established monitoring procedure.

Checklists are extremely useful for ensuring all specified points are monitored according to the planned schedule. All pertinent observations must be recorded.

Daily monitoring of all water systems should include observations of the following:

- Pressure gauges
- Temperature
- Flow rate
- Storage tank level
- Feedwater quality
- Product water quality

As a minimum for WFI, daily samples should be taken at one point-of-use port and tested for chemical and microbial contaminants, as well as endotoxin. (It should be noted, however, that this depends on the system in question.) At the very least, you should test all use points weekly.

Additional samples from upstream system ports, such as incoming municipal water, also should be taken weekly and tested for chemical and microbial contaminants.

For purified water systems, you usually take samples from all points of use and test them for microbial contaminants every week. Chemical testing should be done monthly on samples from all sampling ports.

MAINTENANCE

Maintenance actually begins as early as the design phase. If an easily maintainable system is not designed, problems with the product and/or schedule will result.

Keep a maintenance log, which includes records of all equipment used to calibrate, maintain, and monitor your water system. All critical equipment should be on a calibration program. The type of equipment used to measure calibration standards includes:

- Millivolt potentiometer
- Stop watch
- Thermometer
- Manometer
- Pressure gauges

If the system or any part of it is not in operation, you should explain the situation in the maintenance log.

Depending on the water system design, daily preventative maintenance, which should be documented, should include, but not be limited to, the following inspections:

- Tank level, temperature, and pressure
- Instrument air pressure
- Supply and return temperatures
- Feedwater flowrate, pressure, and quality
- Column temperature
- Condenser temperature
- Production rate
- Delivery temperature
- Product water quality (conductivity)

Include additional checks after review of the system manuals. A checklist is strongly recommended.

Perform additional preventative maintenance on a monthly basis. Inspect all valves and fittings to ensure smooth operation. Any defective fitting or part should be replaced. System pumps should be inspected for leaks, wear, or damage.

In addition to monthly maintenance, preventative maintenance should be performed on a quarterly basis. Review operating logs to ensure the system is operating in a state of control and within all established parameters. (You may want to do this on a daily basis.) All filters should be inspected and replaced where necessary. If strainers are used in the system, make sure they are disassembled, cleaned, and replaced when necessary. If steam is used in the system, the trap should be disassembled and inspected. Replace or repair defective parts. A test of alarm setpoints for low and high water levels should be performed.

You also should perform maintenance on an annual basis. If sterile vent filters are used in the system, they should be replaced. Test the integrity of new and old filter units. Setpoints of the temperature display and the alarm system should be verified by simulating alarm conditions. If steam is used, inspect and test the safety valve. If the valve is found to be defective, it should be replaced (or repaired by an authorized repair company). Piping gaskets and diaphragms should be inspected and replaced when necessary.

You must replace activated carbon beds and recharge the deionization beds on a regular basis. Validation data, as well as vendor recommendations, will determine frequency schedule for tank replacement of these components. Source water varies widely by location, and the quality of the source water has a direct impact on the maintenance schedule for tank media and filter changes.

If improper sanitization is occurring, the build-up of microbial growth increases during the time between carbon bed and deionization tank service. The flow rates, temperature, and bed surface area all effect the build-up of contamination. Special care should be taken during system shut down and intervals of low usage. The "recharge

indicators" may not be a good indicator of the tank condition. Water systems will require continuous maintenance to ensure optimal performance.

CONCLUSION

Water is a key ingredient for many products, and continuous high quality is essential to meet production schedules and product specifications. Proper validation of the installation, operation, and performance of the water system is critical to ensure this continuous supply of high quality water. In addition, and as is true with most complex systems used in industry, water systems require careful monitoring, reproducible testing, and regularly scheduled maintenance. With the combination of a well-designed, validated, and well-maintained water system, the quality of the water produced can be ensured.

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For related articles, see the following issues of the *Journal of Validation Technology:*

February 1995

1. Bob Elms and Cindy Green, *Water Systems: The Basics – Part 1, Design as a Prelude to Validation*

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Benjamin J. Roczniak

A GUIDE TO VALIDATING A PURIFIED WATER OR WATER FOR INJECTION SYSTEM

Validating a pharmaceutical water system is a detailed process that documents and confirms the proper installation, operation, and performance of the system. Validation starts in the conceptual stage and requires interface with the overall project and facility validation efforts. It is imperative that anyone participating in installation, operation, and performance qualification become involved from the beginning.

Sometime this year the requirements for pharmaceutical grades of water will be updated. These changes most definitely will effect current systems

Table 1. Current USP XXII Water Standards

CONSTITUENT	PURIFIED WATER	WATER FOR INJECTION
pH	5.7-7.0	5.7-7.0
Chloride	≤0.5 mg/L	≤0.5 mg/L
Sulfate	1.0 mg/L	1.0 mg/L
Ammonia	≤0.1 mg/L	≤0.1 mg/L
Calcium	≤1.0 mg/L	≤1.0 mg/L
Carbon Dioxide	≤5.0 mg/L	≤5.0 mg/L
Heavy Metals	≤0.1 mg/L as Cu^{+2}	≤0.1 mg/L as Cu^{+2}
Oxidizable Substances[3]	Passes USP Permanganate Test	Passes USP Permanganate Test
Total Solids	≤10 mg/L	≤10 mg/L
Total Bacterial Count	100 CFU/ml[4]	0.1 CFU/ml[6]
Endotoxin[5]	None Specified	0.25 EU

1. The USPC chemical test methods (excpt for pH and Total Solids) are quantitatively based on visual methods.
2. The concentrations listed are the determined numberial equivalents for those tests.
3. Limits for other heavy metals may be determined. Limits for specific oxidizable substances may be determined.
4. Action Guidelines for Microbial Contral of Ingredients Water as issued by the USPC is 50 CFU/ml, effective November 1, 1983. It should be noted the manufacturers frequently impose more stringent internal guidelines.
5. As determined by LAL test.
6. 1992 Action Guidelines.

Table 2.
Proposed USP Water Monograph Changes

CURRENT	PROPOSED
pH	Keep
Endotoxin	Keep
Calcium	Conductivity
Sulfate	Conductivity
Chloride	Conductivity
Ammonia	Conductivity
Carbon Dioxide	Conductivity
Oxidizable Substances	TOC
Heavy Metals	Delete
Total Solids	Delete
Coliforms	Delete
(Microbial Count)	Add (info chapter)

in operation, as well as new systems under design and review. Current and proposed standards are detailed in *Tables 1, 2,* and *3.*

It is important to note that the proposed changes will allow the use of on-line instruments, instead of the currently employed wet chemistry, which includes some tests that date back to 1840. Though these on-line instruments are expensive and must be calibrated regularly, they will reduce lab operating and equipment costs greatly. In addition, they will provide continuous monitoring and trouble-shooting capabilities.

It is easy to see that these changes also will effect the way water systems are validated, as companies will rely more on instrumentation and less on lab work. Standard operating procedures (SOPs) will focus more heavily on traceable calibration procedures and certificates rather than laboratory test procedures.

In addition, the proposed changes may have an impact on system design, and, in some cases, additional treatment may be required. *(See Table 4 on the following page.)*

The lesson here is that validation of a pharmaceutical grade water system is no easy undertaking. Only a painstaking, detailed effort by a team

Table 3.
Proposed USP XXIII Water Standards

pH	5.0 - 7.0
Total Organic Carbon	maximum 500 ppb
Conductivity	Limits of 4.7 to 5.8 µs/cm (depending upon pH)
Bacterial Counts	Purified Water 100 cfu/mL WFI 10 cfu/100 mL
Endotoxin	0.25 EU per LAL test - WFI only

of professionals will ensure its success. To help simplify this process, a step by step procedural outline follows.

STEP #1 – ASSEMBLING A VALIDATION TEAM

It is very important to put a validation team together before starting the project. Engineering, maintenance, quality assurance, compliance, validation, and production management personnel, as well as the vendor, should be part of the team, which is responsible for making joint decisions on issues concerning concept, design, operation, procurement, scheduling, and the validation plan.

Selecting the right vendor is critical to a successful validation project. When deciding on a vendor, keep the following questions in mind:

- Does the vendor have excellent pharmaceutical references?
- Does the vendor provide complete validation documentation?
- Does the vendor have validated systems audited by FDA?
- Does the vendor provide on-going service and support?
- Does the vedndor perform turn-key systems? (This process ensures that one company is responsible for the project, which eliminates finger-pointing.)

Table 4.
Typical Treatment Steps for Pharmaceutical Grade Water

FEED WATER Meet EPA primary drinking water standard
TYPICAL PRETREATMENT STEPS • Sand Filtration • Granular Activated Carbon Filtration • Sodium Bisulphite Injection • Ultraviolet Sterilization • Cartridge Filtration (1-5 micron) • Ultrafiltration
PURIFIED WATER • Reverse Osmosis • Ion Exchange • Continuous Deionization • Distillation
WATER FOR INJECTION • Multiple Effect Distillation • Double Pass Reverse Osmosis

STEP #2 – SYSTEM REQUIREMENTS
The validation team must identify the current and future needs of a system, including water treatment equipment, instrumentation, sanitization, and process control. These requirements should be conveyed to the project engineers who then can draft drawings and system specifications.

STEP #3 – VALIDATION PLAN
Produce a detailed overall system validation plan, which should include:

- Installation Qualification (IQ)
- Operational Qualification (OQ)
- Performance Qualification (PQ)

Qualification documents should allow for deviations or corrections. This prevents having to repeat the complete validation if something non-critical does not meet specifications.

STEP #4 - INSTALLATION QUALIFICATION
IQ ensures that all components and material comply with specifications and are properly installed. During IQ, the following should be executed:

- Review, approval, and filing of shop drawings from vendor.
- Verification and filing of a mill specification certificate for all stainless steel piping, valves, transmitters, and equipment.
- Detailed site verification of each component to certify correct installation.
- Boroscoping of all stainless steel welds, along with weld identification, documentation, and test reports.
- Passivation procedures and certificates upon completion.
- Operator manuals.
- Collection and filing of all vendor purchase orders.
- Recommendation of a spare parts list.
- A certified water analysis for EPA approved primary drinking water.

STEP #5 – OPERATIONAL QUALIFICATION
OQ ensures that the system, as a whole, is functioning with respect to the mechanical, electrical, instrumentation, and controls portions of the system. During OQ, the following should be executed:

- Cycle verification of all backwashable filters and softeners.
- Pump alignment and rotation.
- RO system pressure and flow verification.
- Complete point-by-point verification of process control system and alarms with test reports.
- NIST traceable calibration and certificates for all instruments, transmitters, gauges, and thermometers.
- Overall system start-up report from the vendor.

STEP #6 – PERFORMANCE QUALIFICATION
PQ is the final test prior to bringing the system on line. It asks the basic question: Is the system pro-

ducing WFI or RO purified water quality? In order to ensure compliance, the PQ test period must run between two and four weeks and rigorously evaluate all parameters. Procedures for PQ are as follows:

- Sanitization of all WFI or purified water equipment and piping as necessary prior to starting PQ.
- Use of a preliminary test period of seven days, followed by a 14 to 21 day period. If a problem arises during the preliminary period, it must be corrected before proceeding.
- Maintenance of an overall system master plan with sample points identified.
- Preparation of a master chart, which compares sample points to the two test periods, as well as to the type of test to be performed (e.g., bacteria total count, LAL, TOC, or conductivity).
- Repetition of each sample point every two to three days.
- Completion of all water quality test reports.

STEP #7 – STANDARD OPERATING PROCEDURES

SOPs are detailed, written maintenance protocols for each piece of equipment. These procedures are included with an overall system, master maintenance schedule. SOPs, when completed, must be dated, documented, signed, witnessed, and logged for future audits. Examples of these procedures include:

- Sanitization of a reverse osmosis system.
- Sanitization of an activated carbon filter.
- Sanitization of a storage tank and distribution piping network.
- Calibration of instruments.
- Replacement of membranes, cartridges, or media.
- On-going performance testing.
- Alarm/Alert conditions for each piece of equipment.

STEP #8 – FINAL DOCUMENTATION

You must keep a complete list of documents and records as covered by IQ, OQ, PQ, and SOPs. This documentation should be maintained in a neat, formal format and safely stored. Remember to identify all non-critical, non-conforming details in this documentation.

STEP #9 – ON-GOING VALIDATION

This process is performed with the use of SOPs, equipment repair logs, and smart instruments (i.e., chart recording of temperature, resistivity, and total organic carbons). It is also important to maintain thorough, neat documentation for each SOP or repair carried out.

Changes to a system after validation necessitate a re-validation effort, though they do not always require a "full blown" validation. Such changes, however, do call for amendments to IQ, OQ, and PQ.

CONCLUSION

A properly designed water system, along with a thoroughly documented validation, will ensure that the system operates smoothly and provides all the information needed when an audit is performed.

For related articles, see the following issues of the *Journal of Validation Technology:*

February 1995

1. Bob Elms and Cindy Green, *Water Systems: The Basics – Part 1, Design as a Prelude to Validation*

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PROPER VALIDATION OF A WATER PURIFICATION SYSTEM: AN INHERENTLY FLAWED PROCESS?

Each year numerous seminars, workshops, and technical papers are presented discussing validation in general. While it is difficult to challenge the overall effectiveness of these various technical forums, particularly as they relate to critical process or process-related functions, it appears to the author that basic validation principals are not followed for water purification and related systems. To underscore this point, look no further than papers that have been presented recently at conferences and in publications. For example, over the last five years more articles have appeared discussing validation of computerized systems[1,2] for various pharmaceutical applications than those examining validation of water purification systems[3]. Furthermore, articles, which clearly define requirements for proper water purification system validation, are often the least popular and most infrequently referenced documents. This situation is perhaps most obvious to the independent consultant who not only is familiar with water purification system design, operation, and maintenance, but who also responds to ongoing problems, such as FDA citations, associated with these systems.

This paper will discuss the preparation of an improper and proper Installation Qualification (IQ) for a water purification system. To simplify matters, the article will focus on a specific component, a particulate removal filter, which generally is present in all water purification systems.

DEFINING THE PROBLEM

Several obstacles exist in the production of validation documentation for water purification systems, specifically in relation to the quality of documents for other processes and applications. These factors are as follows:

1. It is suggested that engineers involved in the design of water purification systems do not understand the validation process thoroughly. – Valuable input from technical individuals in related disciplines, such as manufacturing, operations, maintenance, validation, quality assurance, administration, and facilities operations are not factored into system design.

2. Quite often, a Basis of Design is not prepared for water purification systems. – Maximum instantaneous "draw-off" rates at individual points-of-use, as well as the maximum anticipated volumetric demand at each point-of-use, are not considered. These factors often are "projected" using similar manufacturing/production operations, which results in improper design of the water purification system and difficulty with maintaining system quality at point-of-use.

3. Water purification is not considered a "specialty" item by the majority of organizations performing engineering, design, and even validation. – Assuming minimal emphasis is placed on preparation of a Basis of Design, detailed water purification specifications for individual components, as well as anticipated performance, are required. However, these documents generally are not avail-

able, and, when prepared, they often are written around specifications and/or catalog information provided by an equipment supplier. As a result, it is not uncommon for validation specialists to embark on an IQ without sufficient documentation, which makes it difficult to identify the components that have been utilized and how they function in the overall system design.

4. The water purification equipment manufacturer does not play a significant role in the design of water purification systems for pharmaceutical applications requiring validation. – Over the past few years, the author has participated in the annual Pharm Tech Conference (specifically the water purification technical sessions) as either a panelist or moderator[4,5]. Questionnaires filled out by attendees have made it obvious that only a couple individuals from engineering/design and water purification equipment manufacturing organizations attend the conferences. While attendance by these individuals at other pharmaceutical conference water purification seminars may be higher, it should be noted that these seminars generally are moderated by people who directly provide products and services to water purification system "end users."

5. When all of the above factors are considered, it becomes obvious that the anticipated "expertise" required to prepare and execute a validation protocol for pharmaceutical water purification systems often is underestimated. – Quite simply, the detailed engineering, design, maintenance, and operating parameters required for proper validation are not addressed.

SUMMARY SPECIFICATION

To compare improper and proper IQs, it is necessary to provide a summary specification of a multimedia filtration system. The following specification, while obviously ignoring details about code and regulatory requirements, addresses material necessary for the application of the unit and establishes criteria which will assist validation personnel in preparing an IQ.

The multimedia filtration system consists of a lined steel column, required feedwater, product water, backwash and post backwash rinse-to-drain piping, valves, and accessories. The filter column comprises a vertical cylindrical vessel (36" in diameter by 72" straight side height). The interior of the column is lined with 3/16" thick sheet rubber, which is vulcanized in-place. The continuity of the rubber lining is to be verified by a dielectric test. Sheet rubber, utilized for lining of the vessel, should be an acceptable material for the application in question and should not introduce any "foreign substances or impurities," as defined in the *General Notices of the United States Pharmacapea, 23rd Edition*. The vessel is designed, tested, and stamped in accordance with the American Society for Mechanical Engineers (ASME) Code for Unfired Pressure Vessels (Section VIII, Division 1) for operation at pressures to 100 psig. The exterior of the vertical cylindrical column clearly exhibits a label indicating that the interior of the column is equipped with a rubber lining. The label also indicates that heating and other operations (e.g., welding), which could degrade the rubber lining, will not be performed. The vessel is provided with flanged, dished upper and lower heads. A 3" weld neck and flange is included at the top of the dished head for inlet to the unit and at the bottom of the lower dish for outlet from the unit. The column has an access manway, which is mounted on the top dish head or the straight side of the vessel. As a minimum, the manway must be of oval, 12" x 16" configuration. The lower straight side of the column contains a handhole, which allows access to the lower distribution system for repair if required.

Water is distributed through the vessel via backpressure exerted from the lower distributor. The upper distributor is basic in nature, providing "rough" distribution of the feedwater while allowing the removal of entrapped particulate matter from the unit during the backwash operation. The inlet distributor consists of a short section of Series 316L Stainless Steel piping connected to a "double elbow" arrangement, which provides adequate distribution by diverting the feedwater to the dished head at the top of the unit. The lower distributor is a hub-lateral type, with both hub and laterals fab-

ricated of Series 316L Stainless Steel. The stainless steel laterals use either sections of well screen or other techniques for retaining filter media within the vessel, while also providing for proper backwash of the unit. The lower distributor is designed to provide adequate backpressure to achieve a flat velocity profile over the entire cross section of the filtration unit. The equipment supplier must verify that the pressure drop, through a clean (freshly backwashed) unit, is greater than 5 psid and less than 10 psid. Stainless steel material utilized for distributors is passivated. The column is supported by four legs with level adjusting base plates. The top of the column contains a minimum of three lifting lugs to allow field installation of the unit.

Face piping for the unit is of Schedule 80 PVC construction and the use of threaded fittings is minimal. Flanges will make up all PVC to steel (or stainless steel) connections. Threaded PVC to steel (or stainless steel) pipes, valves, and fittings are unacceptable, since the relatively "soft" PVC will eventually slip from the steel or stainless steel mating threaded fitting. The unit's design will provide for the removal of all particles with a nominal size of 10 microns and larger at flow rates to 45 gpm. Backwash flow rate is consistent with manufacturer's recommendations, which are anticipated in the range of 100-125 gpm. The system includes fully automatic controls, which utilize individual pneumatically operated diaphragm valves. Each diaphragm valve is "flanged" into the face piping system, with mating flanges attached to face piping. Each valve is positive acting, air-to-open, spring-to-close, at a pressure of 100 psig, and 0% ³P. The waste piping from the unit contains a transparent section of plastic piping, which allows operating personnel to observe the presence (or absence) of particulate matter during the backwash and subsequent rinse operation. A manual diaphragm valve is provided in the backwash line. This valve enables operating personnel to adjust the backwash rate with alterations in the viscosity of the backwash water, as water temperature changes with seasonal and climatic conditions. It also allows operating personnel to vary the backwash flow rate, ensuring that particulate matter is removed adequately during the backwash operation. The feedwater and product water connections from the unit includes manual isolating diaphragm valves and ends in a 150 l# PVC flange.

Operation of the automatic valves is controlled by individual solenoid valves positioned in a NEMA Type 4 enclosure, which is mounted in the immediate area of the multimedia filtration unit. The solenoid valves are designed with manual override provisions. To avoid interference with unit operation and access, pneumatic tubing from the individual solenoid valves are connected to the individual pneumatically-operated diaphragm valves on the face piping through appropriately sized polyethylene tubing, which is neatly "bundled" or contained in conduit. The solenoid valves receive a signal from a remotely mounted control panel, which also provides control signals to other components in the system.

The unit is equipped with indicators for the following:

- Feedwater temperature, pressure, and flow rate (also capable of indicating the backwash flow rate)
- Product water pressure
- Differential pressure monitoring

The differential monitoring system utilizes feedwater and product water pressure sensors/transmitters, which are capable of feeding signals to the central control panel. Provisions in the central control panel allow the initiation of backwash based on either differential pressure, elapsed time since the last backwash operation, or a preestablished time (and day). Since it is highly desirable for filter "ripening" to occur, backwash generally is executed based on differential pressure. An alarm, with associated indicating light, on the central control panel, is activated when the differential pressure exceeds a value of 7-11 psid above the "clean" (freshly backwashed) differential pressure value.

IMPROPER IQ

Unfortunately, the summary specification outlined above generally is not available to an individual preparing an IQ for a multimedia filtration unit.

Thus, the typical Installation Qualification usually is inadequate and only verifies the following:

- Company which manufactured the unit.
- Model number of the unit.
- Operation of the unit is designed at flows to 45 gpm. (This is achieved using manufacturer's literature.)
- Unit consists of a single filtration vessel, which is 36" in diameter and 72" straight side height.
- Unit is provided with fully automatic controls, as well as feedwater temperature and flow rate indicators.
- Unit contains feedwater and product water pressure gauges.
- Face piping is Schedule 80 PVC.

Often times this is the extent of material provided within an IQ. However, it should be noted that, in most cases, this information represents the extent of detail available to the individual preparing the IQ for the component.

PROPER IQ

In addition to the material provided in the example above, an appropriately-prepared Installation Qualification should answer "yes" to the following questions:

- Does the unit have a nameplate clearly identifying the equipment manufacturer, serial number, date of manufacturer, and other appropriate information?
- Has the unit's serial number been recorded?
- Does the unit include a vertical cylindrical column, which is 36" in diameter by 72" straight side height?
- Is the top of the column equipped with a flanged and dished head of steel construction?
- Is the base of the column equipped with an inverted dish head?
- Does the column have a 3" weld neck and flange positioned at the center of the top dished head, as well as a 3" weld neck and flange at the center of the lower, inverted dished head?
- Does the column contain four support legs with adjustable base plate feet for leveling?
- Is the column level? (You may use the level indicating device on the vertical straight side of the column to verify this.)
- Is the column equipped with a minimum of three lifting lugs, which are positioned on the flanged and dished upper head of the unit?
- Is the column equipped with an access manway (a minimum 12" x 16" oval design that is positioned on the upper dished head or upper straight side of the unit)?
- Does the lower straight side of the unit contain a handhole, which is a minimum of 6" x 8", for access to the lower distributor?
- Has the column been designed, fabricated, and tested in accordance with the ASME Code for Unfired Pressure Vessels, Section VIII, Division 1? (You may verify this by inspecting the "U-stamp" data plate mounted on the face of the unit.)
- Has the appropriate material from the "U-stamp" data plate, including board inspector number and year of manufacture, been recorded?
- Is form U-1 of the "Manufacturer's Data Report for Pressure Vessels," which is provided by the National Board of Boiler and Pressure Vessel Inspectors (Columbus, OH), included in the IQ?
- Has the exterior of the column has been prepared properly, with all welds ground smooth and finished with multiple coats of primer and corrosion resistant paint?
- Does the front of the unit clearly indicate that it is component F-1, which is consistent with the representation on the P&ID for the project?
- Does the front of the column contain a clearly visible label, which indicates that the interior of the column has a rubber lining? That heating or welding of the column not only will destroy the lining, but could produce hazardous fumes and/or vapors?
- Is the interior of the column lined with 3/16" thick sheet rubber, which is vulcanized in place?
- Has a test report, which indicates that the continuity of the rubber lining has been verified by a dielectric test, been supplied by the equipment manufacturer? (Include the test report in the

IQ, and record the test voltage used for the dielectric test.)

- Is the rubber lining made from a material which the FDA has approved for food and drug applications? (Verification should include catalog or other descriptive information of this material and a letter, printed on the letterhead of either the equipment manufacturer or sub-contractor who installed the rubber lining, stating the material meets the appropriate FDA criteria. Include this letter in the IQ.)
- Is the upper distributor of the unit fabricated from Series 316 or 316L Stainless Steel? (If this material cannot be verified visually, provide information on the equipment manufacturer's letterhead clearly stating that the upper and lower distributors are constructed from Series 316 or 316L Stainless Steel. Include the letter in the IQ. If possible, provide a "Mill Certification" verifying that appropriate materials were used in the assembly of the distributors.)
- Does the lower distributor have a hub-lateral design?
- Is the lower distributor constructed from Series 316 or 316L Stainless Steel? (You may use documentation similar to that of the upper distributor.)
- Have the stainless steel inlet and outlet distributors been passivated?
- Is a passivation report available? (This report, or letter on the equipment manufacturer's letterhead, indicating the procedure used for passivation should be included in the IQ.)
- Is there a record of the overall dimension of the unit, including width, depth, and height?
- Does the unit contain the proper amounts of support media? 14 ft^3 of custom selected filter sand? 10 ft^3 of anthracite filter media?
- Is there a record of all support and filter media data from shipping containers or "filter bags" during media loading?
- Is a Material Safety Data Sheet (MSDS) available for all support media? For all filter media? For support sand and anthracite? (Include the MSDS in the IQ.)
- Is a "sieve" analysis available for all support media? For all filter media? (Include this analysis in the IQ.)
- Is a chemical analysis available for all support media? For all filter media, including sand and anthracite? (Include this analysis in the IQ.)
- Is the "face" piping for the multimedia filtration unit a 2" Schedule 80 PVC?
- Are the automatic valves for the unit a diaphragm type?
- Is catalog information available for the diaphragm valves used as part of the system? (Provide this material, including maintenance and trouble shooting information, in the IQ.)
- Are the automatic valves positive acting, air-to-open, spring-to-close?
- Is the sizing of the automatic valve actuators such that they will close positively at 100 psig and 0% ^3P? (You may use manufacturer's literature to verify this.)
- Is each automatic valve "flanged" into the piping system? Properly labeled in accordance with designation on the P&ID for the project?
- Is a manual, diaphragm valve positioned in the backwash line, enabling operating personnel to adjust the backwash flow rate?
- Is catalog information available for this valve? (Include this information in the IQ.)
- Does the feedwater piping to the unit contain a pressure gauge, with a tag number, range of 0-160 psig, and calibration of 2 psig (maximum) increments?
- Is there a record of the calibration data for the feedwater pressure gauge? (Include a" Certificate of Calibration" in the IQ, and place a calibration sticker on the face of the gauge.)
- Does the product water piping to the unit contain a product water pressure gauge, with a tag number, range of 0-160 psig, and calibration of 2 psig (maximum) increments?
- Is there a record of the calibration data for the product water pressure gauge? (Include a" Certificate of Calibration" in the IQ, and place a calibration sticker on the face of the gauge.)
- Does the feedwater piping to the unit contain a manual isolation valve with its tag number? (Include this information in the IQ.)

• Does the product water piping from the unit contain a manual isolation valve with a tag number? (Include this information in the IQ.)

• Does the feedwater line to the unit contain a direct reading temperature gauge, which is calibrated from 35-120° F in 2° F (maximum) increment? (Include a "Certificate of Calibration" in the IQ, and place a calibration sticker on the gauge.)

• Does the feedwater piping have a variable area flow meter? (Include a "Certificate of Calibration" in the IQ, and place a calibration sticker on the meter.)

• Is the model number of the flow meter recorded?

• Is the range of the flow meter between 0-250 gpm?

• Is catalog information available for the feedwater and product water pressure gauges? For the feedwater temperature gauge and flow rate meter? (Include this information in the IQ.)

• Is a feedwater sample valve, with tag number, positioned in the feedwater piping to the unit?

• Is this sample valve a needle type of Series 316 or 316L construction?

• Is a product water sample valve from the unit provided? (This valve should be a needle type and have a tag number.)

• Is this sample valve fabricated from Series 316 or 316L Stainless Steel?

• Is catalog information provided for the feedwater and product water sample valves? (Include this information in the IQ.)

• Do the feedwater and product water piping lines contain pressure sensors and transmitters, which will relay signals to the central control panel?

• Are the feedwater and product water flow sensors properly labeled in accordance with the P&ID for the project?

• Is catalog information available for the feedwater and product water flow sensors and transmitters? (Include this information in the IQ.)

• Is the unit equipped with a NEMA Type 4 electrical enclosure, which contains individual solenoid valves for each of the automatic valves?

• Is catalog information available for the individual solenoid valves? (Include this information in the IQ.)

• Does flexible polyethylene tubing connect the individual solenoid valves to the individual, pneumatically-operated diaphragm valves?

• Is this tubing properly labeled to indicate the valve termination number?

• Does the NEMA 4 enclosure have an Underwriter Laboratories stamp or sticker?

• Will the central control cabinet begin backwash of the unit, after initiation by either differential pressure, elapsed time since last backwash, or at a specified date and time?

• Is a control wiring diagram available for the solenoid enclosure? (Include this diagram in the IQ.)

• Is there a record of the electrical requirements for the control enclosure, including voltage and amperage?

• Does the system have a 2" waste to drain connection, which is connected to a depressurized sanitary drain?

• Does the waste line from the unit contain a transparent section of piping?

• Is there a record of the diameter and length of this section of piping?

• Are the terminal connections at the feedwater and product water piping #150 Schedule 80 PVC flanges?

• Is an Operating Manual available for the unit? A spare parts list? A manufacturing/assembly drawing? A manufacturing "Bill of Materials? (Include this information in the IQ.)

• Is a P&ID, which diagrams the unit, and a detailed specification included in the IQ?

SUMMARY

Obviously there is a considerable difference in the material presented in the two Installation Qualifications above. The author admits it is reasonable to challenge the depth of information provided in the second IQ. However, the author feels that it is impossible to verify that an individual component within a validated water purification system has been provided as specified, if information associated with all support accessories is not

available. Furthermore, when a detailed IQ, such as the above example, is executed properly, it will familiarize operating personnel with all items necessary for successful system operation and maintenance. Finally, a thorough IQ will underscore the importance of the validation operation, particularly the requirement to document items, to appropriate personnel.

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For related articles, see the following issues of the *Journal of Validation Technology:*

February 1995

1. Bob Elms and Cindy Green, *Water Systems: The Basics – Part 1, Design as a Prelude to Validation*

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1. Agalloco, J., "Testing during the Start-Up and Performance Qualification of Computerized Process Control Systems," *Pharmaceutical Technology,* Volume 19, Number 3, March 1995 pages 114-122.

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Brian Scott, Jeff Hargroves, and Jerry Bauers

VALIDATION OF HVAC SYSTEMS IN PHARMACEUTICAL & BIOTECHNOLOGY FACILITIES – PART 1

Editor's Note: *The following article is the first in a two-part series. Part One addresses the fundamental requirements and installation qualification of HVAC systems. Part Two, which will appear in the May issue of the Journal, will discuss the operational qualification and performance qualification of these systems.*

An HVAC system, which encompasses heating, ventilation, and air conditioning, is an integral component of a facility's functionality. It impacts the safety of scientists and technicians working in a lab or production facility, the integrity of processes, and the environment outside.

There are three core phases of HVAC system validation: installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ). An important element of successful HVAC validation is prevalidation design work. This article explores the correlation between preliminary design and each phase of validation.

HVAC SYSTEM FUNDAMENTALS

Construction and validation of an HVAC system usually involves compiling the following documents, which typically are developed in the order presented in *Figure 1*:

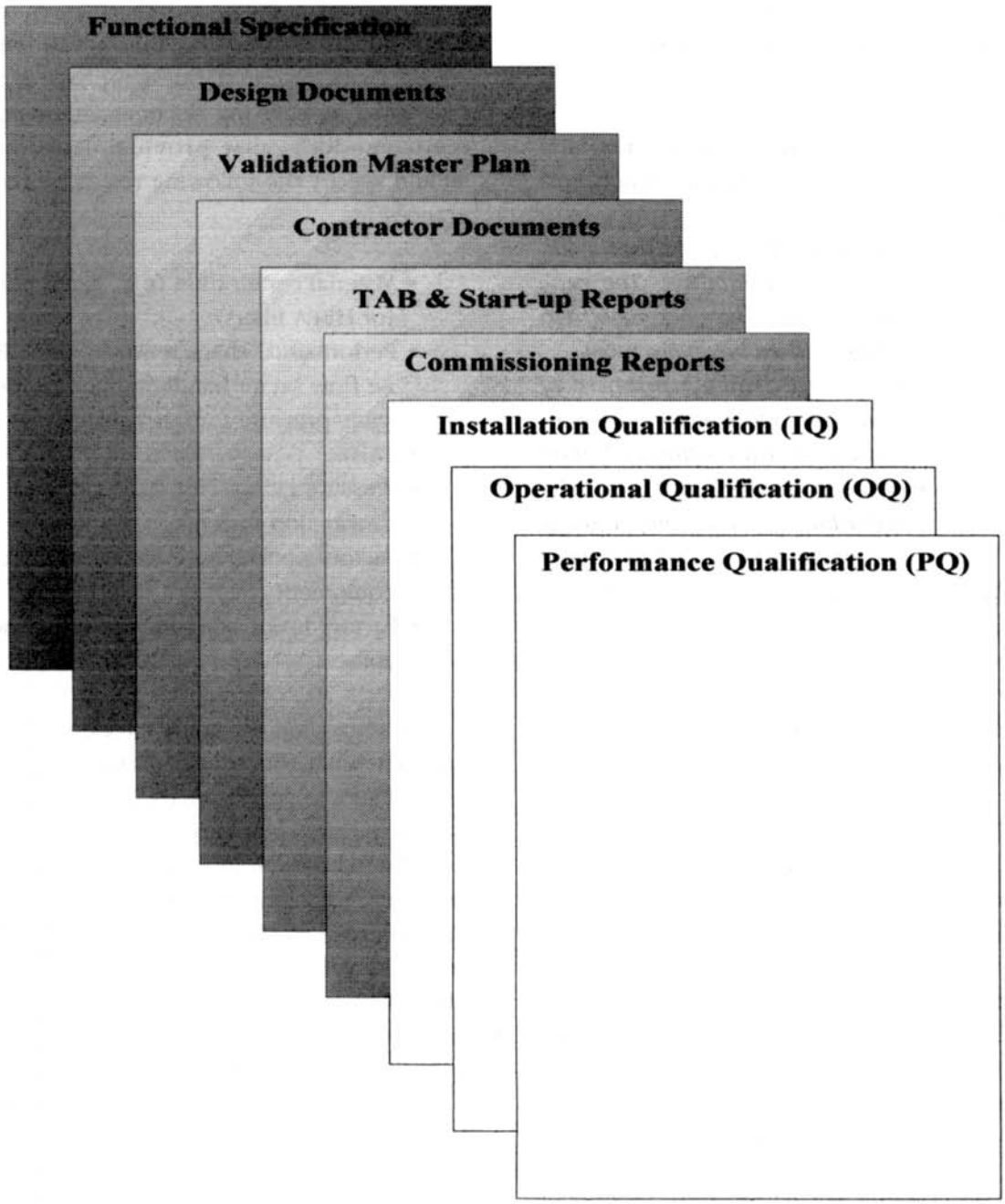
- Functional Specification (the conceptual design)
- Design Drawings, Plans, and Specifications
- Validation Master Plan
- Contractor Documents (e.g., shop drawings and submittals)
- Testing, Adjusting, and Balancing (TAB) and Start-up Reports
- Commissioning Report (The actual execution of validation protocols may commence; commissioning may be performed as part of the "development" phase of validation.)
- Validation (IQ, OQ, & PQ)

When PQ is complete, process validation commences and product manufacture (or laboratory processes) can begin.

Whatever the components of an HVAC system, the functional requirements must be determined up front. In fact, functional specifications are the cornerstone of any project.

It is important that design criteria is not the sole basis for establishing validation acceptance criteria. Design criteria may be written with extreme precision, but acceptance criteria for validation may not need to be so stringent. This determination comes from understanding the process in question. The design team must understand and assist in determining what a system needs to "do" in the context of processes and other operations carried out within a facility.

Figure 1
DOCUMENTATION SUPPORTING CONSTRUCTION
AND VALIDATION OF AN HVAC SYSTEM



A description of functional requirements should include:

- HVAC system functionality as it relates to processes.
- Points in a process that expose a product to the environment.
- Source of design guidelines (e.g., an existing similar facility, a domestic or foreign regulatory body).

The following is an excerpt from a functional requirements description for a typical manufacturing facility:

"Air handling unit AHU-01 serves an aseptic filling suite in the New Product Facility. The suite includes an aseptic area, clothes changing room, two equipment pass-throughs, and an incubator room.

The air handling unit draws a mixture of makeup air and return air into a mixing section, through a series of filters, and a cooling coil; then blows the air through a heating coil and discharges it into distribution ductwork. Filtration is provided by 30% ASHRAE efficiency pre-filters, 95% ASHRAE efficiency bag filters, and 99.97% HEPA filters. Terminal 99.995% HEPA filter diffusers provide final filtration and air distribution in each room. Air is returned through low wall louvered return grilles. Temperature is maintained at 66 ±2° F. Humidity is maintained between 20% and 50% RH. Space pressurizations are shown on Drawing XX-101-AA."

Once designers understand the functionality of a facility, the next questions are who or what holds regulatory responsibility and what are the particular performance requirements. The answers to these questions lead to perhaps the most significant issues in validating an HVAC system: The processes that the system is supporting and who monitors the performance of the facility. Validation criteria must be established within this context and not in a vacuum or against arbitrary "right" or "wrong" conditions.

Personnel responsible for HVAC validation should be involved in the design process from early conceptual meetings through periodic design reviews to final design approval. In doing so, they have a voice in identifying the criteria against which a system should be validated and can offer observations and recommendations about design which might ultimately impact validation.

VENDOR REQUIREMENTS

There are many reasons that a validation team should participate in the design phase of a project. One is to identify the documentation that equipment vendors must provide. Documentation should specify the following requirements and tolerances:

- Material certification (e.g., serial numbers for HEPA filters)
- Performance characteristics (e.g., CFM for air flow on air handling units; air flow vs. static pressure for fans)
- TAB
- Pressure ratings (for ductwork and the distribution system)
- Factory performance testing of critical equipment
- Factory leak testing for cooling or heating coils

If contractors and equipment vendors are not told up front what they are required to provide, it's very difficult to get necessary information as a project progresses. In many scenarios, specifications typically are written just for acquisition and installation of equipment. A better procedure—one that will make the validation process more efficient—is to require vendors to supply supporting documentation. Requirements also should be applied to any software that may be part of controls or building management systems.

In addition to outlining documentation that vendors must furnish, this is the time in the validation process to define responsibilities for delivery, installation, and start-up or commissioning. This procedure encompasses activities such as starting air handling unit motors, verifying correct fan rotation, and point-to-point verification of control loops.

INSTALLATION QUALIFICATION

The goal of IQ is to verify and document the quality, installation, and integrity of HVAC system components. Use design documents and literature provided by vendors to develop IQ protocols, which often take the form of inventories or checklists. Execution of IQ protocols provides assurance that an HVAC system is installed according to the manufacturer's recommendations and requirements for the specific facility being validated. (Note: Some readers may find that the requirements listed in the following discussion are more typical of aseptic areas and may not be universal for all HVAC systems.)

A Description of Operation (System Description) identifies an HVAC system, as well as the processes it supports and areas it serves. It should give a clear and concise description of the system in question, focusing on operational attributes of the system rather than technical specifications of equipment. (In most cases, a one-paragraph description is sufficient, unless a system is unusually complex.) When appropriate and useful, include diagrams showing temperature and humidity control zones, room pressure relationships, and other key information.

It is important to avoid "over specifying" system attributes. For example, a diagram with arrows to indicate room-to-room directional air flows may be more useful than a drawing showing numeric pressure relationships.

Information provided in a Description of Operation should cover the following:

- Brief description of the system
- Identification of all the spaces served by the system
- Room temperature setpoints, including acceptable deviations (±)
- Room humidity setpoints, including acceptable deviations (±)
- Minimum space air change requirements
- Space particulate classifications

IQ documentation generally is broken down into the following major sections:

Installation Drawings & Specifications (List) – Documents as-built drawings and design specifications for an HVAC system about to be qualified (validated). As-built drawings normally are supplied by mechanical contractors. These drawings offer a record of system installation in its validated state, provided they reflect changes made to the system during validations.

Document the sheet number, description, and latest revision date of each drawing. Compare the finished installation to as-built drawings to make sure that installation conforms to the drawings. Major discrepancies between as-built drawings and conditions found during validation should be marked on the drawings and reported to the appropriate personnel.

Execution of IQ may be easier if an "installation checklist" is generated based on information in design drawings and specifications. This checklist should include all fans, fan motors, coils, and filters in the air handling unit. Zone reheat coils and terminal HEPA filters also may be incorporated.

If construction is complete before validation starts, some HVAC devices may become concealed by insulation or architectural elements. In these cases, packing lists, purchase orders, or other documentation should provide evidence that installed equipment meets design requirements. The source of information used to verify acceptance should be noted in a protocol. In addition, duct leak test reports may be referenced and attached as evidence that ductwork has been installed in accordance with industry standards (e.g., ASHRAE, SMACNA standards).

Materials in Product Contact – Normally does not apply to most HVAC systems. However, in a clean process environment where product or ingredients are exposed to air provided by an HVAC system, this evaluation must consider materials used in construction of the system that may become airborne and directly contact product. Because of the risk of contamination to the system, such materials should be appropriate and safe for product contact and "non-particle shedding." In other words, construction materials should not be "reactive, addi-

tive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug beyond the official or established requirements." (*21 CFR 211.94 – Drug product containers and closures.*)

IQ documentation may include materials in final filters, along with any devices downstream of them that serve an area in question. These materials should meet industry-accepted standards for suitability in drug processing, packaging, labeling, or other activities taking place.

Lubricants – Identifies lubricants used to maintain an HVAC system. This list may be as simple as "fan bearing grease." A more detailed list would include lubricants provided with system components prior to installation, such as damper lubricants.

Food or pharmaceutical grade lubricants should be used if there is potential for product contact (where equipment design permits possible product contamination by the lubricant). Consult a maintenance supervisor or other maintenance personnel to ensure that all applicable lubricants are listed here.

Utilities – Lists utilities critical to the operation of an HVAC system. All systems require supporting utilities to function properly. Include applicable design and actual data for utilities as follows:

- Electrical requirements and provisions for each HVAC utility (e.g., fan, pump, condensing unit, etc.) – Document voltage, phase, full load amperage, and conductor size.
- Steam requirements (e.g., plant steam or clean steam, as applicable) for each steam coil or humidifier, including line size and steam pressure for each device – Steam flow (usually expressed in pounds per hour) is not easily measured and usually not included here.
- Hot and chilled water coil requirements, including supply temperature, pressure, and flow rate – If a TAB contractor has made adjustments to a system, reference the TAB report (submitted by a contractor certified by the National Environmental Balancing Bureau) for information provided in this section.

Instrumentation Calibration – Ensures accurate control of critical operational parameters. List all calibrated instruments critical to system operation. Instrument calibration should be current at the time that IQ is performed. Document the dates that calibrations were executed and that recalibrations are due.

In some cases, the only devices included in a routine calibration program are those used for closed-loop control or critical system alarms. For example, pressure gauges in chilled water lines entering and leaving a cooling coil may be considered "non-critical," but temperature sensors in spaces served by the cooling coil may be considered "critical." If the temperature sensors are critical, they require routine calibration. If calibration data sheets are available, they may be attached to the protocol.

Preventive Maintenance – Identifies procedures used to maintain an HVAC system in good operating condition. Preventive maintenance (PM) also provides assurance that a system will be kept in a validated state.

List preventive maintenance numbers and effective dates. PM procedures for an HVAC system may include inspection of filters, bearings, belts, gaskets, and any other moving parts, as well as parts with limited lifespans. Maintenance personnel normally write PM procedures.

Spare Parts – Identifies filters, belts, or other items that will be replaced according to a regularly scheduled preventive maintenance program. During the life of a typical HVAC system, certain parts will need to be replaced as a result of expected wear and tear. Record the manufacturer and model number of each item. Spare parts should be identical or equivalent to original parts. A facility's maintenance department should keep these parts in stock.

Special Procedures – Identifies special procedures, such as a controls system software walk-through and initial HEPA filter integrity testing. Certain procedures involved in HVAC system start-up should be documented as evidence of proper configuration or performance of system elements. Some of this information may be useful for troubleshooting

in the future. Duct cleaning procedures and system pressure testing documentation also may be referenced and attached to the protocol.

Major Purchase Orders – Provides evidence that HVAC equipment and services purchased for the system meet the requirements specified in design documents. "Major"—as it applies to purchase orders—varies from project to project. For many HVAC systems, the only purchase order (PO) considered major is the one needed for the air handling unit. Some companies may require that IQ protocols reference POs for the purchase and installation of every fan, damper, valve, actuator, coil, filter, and duct fitting. These documents normally are obtained through a company's purchasing agent or department.

For each PO number listed, include a description of the equipment or installation covered by the order, the name of the supplier to which the order is written, and the date of the order. In most cases, copies of POs should be attached to IQ protocols.

Change Control – Provides documentation of changes to a system. This procedures also will maintain a system in a validated state, as replacement (spare) parts are installed and maintenance is performed.

A final note on IQ protocols: Change control should be in place before IQ is complete. Throughout the life of a system, it may be necessary to evaluate changes and determine whether revalidation is required.

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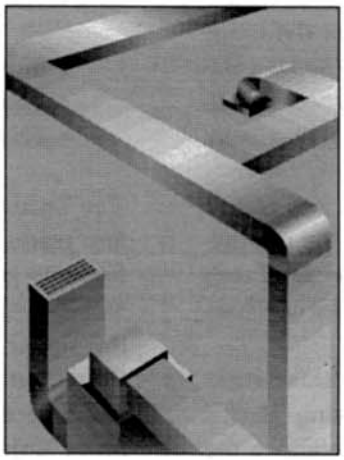
VALIDATION OF HVAC SYSTEMS IN PHARMACEUTICAL & BIOTECHNOLOGY FACILITIES

~ *Part 2* ~

Brian Scott, Jeff Hargroves and Jerry Bauers

HVAC systems are integral to the efficient operation of any facility. This article, the second and final installment of this series, discusses OQ and PQ for them. While this paper focuses on aseptic processes, readers also should consider how HVAC systems affect non-sterile dosage forms.

OPERATIONAL QUALIFICATION



The purpose of OQ is to verify and document that an HVAC system provides acceptable operational control under at-rest (static) conditions. "Acceptable operational control" may be demonstrated by any or all of the following:

- Ability to maintain temperature, humidity, and pressure set points.
- Timely response to system upset.
- Air of sufficient quantity and quality (cleanliness) is provided by the system in a manner that does not contribute to cross-contamination.

Operation and Alarm Testing

Building-automation systems or building-management systems, which should be validated whenever building environmental conditions are considered to have an effect on product quality, control most new HVAC systems installed in pharmaceutical and biotechnology facilities. The user interface software associated with these control systems lets building and equipment operators use a PC interface to monitor equipment status or process variables. In cases where a system consists of several pieces of equipment and instrumentation, which is the case for most HVAC systems, system designers or programmers may create charts or schematic graphics so that operators can easily view the status of an entire system on a single screen.

Operation and alarm testing should demonstrate the functionality of critical temperature, humidity, and pressure control loops of an HVAC system. Alarm testing should verify proper reporting of temperature, humidity, pressure, and fire and smoke alarms linked to the system. Any alarm print-outs generated during testing should be attached to the OQ protocol.

Some facilities or areas where viruses or other biohazards are present require periodic fumigation using formaldehyde or other toxic substances.

Verify the functionality of the mechanical equipment and instrumentation associated with pressure control and fumigant containment during this process. Efficacy of the fumigation process normally is validated separately.

Figure 1 on page 194 demonstrates the ability of room pressure control loops to respond to pressure set point changes associated with a fumigation cycle. In this example, other spaces served by the same exhaust system were monitored to verify that no adverse changes in pressures occurred. (See *Figure 2* on page 195.)

Loop Response Testing

Loop response tests are performed to demonstrate that the temperature, humidity, and pressure control loops of an HVAC system respond as designed to sudden changes. The forces of nature typically cannot provide a sudden increase in heating, cooling, or other demands predictably, so loop response tests normally are performed by changing set points and monitoring the response of associated control loops in the system. Calibration of system instruments that are critical to controlling each parameter tested should be verified prior to each test.

The following loop response tests may be included:

- Cooling and heating control
- Humidity control
- Fan speed control (or duct static pressure control)– Applies when a variable frequency drive is used for fan speed control
- Room pressure control

Figure 3 on page 197 illustrates a cooling loop response. For this specific test, the room temperature set point was lowered from 68°F to 63°F. The graph shows that temperature stabilized at 63°F, ±2°F, within six minutes of the set point change.

Figure 4 on page 198 illustrates a fan speed control loop test, which demonstrates the ability of a fan speed control loop to respond to duct static pressure set point changes. The fan speed control loop consists of a supply duct static pressure transducer and variable frequency drive.

Air Change Rate Verification

The airflow per unit volume of a space, along with other factors, is a measure of the cleanliness of the space. An air change rate verification procedure consists of a calculation based on space dimensions and the supply of airflow to the space. Space dimensions may be obtained by field measurements or taken from as-built drawings. Large enclosed volumes permanently occupied by objects in the space may be deducted (e.g., a sterilization tunnel). Airflow readings may either be read by validation personnel or taken from testing and balancing documents. The following equation is used to calculate air change rate:

$$ACH = \frac{CFM \times 60}{V}$$

ACH = air change rate (air changes per hour)
CFM = total supply airflow to space (cubic feet per minute)
V = space volume (cubic feet)

Table 1 lists recommended air change rates based on cleanliness classifications, which are derived from the number of 0.5 micron particles per cubic foot of air allowed.

Table 1

CLASS	AIR CHANGES/HOUR
100	670
1,000	60
10,000	20
100,000	30

*VALUES WERE DERIVED FROM "STUDY COURSE FOR CERTIFIED TESTING OF CLEAN ROOMS," NATIONAL ENVIRONMENTAL BALANCING BUREAU, 1989

Steady-State Testing

Steady-state testing demonstrates the ability of an HVAC system to respond to load changes over a typical 24-hour (or longer) period. The test may be performed over three 24-hour periods to demonstrate repeatability of system response to daily temperature and humidity swings, as well as to activity in the building. In order to control test

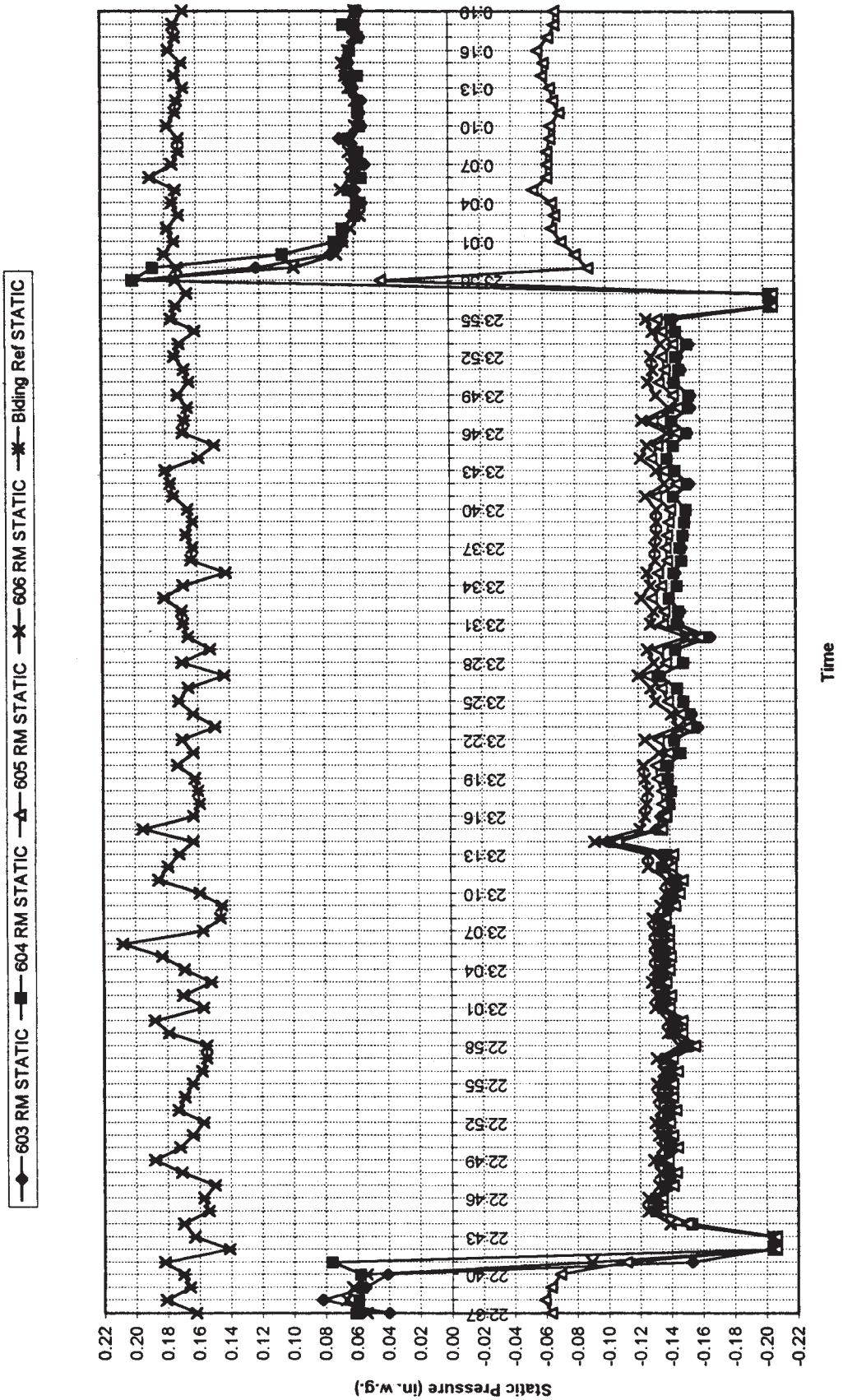
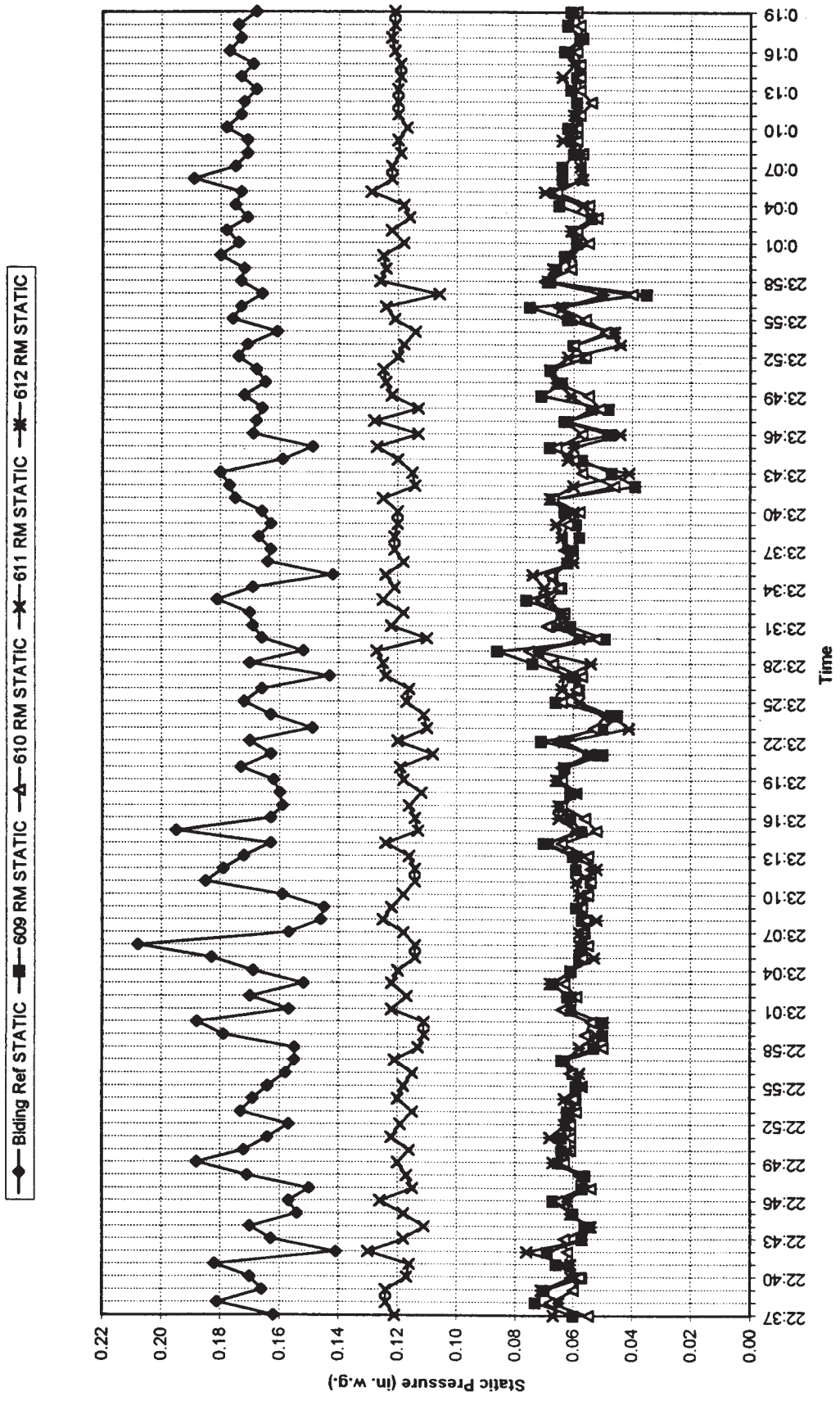


Figure 1
SUITE 605 FUMIGATION

Figure 2
SUITE 611 DURING SUITE 605 FUMIGATION



conditions (and provide the validation team with the ability to define and simulate "normal activity" for the sake of the test), activities and traffic should be restricted in areas being tested. This is especially important for pressure control.

If a building automation system provides HVAC system control, point trending capabilities (recording of values sensed by system instrumentation) may be used to record required temperature, humidity, and pressure data. If a building automation system cannot be utilized or if system instrumentation does not provide enough information, data logging equipment may be required.

Temperature and Humidity Requirements

A representative guideline may recommend temperature control at 72°F, ±2°F, and humidity control at 30 percent to 50 percent RH. For areas where gowning is required, 65°F to 68°F and 40 percent to 50 percent RH is recommended. Lower humidity setpoints (20 percent RH or less) may be required in powder fill areas. Equipment and instrumentation requirements also may be a consideration. For example, certain instrumentation is sensitive to temperature or humidity. Static electricity may be a concern in low humidity areas.

Acceptance criteria used for validation should demonstrate the ability of an HVAC system to maintain adequate temperature and humidity control based on the design criteria. As noted earlier, design criteria may be more stringent than the requirements of the actual process being performed in an area. Therefore, the protocol writer should exercise caution to avoid establishing validation acceptance criteria that are beyond the requirements of the actual process.

Figure 5A and *5B* on pages 200 and 201 illustrate steady-state test results. This specific test was performed to demonstrate the system's ability to control temperature at set point, ±2°F, and humidity at 55 percent RH or less. Temperature deviations occurred when the humidity control loop opened the chilled water valve to provide dehumidification. Cleaning activities in the associated laboratory caused the high humidity levels and unstable temperatures. These results demonstrate the importance of restricting access to areas under test.

Pressurization Requirements

Steady-state pressure testing should verify that required pressure relationships are maintained with all doors closed. In most cases, clean areas are maintained at a higher pressure than less clean areas. And in cases where containment in a clean area is necessary, isolation airlocks may be used to prevent cross-contamination.

The recommended minimum pressure differential to be maintained between a clean and less clean space is 0.05 in. w.g. Exercise care in specifying pressure control tolerances (as reflected in acceptance criteria). Even though access to spaces to be tested may be prevented or restricted, pressure variations in the space used as a pressure reference (often a corridor) may have an apparent effect on room pressures being monitored.

Figure 6 on page 204 illustrates a steady-state pressure test. This graph of steady-state pressure test data underscores the importance of restricting access to spaces being tested. (Most pressure "spikes" were caused by traffic in the building.)

Air Quality Testing

For clean rooms or clean zones, air flow laminarity testing and particle count testing should be performed under static conditions in OQ. Any deficiencies related to HVAC system performance then may be corrected prior to the start of PQ, in which testing of the system is performed with equipment and personnel simulating actual operating activities.

Airflow Laminarity Testing

In most applications, the primary purpose of contamination control is to protect products or processes. Laminar airflow (as opposed to turbulent airflow) can be considered a cleansing agent which carries airborne contaminants away from aseptic products and processes in a controlled manner.

Critical work zones (i.e., filling lines) may require laminar airflow. Laminarity may be demonstrated by measuring velocity on a uniform grid within one foot of work zone height. Typical

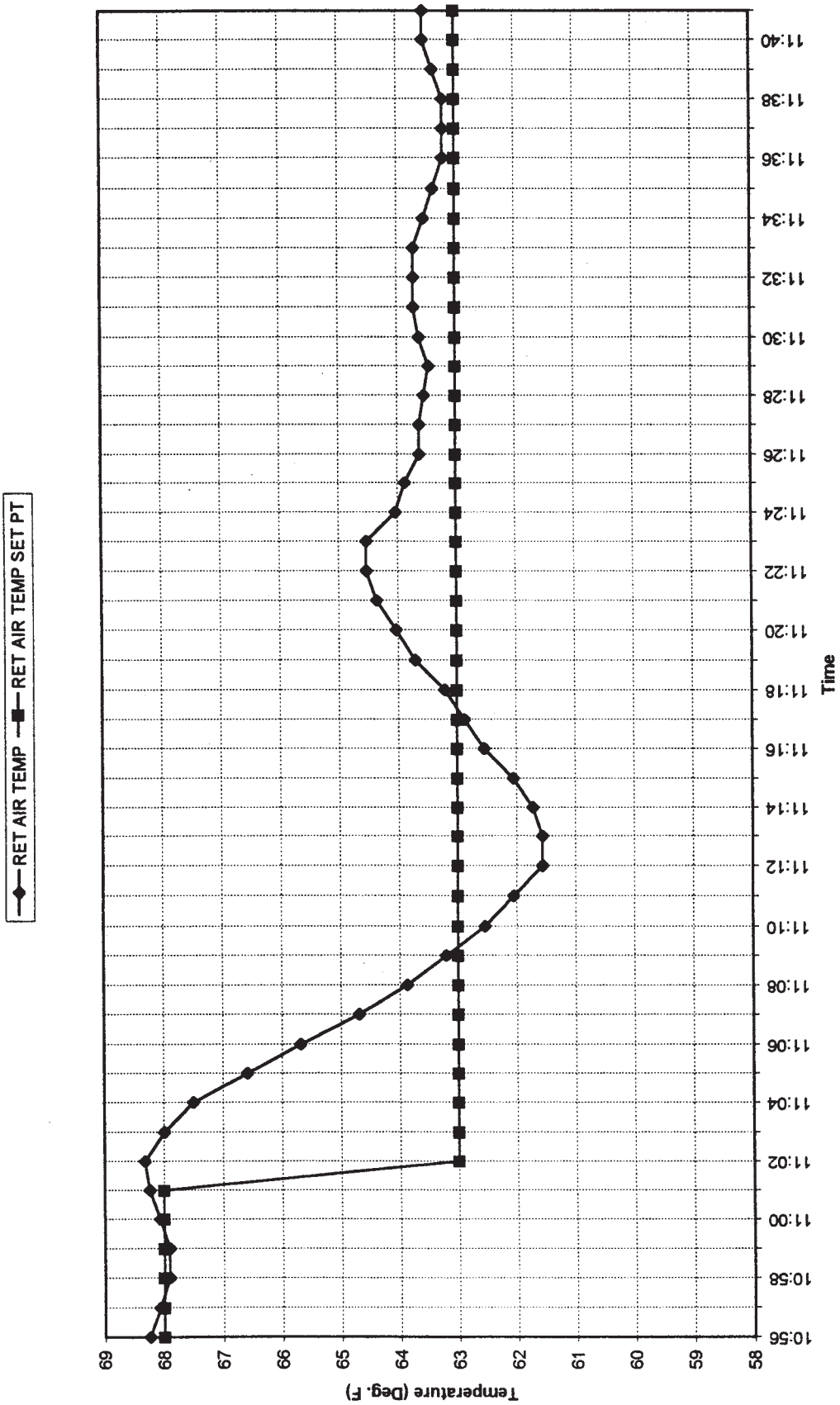


Figure 3
AHU-30 COOLING RESPONSE

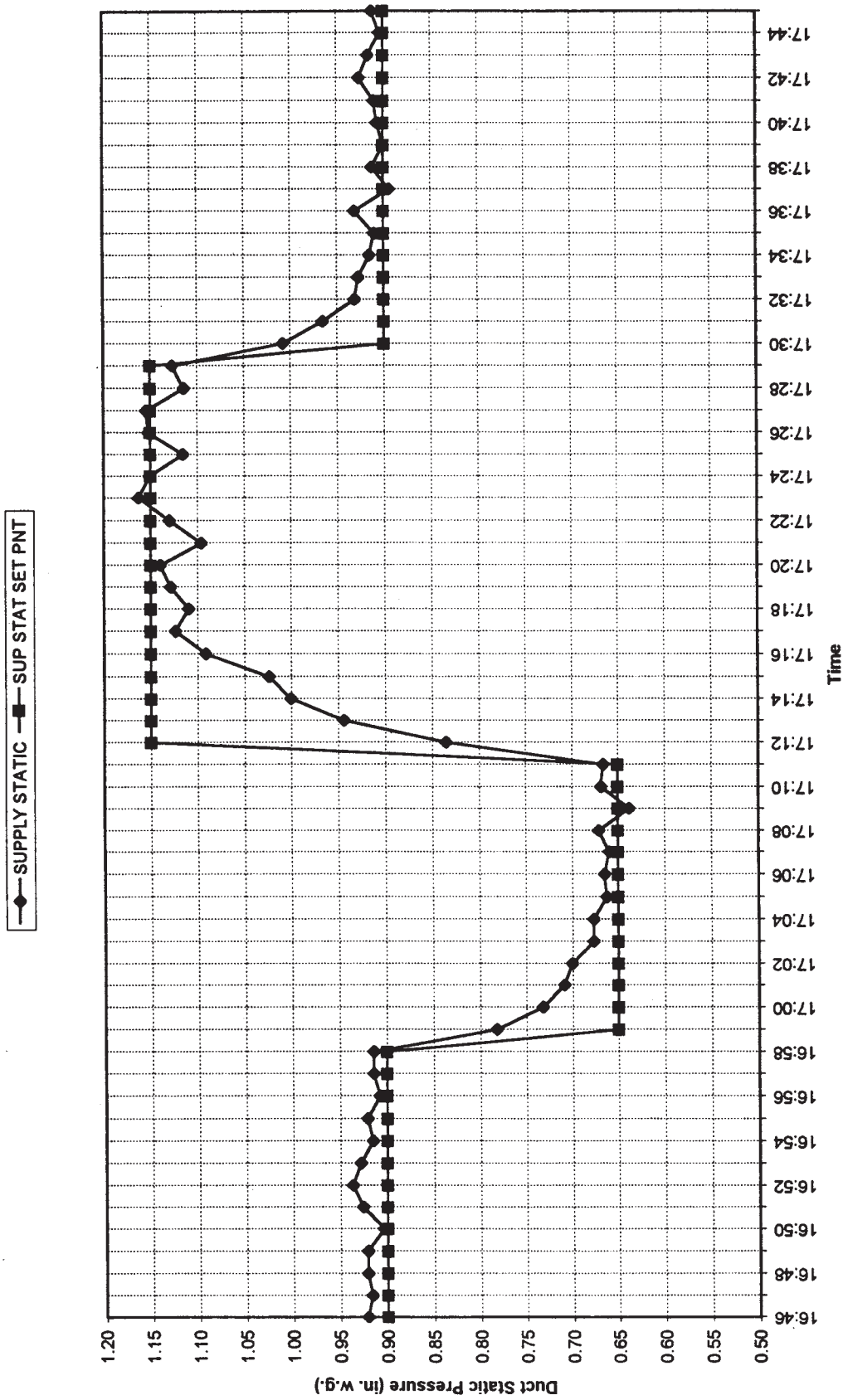


Figure 4
AHU-34 FAN SPEED CONTROL

velocity requirements are in the range of 90 feet per minute, ±20 feet per minute. Higher velocities may be needed where activities generate high particulate levels or where the equipment configuration disrupts laminar flow.

Smoke sticks or a dry ice fog generator can be used to demonstrate visual verification of laminarity. The medium used to generate smoke or fog should not threaten the equipment or the process it is used to qualify. A dry ice fog with purified water usually meets this requirement.

A smoke or fog test may be recorded on videotape, if required. Match the discharge speed of the fog or smoke to the air speed of the air stream in which it will be ejected to avoid false visual indications. The procedure should demonstrate smooth downward airflow, with no billowing of smoke or fog over work surfaces. Smoke or fog should not re-enter a work zone after it is drawn away.

Particle Count Test for OQ

A calibrated particle counter, capable of delineating particle sizes at 0.1, 0.2, 0.3, 0.5, and 5.0 µm per cubic foot, should be used. Several particle counters are now available on the market to take particle samples, perform statistical analysis of these samples, and store data from many different samples throughout a day.

Particle count tests usually are based on the requirements of Federal Standard 209E. Typical acceptable particle count class limits are shown in *Tables 2A, 2B* and *2C* on pages 202 and 203.

PERFORMANCE QUALIFICATION

Before performing the PQ of an HVAC system all IQ and OQ tests should be executed and the data thoroughly reviewed. Re-execution of PQ tests typically is very time consuming and, therefore, expensive. Coordinating such an effort also is difficult because it involves equipping a room with operators, equipment, video cameras, and other support equipment. In addition, the use of areas is restricted during execution of tests to ensure that doors or airlocks are not opened inadvertently.

It is important to understand the difference between OQ and PQ for an HVAC system. In this article, OQ tests include those executed under essentially static conditions, with no operators in the given area and no equipment running. On the other hand, PQ tests are dynamic tests, demonstrating performance capabilities during operating conditions, with equipment running and rooms staffed with normal numbers of equipment operators.

There are no hard and fast rules stating that certain tests must be performed in OQ and other tests in PQ. Some owners refer to all of these tests together as an OQ and, consequently, have no PQ. The bottom line is that all necessary tests must be performed in a logical sequence to demonstrate the effectiveness of an environmental control system for a specified area.

A frequent question regarding the PQ of an HVAC system is "When are HVAC PQs appropriate?" PQs are most often performed for areas of Class 10,000, 1000, 100, and cleaner, which generally involve areas with sterile product handling conditions, such as open vessels, sterile filtration, and, of course, sterile filling. PQs also may be required for non-sterile solid and liquid dosage forms where temperature, humidity, or cross contamination issues are considered critical process parameters.

Another important consideration of PQ is that testing accurately reflects actual operating conditions. Keep in mind that these tests are for the benefit of the owner, not to generate paper for regulatory officials. If there is a problem with the ability of a system to control contamination—regardless of whether that problem stems from inadequate air changes, lack of laminarity, or another source—PQ is the time to uncover it. In sterile filling areas, media fills typically follow the PQ, and this is not the time to discover contamination problems.

Particle Count Test for PQ

Based on the particle count requirements for a specified area, tests should be performed under dynamic conditions in order to demonstrate that a system can maintain compliance (i.e., will continue to operate in a validated state). Filling lines or other

(continued on page 205)

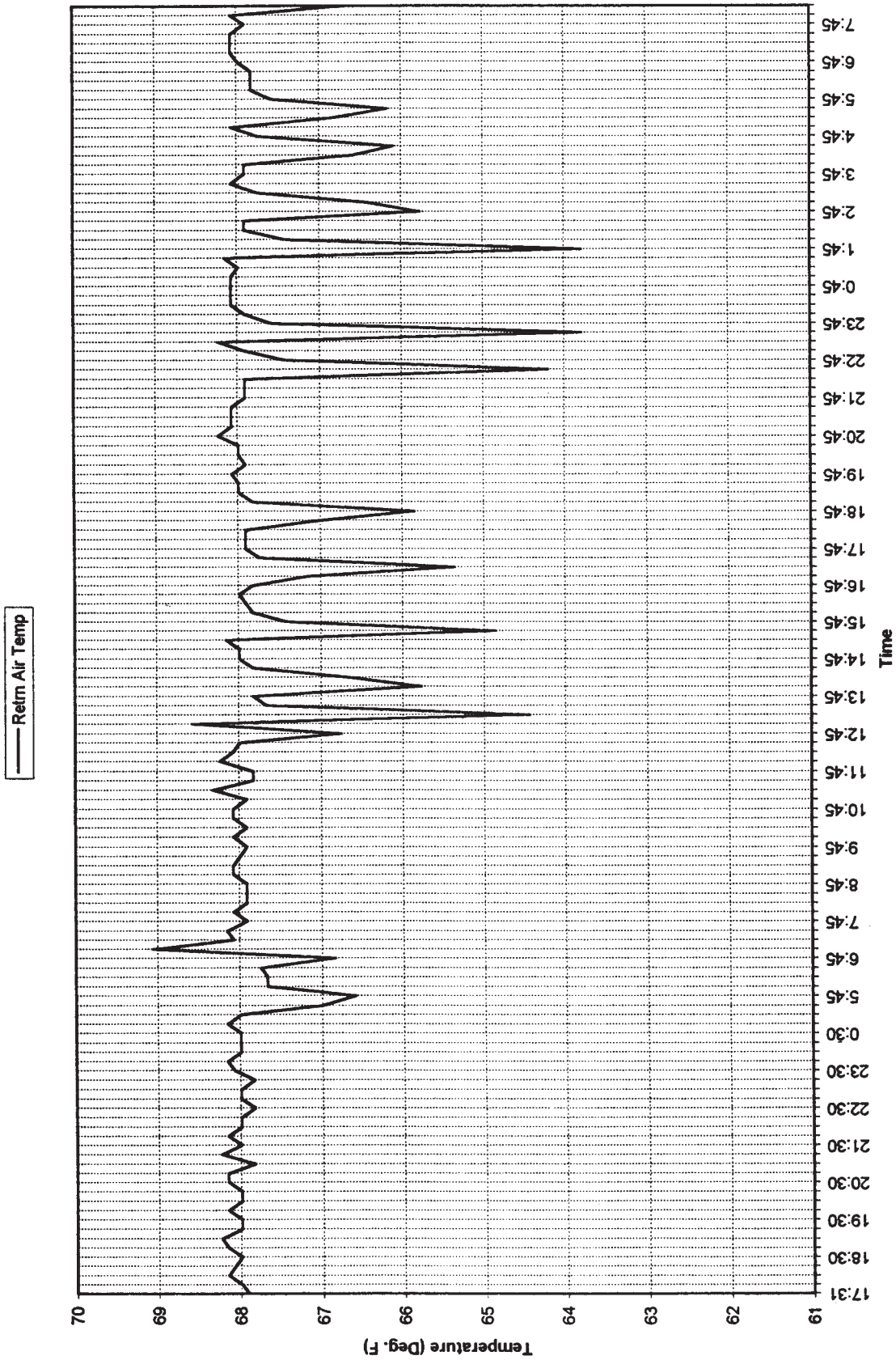


Figure 5A
AHU-30 STEADY STATE TEMPERATURE TEST

Figure 5B
SUTIE 605 STEADY-STATE HUMIDITY TEST

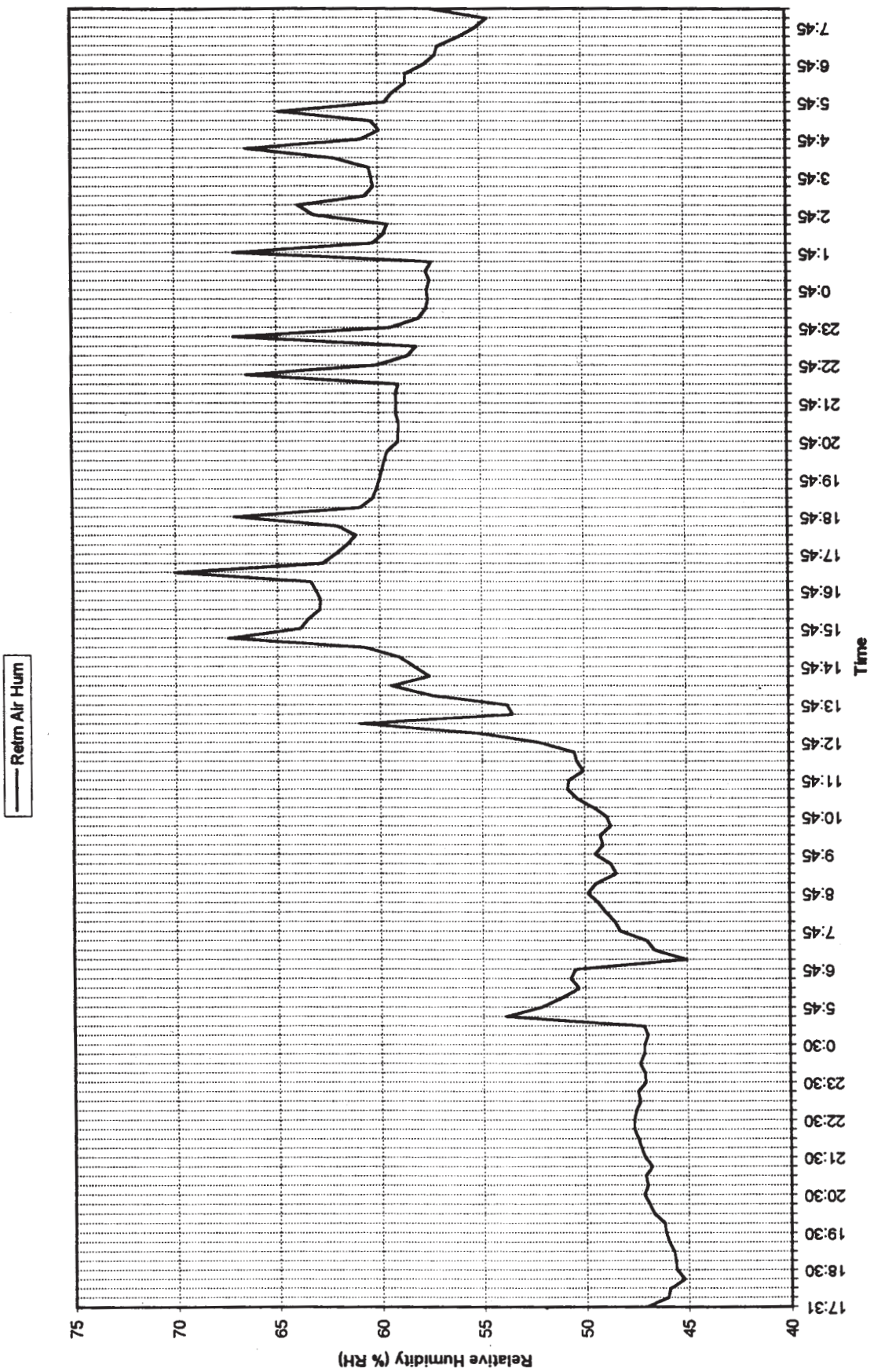


Table 2A
ACCEPTABLE PARTICLE COUNT CLASS LIMITS

CLASS	0.1	0.2	0.3	0.5	5.0
1	35	7.5	3	1	n/a
10	350	75	30	10	n/a
100	n/a	750	300	100	n/a
1,000	n/a	n/a	n/a	1,000	7
10,000	n/a	n/a	n/a	10,000	70
100,000	n/a	n/a	n/a	100,000	700

Particle Count Class Limits – Class limits in particles per cubic foot of size are equal to or greater than particle sizes shown in *Table 2A*. Federal Standard 209E specifies the minimum number of sample locations for an area with non-unidirectional airflow as:

$$\frac{\text{Square feet of floor area of the clean zone}}{\text{Square root of the airborne particulate cleanliness class designation}}$$

However, for an area with unidirectional airflow, the minimum number of sample locations is the lesser of the following two formulas:

$$\frac{\text{Area of the airflow entrance plane to the clean zone}}{\text{Square root of the airborne particulate cleanliness class designation}}$$

or

$$\frac{\text{Area of the airflow entrance plane to the clean zone}}{25}$$

Typically no less than two sample locations are taken for any clean room area. It is recommended that no less than three samples be taken at a particular location in order to establish repeatability. Average these samples to yield an average particle concentration, (A), at a given location.

According to Federal Standard 209E, a clean room or clean zone meets acceptance criteria for an airborne particulate cleanliness class if:

– The average of the particle concentrations measured at each location falls at or below the class limit.

AND

– The mean of these averages falls at or below the class limit with a 95 percent confidence limit.

The upper confidence limit (UCL) of the mean of these averages for a given clean room area is determined as follows:

The 95 percent UCL of the mean of averages (M) is determined by adding to the mean the appropriate UCL factor multiplied by the standard error (SE):

$$UCL = M + (UCL\ factor \times SE)$$

The mean of the averages (M) for a specific clean room area is:

$$M = \frac{A1 + A2 + \ldots + AL}{\text{number of locations}}$$

The 95 percent UCL factor can be obtained from a statistical table based on the number of sample locations. The UCL for a given clean room area must be below the class limit as specified in *Table 2B*.

Table 2B
UCL FACTOR FOR 95% UPPER CONTROL LIMIT

NUMBER OF LOCATIONS (L)	2	3	4	5-6	7-9	10-16	17-29	>29
95% UCL FACTOR	6.3	2.9	2.4	2.1	1.9	1.8	1.7	1.65

The standard error (SE) of the mean of the averages (M) is determined by dividing the standard deviation (SD) by the square root of the number of locations:

$$SE = \frac{SD}{\sqrt{L}}$$

And the standard deviation (SD) of the averages is the square root of the sum of the squares of differences between each of the individual averages and the mean of the averages $(Ai - M)^2$ divided by the number of locations (L) minus one:

$$SD = \sqrt{\frac{(A1 - M)^2 + (A2 - M)^2 + \ldots + (AL - M)^2}{L - 1}}$$

The minimum sample volume during particle count sampling is also important to ensure that a significant and representative sample of the air is obtained. Recommended minimum sample volumes are given in *Table 2C.*

Table 2C
MEASURED PARTICLE SIZE *(micrometers)*

CLASS	0.1	0.2	0.3	0.5	5.0
1	0.6	3.0	7.0	20	n/a
10	0.1	0.3	0.7	2.0	n/a
100	n/a	0.1	0.1	0.2	n/a
1,000	n/a	n/a	n/a	0.1	3
10,000	n/a	n/a	n/a	0.1	0.3
100,000	n/a	n/a	n/a	0.1	0.3

Minimum sample volume in cubic feet of air for air cleanliness class and measured particle size shown.

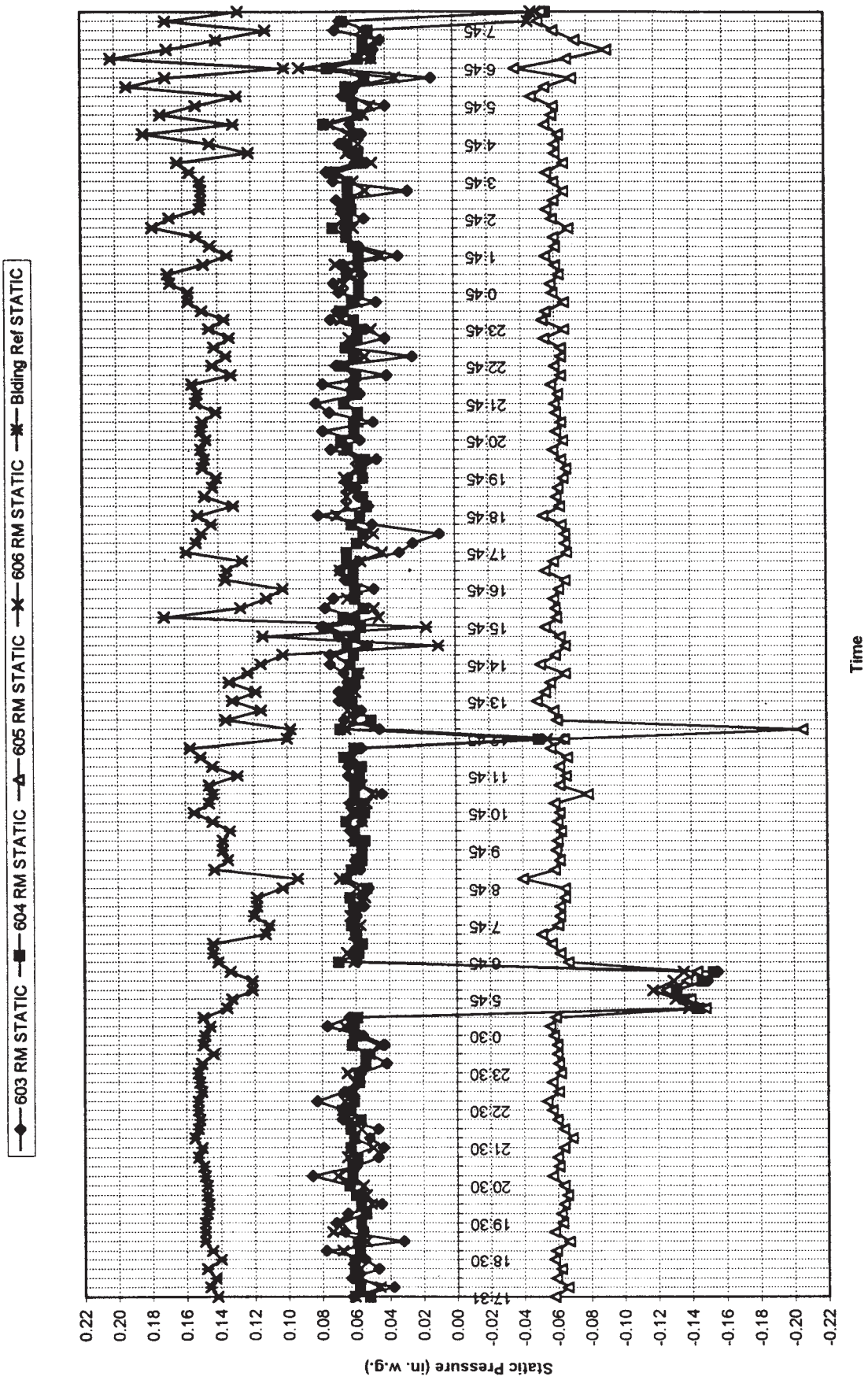


Figure 6
SUTIE 605 STEADY-STATE PRESSURE TEST

equipment should be operating, and personnel should simulate normal working movements and traffic. The sampling patterns used during OQ should be repeated. These tests should be performed in triplicate to show repeatability of results.

Recovery Tests

Recovery tests also should be performed in critical areas, particularly Class 100 laminar flow applications. These tests should demonstrate a system's ability to recover from an upset condition.

To simulate an upset condition, a particle generator can be used to imitate a contamination source. The ability to recover from contamination typically is tested for each critical processing zone. For large areas, the zone being tested should be subdivided into grids no larger than 10 square feet. Contamination should be introduced into the air stream for a specified period of time (usually one to two minutes). After a reasonable waiting period (approximately one minute), the particle count in the contaminated area is measured. This inflated count should return to the count measured during static conditions within two minutes.

Microbial Sampling

Microbial sampling is performed to demonstrate the effectiveness of an environmental control system in limiting the number of microbial contaminants. Several types of air samplers are available from several manufacturers (including Anderson, SAS, Q-Vac, and RCS) to capture a predetermined volume of air and then pass the air over an agar plate containing growth media. The sample volume and time are adjusted to allow contamination levels to be measured in the following format:

$$\frac{\text{Colony-forming unit (cfu)}}{\text{Cubic foot of air}}$$

After sampling a predetermined volume of air, the plates are incubated to facilitate growth of microbial contamination. Industry-accepted maximum contamination levels for Class 100, 1,000, and 10,000 areas are shown in *Table 3*.

Surface sampling also is an important piece of the qualification of an environmental system used for a sterile processing area. Most often, surface samples are performed using Rodac plates containing nutrient agar. The plates are pressed directly against surfaces within the room to yield a sample of the microbial contamination level. The plates then are incubated and the colonies counted, similar to the methods used with airborne microbial sampling. The surface sampling performed during the initial validation typically becomes the baseline for establishing action limits and alert limits for sampling after the room goes into operation.

Table 3
MAXIMUM CONTAMINATION LEVELS

AREA CLASS	CFU/CUBIC FEET OF AIR
100	0.1
1,000	0.5
10,000	2.5

SUMMARY

The compilation of meaningful data during IQ, OQ, and PQ is paramount to the continued efficient operation of critical process areas. Data must be organized and summarized to facilitate investigations of future problems and maintain an HVAC system in a validated state.

In addition to demonstrating the initial operational adequacy of a system, validation documents are an important troubleshooting tool. When—usually not if—problems occur in critical process areas, the validation package should be a readily available source of information on how the system was configured when it was operating within specifications. For example, maintenance and production personnel should be able to refer to validation documents to see whether a motor was replaced with an identical model, which if not done would cause airflow volumes or pressurizations to change within the critical environment.

In summary, the validation of an HVAC system should be designed to provide meaningful data for regulatory authorities, facility engineers, production personnel, and quality assurance departments. This documentation should demonstrate that a system is operating in accordance with design criteria and include all necessary information to facilitate future investigations as they inevitably occur.

For related articles, see the following issues of the Journal:

February 1996

1. Brian Scott, Jeff Hargroves, and Jerry Bauers, *Validation of HVAC Systems in Pharmaceutical & Biotechnology Facilities – Part 1*
2. Rae Anne Leitner, Christian Whitmyre, R. Scott Rushing, Thomas F. Helm, *An Overview of the Single-Source Approach to Validation of Mechanical Systems*

Drew Coleman and Douglas Burns

PYROGENS AND ENDOTOXINS: THEIR GENERATION AND PREVENTION IN PHARMACEUTICAL WATER SYSTEMS

"Science ought to teach us to see the invisible as well as the visible in nature; to picture to our mind's eye those operations that entirely elude the eye of the body; to look at the very atoms of matter, in motion and in rest, and to follow them forth into the world of the senses." **Tyndall**

Usually, a casual observer on his first tour of a biotechnology facility cannot help but notice the massive array of pipes, valves, fittings, gauges, and tanks. This infrastructure comprises utility systems and process equipment used to produce products from recombinant organisms.

The principal component of biotechnology products, constituting 95 percent to 97 percent by weight, is Water for Injection (WFI). By USP definition, WFI may be produced by purification methods using distillation or reverse osmosis (RO) technology and cannot contain more than 0.25 USP endotoxins units per milliliter (EU/ml).

To the casual observer mentioned earlier, this type of language is most likely a source of confusion. What is a pyrogen? What are endotoxins? Where do they come from? How do they enter WFI? How can they be expelled? This article will attempt to answer these questions. In addition, it will discuss strategies for validating pyrogen and endotoxin removal.

PYROGENS

Research History

Pyro, meaning fire in Greek, is the root for the term pyrogen, referring to any fever-causing substance. Billbroth first coined the term "pyrogen" when he produced hyperthermia in dogs by injecting distilled water.

In the late 1800s, Centanni coined the term "Fever Toxin" to describe bioactive substances derived from pyrotoxina bacteria. He developed a general method for fever toxin purification that yielded a highly pyrogenic white powder and involved the growth of gram-negative bacterial cultures, autolysis of the culture, sterile filtration, alcohol fractionation, and drying. Centanni was the first to recognize the cause and effect relationship between endotoxin, pyrotoxina, and the production of fever. He further discovered "pyrogenic tolerance," a process that makes animals unresponsive through repeated injections of endotoxin.

Other injections or concoctions known to cause pyrexia include those of putrid material and Salmonella typohsa lysate. In 1927, the Nobel prize was given to von Jauregg for his development of typhoid vaccine, tuberculin, and malaria parasites for treatment of paralysis.

In characterizing fever toxins from a variety of sources, Panum concluded that fever-inducing substances are generally heat stable and water soluble and that fever toxins purified from dead

materials are different than those from living bacteria. Gasperd confirmed Panum's conclusion by demonstrating that injections of cow's milk, beef broth, or human urine do not elicit as strong a reaction as do small infusions of putrid material.

Wechselmann and Mueller underscored the role of bacterial contamination of distilled water used in preparations. Salt Fever, the pyrexia associated with the administration of crude saline solutions, was not caused by salt but rather by salt solutions prepared with contaminated water. Fever often accompanied the administration of therapeutic agents. Heat sterilization or filtration failed to eliminate the pyrogenicity of these preparations.

In 1912, Hort and Penfold designed the standardized rabbit test, classifying bacteria into pyrogenic and non-pyrogenic types. They determined that gram-negative (staining) bacteria are pyrogenic and that gram-positive (staining) bacteria are non-pyrogenic. Comparing the response from live gram-negative cultures against those that had been killed, they correlated pyrogenicity of water purified from sources with differing bacterial concentration.

Basic Definitions

Pyrogens are classified into two groups: exogenous and endogenous.

Exogenous pyrogens originate outside the body and induce temperature elevations when injected into humans and animals. Lipopolysaccharide (LPS) is the most ubiquitous and important exogenous pyrogen. Others include:

- microbes
- microbial components of gram-negative bacteria
- gram-positive bacteria
- fungi
- viruses
- non-microbials, such as drugs, steroids, plasma fractionations, and the adjuvant muramyl dipeptide

Endogenous pyrogens, the primary mediators of fever, are homogeneous substances produced internally by a host in response to stimuli by various exogenous pyrogens. Examples include:

- IL-1
- 1L-2
- TNF
- platelet activating factor

Protein or liquid deviations are produced in response to exogenous pyrogens by specific immune system cell types, including neutrophils, macrophages, eosinophils, and monocytes.

Figure 1 shows the proposed mechanism for fever production. Starting at the bottom of the figure with external stimuli from exogenous pyrogens, phagocytic leukocytes produce endogenous pyrogens. In turn, these pyrogens activate the thermoregulatory center and finally the monamines, cyclic AMP, and prostaglandins that cause O2 consumption/heat conservation, which results in fever.

Figure 1
PROPOSED MECHANISM FOR
FEVER PRODUCTION

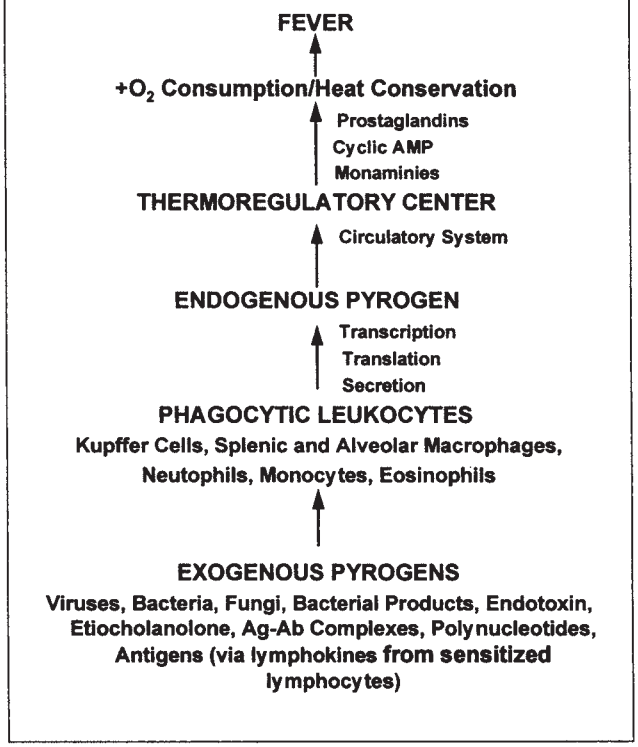


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Figure 2 diagrams a gram-negative cell membrane. Pay close attention to the "O" antigen side chains, which contain the "O" specific chain, core polysaccharide, and lipid A.

Lipid A is the sole portion of the gram-negative bacterial cell membrane responsible for antigenic activity. It is linked to core heteropolysaccharides by 2-keto-3-deoxyoctonic acid (KDO), an eight carbon sugar acid that is unique to bacterial lipopolysaccaride. KDO, together with core polysaccharides, acts as a solute carrier for the lipid portion in an aqueous medium, such as WFI. Lipid A is hydrophobic, permitting it to interact and form higher molecular weight aggregates, especially in aqueous solutions. (See *Figure 3*.)

Figure 2
DIAGRAM OF A GRAM-NEGATIVE CELL MEMBRANE

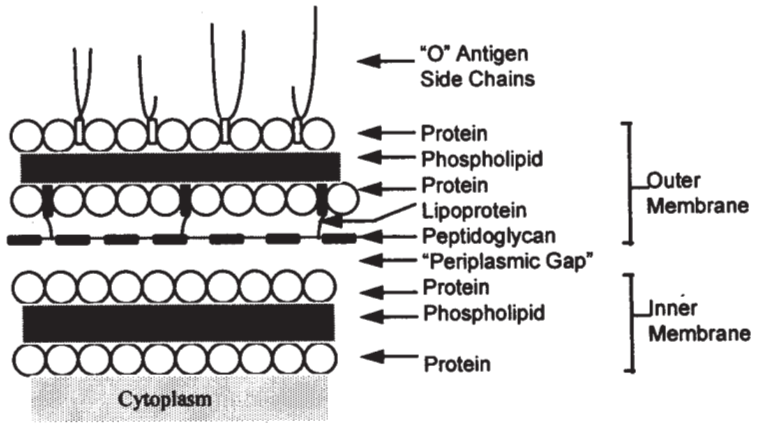

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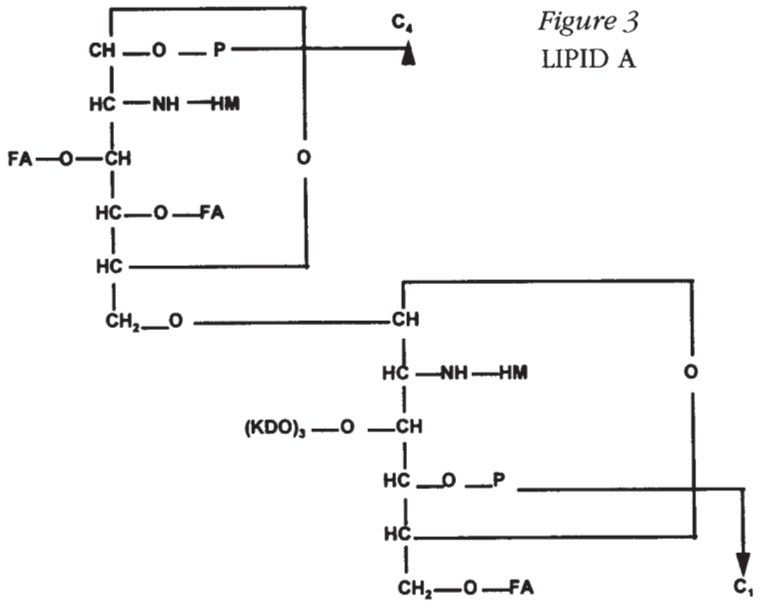
Figure 3
LIPID A



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ENDOTOXINS

Basic Definitions

Bennet said that endotoxins "possess an intrinsic fascination that is nothing less than fabulous." These substances can be broken down into two major parts: the hydrophilic polysaccharide (sugar) chain and the hydrophobic lipid (fatty) group. The hydrophilic polysaccharide chain is responsible for the antigenic individuality of gram-negative bacteria and thus gives rise to thousands of observed serotypes. The core lipoprotein (hydrophobic lipid fatty group) to which its polysaccharide chain is attached is remarkably uniform in many diverse groups of gram-negative bacteria.

Endotoxins contribute to the antigenic heterogeneity and homogeneity of gram-negative bacteria. Due to their tendency to aggregate, endotoxins can have an apparent molecular weight of greater than 106 daltons in aqueous solutions. The longer the polysaccharide chain, the more water soluble the endotoxin molecule. These high molecular weight complexes are associated with the outer membrane of gram-negative bacteria. During autolysis, endotoxin is released from a cell into

surrounding medium. Unpurified endotoxins contain lipid, carbohydrate, and protein. When protein is removed, the purified composition is termed an LPS to emphasize its chemical composition. Endotoxins are heat-stable in solution and may be inactivated by dry heat, alkali, acid, and exposure to polymyxin B.

Removal

Ultrafiltration units with molecular weight cutoffs of 20,000 to 100,000 daltons often are used to remove endotoxins from solutions. Distillation by means of phase transformation and liquid separation systems has been known to effectively separate endotoxin from the resulting vapor and subsequent distillate. Various methods are used to detect endotoxin, and a comparison of these tests is provided. (See *Figure 4* on page 126.)

The most efficient method for endotoxin removal is a distillation unit that incorporates a baffling system. Separation is effected by the change in state from liquid to vapor to liquid. The baffling system is used to increase the efficiency of the phase transition. Many distillation units employ various devices, including "the famed" Q-baffle, spiral separators, demister pads, cyclone separators, and combinations of these.

RO systems also are used; however, they tend to have weak links that can leak. For example, interconnection seals, chevron seals, and membranes may be prone to disintegrate and/or foul. These units must be monitored and sanitized regularly to be used effectively.

Ultrafiltration systems, which use plate technology or hollow fiber units employing 5,000 to 20,000 molecular weight cutoffs, are becoming the units of choice. Though not extensively used in the United States, these steamable ultrafiltration units are likely to take the place of distillation in the years to come.

Other methods include charge modified media filtration (e.g., Pall's Posidyne filters), microporous membrane filtration, and other membrane filtration systems which may be either hydrophobic or hydrophilic.

MICROBES IN PHARMACEUTICAL WATER SYSTEMS

In 1991 Motomura and Yabe isolated 127 species of organisms from pure water, 80 percent of which were Pseudomonads. (The remainder were Acinetobacter, Alcaligenese, and Flavobacterium.) Another known species of organisms deleterious to water systems are glycocalyx bacteria. Glycocalyx, which refers to the bacterial envelope of most immotile bacteria observed in nature, results in a holdfast that allows growth of biofilm and protects survival of an organism in low nutrient environments. Glycocalyx bacteria have been known to generate different endotoxin levels depending upon the assay used, thus making it difficult to determine the true endotoxin content of the infected system.

MICROBIAL GENERATION

Common inoculation and incubation sites in pharmaceutical water systems are sand filters, carbon beds, deionization resins, deadlegs, storage vessels, and fill lines to storage vessels.

Sand filters and their associated carbon beds are microporous in nature and often left unsanitized. In as much as all microbes need a carbon source, when left unattended these units become perfect brewing grounds for microbes, providing an inoculation system for RO membranes. These membranes—thin film composite, polyamide, or cellulose acetate in composition—are known to support microbial growth.

Deionization resin tanks harbor microbes and may be difficult to sanitize due to resin channeling and other structural characteristics. Storage vessels and surge tanks often support biofilms due to their smooth walls and slow flowing water systems.

Dead legs and stagnant flow sections can accumulate microbes. These problem areas are found most commonly in connections to glasswashers and pure steam generators.

The fill line from a distillation unit to a WFI tank can become a breeding ground during periods of repair or maintenance. A well designed system places a divert valve just before the WFI storage tank. Consequently, when the still is turned back on, the initial WFI is rejected at the entrance

Figure 4

COMPARISON OF LAL TEST METHODS

	Gel-clot	Endpoint Turbidimetric	Kinetic Turbidimetric	Endpoint Chromogenic	Kinetic Chromogenic
Cost	Lowest equipment cost	Relatively inexpensive, widely available instrumentation	Moderate to expensive instrumentation	Relatively inexpensive, widely available instrumentation	Most expensive instrumentation
Sensitivity	Sensitive - up to 0.03 EU/ml. Sensitivity standardized by the manufacturer	Most sensitive (detection limit of 0.001 EU/ml)	Most sensitive (detection limit of 0.001 EU/ml in LAL-5000)	More sensitive (detection limit of 0.005 EU/ml)	More sensitive (detection limit of 0.005 EU/ml)
Maximum test range	NA	1 log e.g. 0.1 -1 or 0.01 -0.1 EU/ml	0.001 - 100 EU/ml	1 log e.g. 0.1 -1 or 0.01 -0.1 EU/ml	0.005 - 50 EU/ml
Resolution	plus or minus one twofold	+/-25%	+/-25 or 50%*	+/-25%	+/-25 or 50%*
Susceptibility to interference	Resilient - often less affected by interference than other methods	May show more interference than gel-clot, but greater sensitivity gives more scope for dilution to overcome it			
Timing	Must be on hand to read test after one hour	Critical - reaction must be timed carefully	Automated instrumentation handles timing	Critical - reaction must be timed carefully but can be stopped for reading - easier than end-point turbidimetric	Automated instrumentation handles timing
Reaction vessel	Soda lime glass culture tubes	Borosilicate glass culture tubes or microplates**	Borosilicate glass culture tubes (in LAL-5000) or microplate**	Microplate**, sometimes glass culture tubes	Microplate** - allows for quick, easy dilutions
Other Comments	USP compendial method. Results are easy to interpret. Can process many samples at a time.		LAL-5000: -very good temperature control -individually controlled timing for each well -samples can be added to a test in progress	Diazo option allows testing of samples that absorb at 405 nm	

*The resolution of kinetic methods depends on the spike recovery range used. The 1987 FDA "Guideline on Validation of the Limulus Amebocyte Lysate Test...." specifies that spikes be recovered within +/-25%. This was increased to +/-50% in the 1991 FDA "Interim Guidance for Human and Veterinary Drug Products and Biologicals: KINETIC LAL TECHNIQUES". This change did not apply to medical devices.

**Microplates cannot be practically depyrogenated by the user. Occasional contaminated wells ("hot wells") are to be expected when used. An appropriate source of relatively clean plates is necessary. Pyroplates are available from Associated of Cape Cod, Inc. and are provided with a certificate of analysis.

Courtesy of: Associates of Cape Cod, Inc., Woods Hole, Massachusetts

Figure 5A

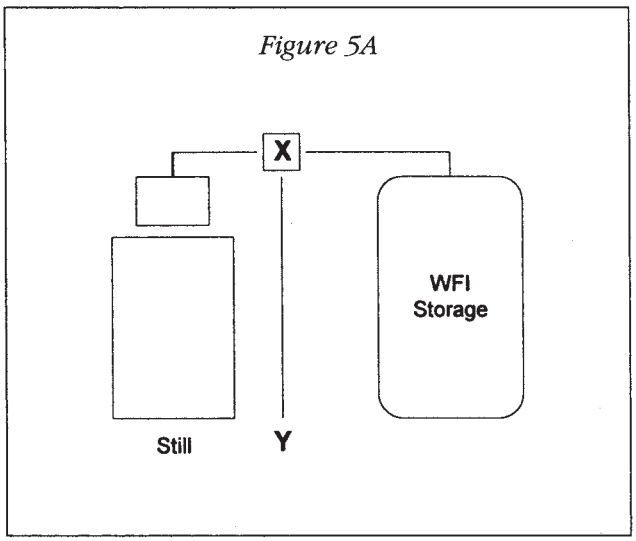
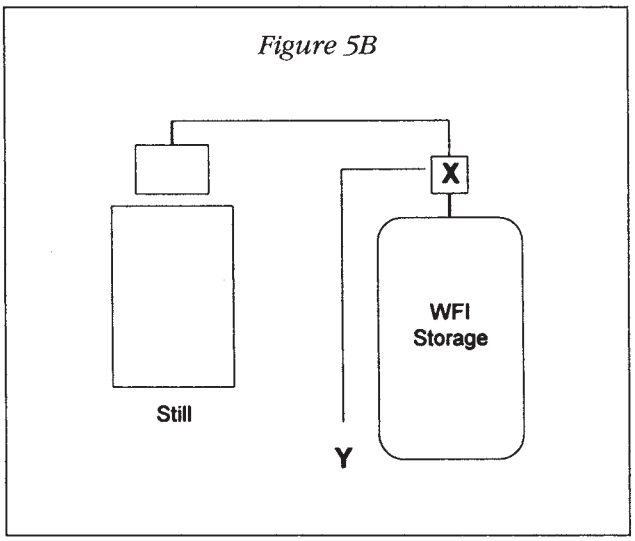


Figure 5B



to the tank. If the divert valve is placed further upstream, it does not provide adequate sanitization of the line feeding the vessel. *Figures 5a* and *5b* show the two styles of rejection systems.

The best way to avoid inoculation of microbes, and henceforth pyrogens, in a water system is by designing a system that cannot be easily inoculated and/or colonized. *Figures 6* and *7* show differing pretreatment systems. (See page 128.)

The system in *Figure 6* relies on a well-executed preventive maintenance program complete with a provision for sanitization. *Figure 7* eliminates components that harbor microbial growth. (Note: When creating this design, the authors attempted to provide maximum protection for production units and allow ease of operation. Missing from this pretreatment design are sand filters and carbon beds. These were eliminated due to their need for high maintenance and the tendency to foul. A 0.05 micron hollow fiber is positioned in their place. In addition, the provision to chemically sanitize the system with Minncare and the use of a heat exchanger to "hot-water" sanitize the system were included.)

SYSTEM SANITIZATION

When systems become contaminated with bacteria many popular chemical agents are used to sanitize them. These are listed in *Figure 8* and ranked by their efficacy in *Figure 9*. (See page 129.)

Many times hot water sanitization and/or steam sanitization may be used to rid a system of microbes. However, the use of these methods can create an upheaval of biofilm and true elimination may not be accomplished.

SYSTEM VALIDATION

Thus far this article has provided information about pyrogens and endotoxins, a review of existing systems, and problems created by having pyrogens and endotoxins in a system. What now should be done to determine whether a system has the ability to remove these substances? What is the next logical step to validate this function?

The validation process involves a detailed outline of the discrete processes involved in the production of pure water and a complete description of the equipment used for each step. Accompanying these documents should be a block diagram, PFDs or P&IDs , and other descriptive documentation.

An important component of this basic information section is the inclusion of a schematic system diagram that identifies sample point locations, as shown in *Figure 7*. The sampling and testing schedule should reference this schematic and include space for acceptance criteria and test values. This format will facilitate data entry, which will be used later for trending.

An endotoxin removal method is validated by spiking the supply water with purified endotoxin prior to the start-up of the RO unit or still, process-

Figure 6
A TYPICAL PRETREATMENT SYSTEM

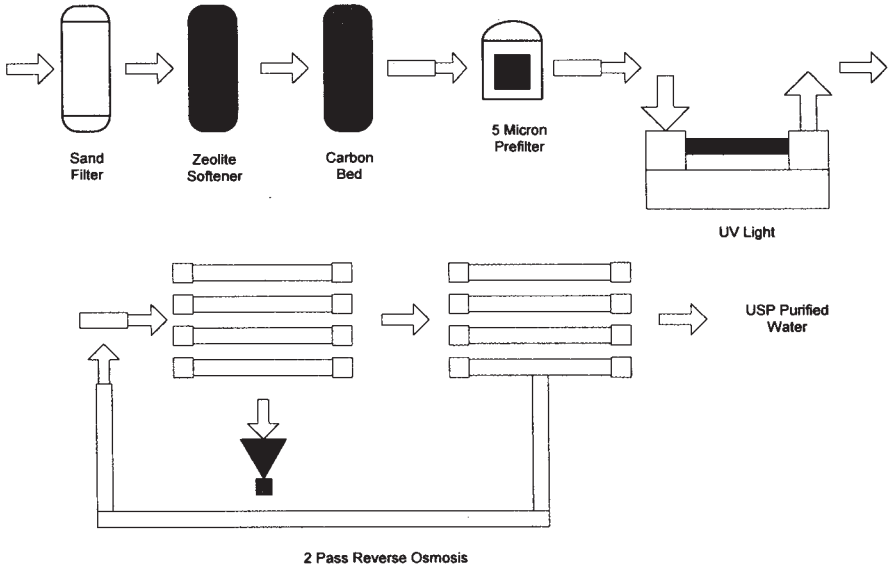


Figure 7
A PREFERRED PRETREATMENT SYSTEM

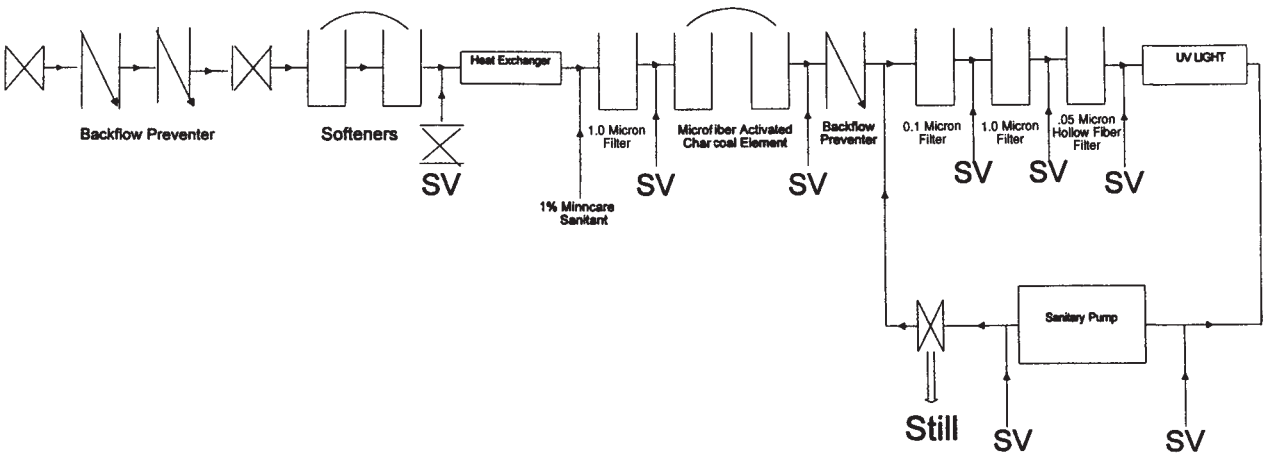


Figure 8
COMMONLY EMPLOYED SANITANTS FOR WATER SYSTEMS

Some popular chemical agents used to sanitize are:

- H_2O_2
- 0.25% H_2O_2 in a 1% solution of NaOH
- Ammonium Salts
- Mineral Acids (HCl; H_2SO_4; H_3PO_4; HNO_3)
- Ozone
- NaOH
- 5.25% Sodium Hypochlorite
- Household Bleach
- 0.5-1.0% Peracetic Acid
- Household Detergents

Figure 9
EFFECTIVENESS OF COMMON BIOCIDE AGENTS

Exposure Time	Minncare (1%)	Formaldehyde (2%)	Sodium Hypochlorite (0.001%)	Hydrogen Peroxide (0.2%)	Hydrogen Peroxide (5%)	Hydrogen Peroxide (10%)
15 minutes	$1.1x10^6$	$2.3x10^6$	$2.2x10^6$	$2.3x10^6$	$2.0x10^6$	$2.0x10^6$
30 minutes	$3.0x10^6$	$2.1x10^6$	$1.1x10^6$	$2.3x10^6$	$2.0x10^6$	$2.0x10^5$
60 minutes	<10	$2.0x10^6$	$4.0x10^4$	$2.0x10^6$	$1.0x10^5$	<10
2 hours	<10	$1.5x10^5$	$1.0x10^4$	$2.0x10^6$	<10	<10
12 hours	<10	<10	<10	$1.0x10^3$	<10	<10
24 hours	<10	<10	<10	<10	<10	<10
D values	6 min	113 min	69 min	250 min	22 min	11 min

ing the water through the purification unit, and then testing for endotoxin in the processed water. It is very important to prepare these challenges carefully, making sure that the information gathered is accurate. In Drug, Device and Diagnostic Manufacturing, Carol DeSain provides a good outline of these procedures. In summary, they reflect the following:

1. Use of purified endotoxin, standardized against USP reference standards.
2. All contact surfaces must be inert to endotoxin.
3. Introduced endotoxin must be as concentrated as possible.
4. Accurate measurement of endotoxin actually introduced into the system.
5. Shelf life of endotoxin must be verified.
6. Positive and negative controls must be run by QC with each challenge.

Remember that the quantification test chosen must be appropriate for the product being manufactured and capable of detecting levels in the appropriate range. (See *Figure 4* for LAL test methods). For WFI, there can be no more than 0.25 EU/ml.

The next step is to determine the range of EU/ml that normally exists in untreated feed water during the course of a year. The endotoxin challenge should be at least 1.5 to 2.0 times greater than the largest amount expected in the raw feed water. Be sure to have enough data (perhaps 12 months worth) to support the amount of endotoxin to be spiked into the feed water.

Once the EU/ml range is determined, calculate the total amount of endotoxin that is needed for the challenge. The following hypothetical system is presented as an example:

1. Determine the total quantity of endotoxin required.
Assume that at the start of the spike challenge the tank will be empty and subsequently filled to 100 percent capacity. The maximum amount of endotoxin required in the spike is calculated in the following manner:

If Tank Volume = 1000L
and Potential High Volume = 60EU/ml,

Then 60 EU/ml x 1000 l x 1000 ml/l x (1.5 to 2.0) = 9.0 to 12.0 x 107 EU.

2. Choose the inoculation site.
Since the RO unit (or still) will remove the endotoxin, the inoculation will be made into the last available port upstream of the purification unit.

3. Inoculate with endotoxin.
Turn off the RO (or still); empty the storage tank; shut off the supply to the purification unit; inoculate the supply line; open the supply line to the unit, and turn on the RO (or still).

4. Sample collection.
Allow the system to run until the tank is 100 percent full. Following sterile sampling procedures, collect samples from the production unit outlet and storage tank for analysis as it is being filled. The reported EU/ml concentrations then are evaluated for adherence to the previously described acceptable limits.

This procedure will provide the baseline information needed for evaluation of further validation studies. The purification system eventually will run with water from the pretreatment system. At this time, the proposed sampling from the selected sample valves will begin, providing continual information on endotoxin loads. Once the purification system has been validated, it becomes apparent when increases in EU/ml in the circulation system are probably being generated within the circulation loop itself rather than in the purification system.

CONCLUSION

Protection of a water system begins in the design phase. Systems should be designed to prevent microbial contamination of water and for easy eradication of sanitizing agents. "Tried and true methods" of pretreatment now are being carefully scrutinized by regulatory agencies. Long gone are the days of "we've always done it this way."

It is essential that companies look at water purification as a means to eliminate microbial

contamination during each step in the purification process. Systems must be maintained properly to produce high quality water routinely. Sampling valves must be located strategically throughout a system to measure its effectiveness.

It is every pharmaceutical manufacturers' duty to produce pharmaceutical WFI that is free of microbes, pyrogens, and chemical contamination. In so doing, companies are able to produce biomolecules and pharmaceuticals with the purity that they desire and that the patient deserves.

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1. Bruce Fessenden, *A Guide to Water for the Pharmaceutical Industry: Part 1 – Basic Chemical, Physical, & Dynamic Concepts*

May 1995

1. Bob Elms and Cindy Green, *Water Systems: The Basics – Part 2, Validation and Maintenance*
2. William V. Collentro, *Proper Validation of a Water Purification System: An Inherently Flawed Process?*
3. Benjamin J. Roczniak, *A Guide to Validating a Purified Water or Water for Injection System*

February 1995

1. Bob Elms and Cindy Green, *Water Systems: The Basics – Part 1, Design as a Prelude to Validation*

Conducting a Water Quality Failure/ Incident Investigation

This article, based on various procedures developed by the author over the years, will provide an overview of such an SOP with special references to water quality failure investigation...

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Quality systems and procedures are implemented to minimize quality defects, with an the aim of creating a zero-defect manufacturing environment. In reality, there is no such thing as a perfect system. Quality defects and failures are part of any manufacturing operation, and pharmaceutical manufacturing is no exception. cGMPs require that all quality failures/incidents should be investigated, documented, and corrective actions implemented to prevent recurrence of the quality defects. Most pharmaceutical manufacturers have established detailed procedures on how to investigate out-of-specification data originating in analytical laboratory following the Barr Decision. However, there is a need to have separate procedures to address other operational quality issues, i.e., quality failure/incidents. Quality failure incident investigation procedures offer a number of benefits, such as:

- Standardized investigation formats
- Useful communication and training tools
- Improved processes and procedures
- Long term cost savings
- Enhanced overall compliance
- Timely resolution of quality issues

This article, will provide an overview of such an SOP, with special reference to water quality failure investigation, both during validation and routine monitoring of the system. Considering the depth of the subject, this article will be divided into two sections: Section I will address general quality failure incident investigation procedure, and Section II will address water quality failure investigation. This article is based on various procedures developed by the author over the years.

What is Quality Failure/Incident?

Quality failure refers to a situation where a finished drug product, process, or service does not meet its expected attributes or specifications. Quality incident, on the other hand, could be a failure of the quality system practices, which may or may not lead to a quality failure of a product, process, or service. Both cases, however, should be fully investigated and documented.

Section I
Quality Failure/Incident Investigation Procedure

A quality failure/incident investigation procedure should address the following areas as appropriate, (see *Figure 1* for a summarized list):

Figure 1

Elements of Quality Failure/Incident Investigation Procedure

Define quality failure/incident
Define quality significance of the failure/incident
Define the cause of quality failure/incident
- *Facilities*
- *Utilities*
- *Components*
- *Equipment*
- *Process*
- *Drug product*
- *Analytical*
- *Personnel*

Quality failure/incident investigation
- *Facilities*
- *Utilities*
- *Components*
- *Equipment*
- *Process*
- *Drug product*
- *Personnel*
- Procedures and documentation practices

Corrective action plan
Summary, conclusion, and sign off

Define quality failure/incident

It is extremely important that the quality failure/incident be defined in a clear and concise manner, detailing exactly what happened.

Define quality significance of the failure/incident

Most quality failure/incidents can be classified as critical, major, minor, or for information only. In some cases, the quality data is also measured against alert and action limits, e.g., total aerobic count for an environmental monitoring sample for a given area. This classification can be a useful tool in determining the extent of the investigation as well as the scope of corrective actions needed, including disposition of drug product or products involved.

Define the cause of quality failure

A quality failure/incident could be caused by one or more of the following; however, use the process of elimination to narrow down this list as much as possible.

Facilities

An example of facilities as a possible cause of quality incident/failure could be improper cleaning/sanitization of manufacturing areas leading to increased bioburden in the environment with the potential for drug product contamination.

Utilities

Malfunction of any of the following utility systems can cause a quality failure/incident leading to a drug product failure:

- HVAC system
- Water purification system
- Compressed air system
- Dust collection system

Components

Both chemical raw materials and packaging/labeling components can cause a quality failure/incident.

Equipment

Equipment breakdown, as well as improper cleaning, can lead to quality failure/incident.

Process

Manufacturing process, as well as process conditions, can contribute to a quality failure/incident.

Drug Product

Failure to meet drug product specifications is the ultimate quality failure/incident.

Analytical

Most analytical laboratory quality issues are related to analytical data and are usually investigated according to an out-of-specification (OOS) data investigation SOP. An OOS investigation will likely involve some of the aspects being discussed here.

Personnel

Personnel expertise and level of training can also significantly contribute to quality failures.

This listing should not be considered all inclusive, and there could be other factors involved. One should review all possibilities and attempt to define the most probable causes of the quality failure/incident.

Quality Failure Investigation

A quality failure/incident investigation should include a review of the following, depending on the most probable causes. Concentrate on those areas that may have contributed to a given quality failure/incident. The investigation phase is, in fact, already underway as the probable causes of a given quality failure/incident are being defined, and therefore, the two cannot be totally separated from each other. Quality Assurance must lead the investigation phase in cooperation with other departments, as these findings will be the basis of any corrective action plan.

Facilities

If facilities are a possible cause of quality failure/incident, review the state of repair of manufacturing and packaging areas as well as the temperature and humidity conditions in the plant. Also, if the microbial environment is monitored, the data for the particular incident should be reviewed along with data for the past four to six weeks to identify any adverse trends.

Utilities

If any of the utility systems is a potential cause for a quality failure incident, review the system in question in detail. Some items to be checked if one or more of the following utility systems is under suspicion:

- HVAC System – Temperature/humidity profile of the area and potential temperature/humidity exposure of the components and drug product(s) involved.
- Water purification system – Both chemical and microbial quality of purified water and water for injection can impact the quality of the finished drug product. Quality failure investigation for a water purification system will be discussed in detail in Part II of this article.
- Compressed air system – Possible presence of oil droplets in an oil-free compressed air system can cause contamination.
- Dust Collection System – Malfunction of a dust collection system can cause excessive dust in the area with potential for cross contamination, especially where conditioned air is recirculated.

Components

Always review the sampling/inspection and release processes if a component is a potential cause for a quality failure/incident. Sample manipulation can have potential negative impact on the quality of the material being sampled.

Both active and inactive raw materials can have a direct bearing on drug product quality if these are not of desired quality or their quality is compromised either during sampling process or due to improper storage conditions.

Packaging/labeling component quality defects can cause potential stability concerns as well as mislabeling situations. Almost one-third of all the drug product recalls in recent years were due to mislabeling of drug products, per FDA enforcement reports.

Equipment

If manufacturing/packaging equipment is a potential cause for a quality failure/incident, review the following:

- Cleaning and sanitization records
- Calibration status of critical equipment
- Maintenance records
- Performance history
- Equipment qualification records

Process

Review the manufacturing process in detail to see if there were any deviations or anomalies. Also review the process conditions, like temperature, humidity, machine speed set ups, order of addition of ingredients, process time limits, etc. A review of process validation records might well be in order if considered necessary.

Drug Product

Review other batches of the same drug product to see if this is a product-specific quality issue or an isolated incident. Also review batches of related drug products manufactured under a similar set of conditions. This will help determine if other drug products are also involved. This part of the investigation demands extreme diligence on the part of the quality management team, as it can have far-reaching implications. In recent years, FDA has repeatedly cited pharmaceutical manufacturers for failure to perform an in-depth investigation of quality failure/incidents.

Personnel

This is an issue that is difficult to measure, as it tends to indirectly validate the effectiveness of an

employee training program. Make sure that the individuals involved in all phases of a given quality failure/incident have the knowledge, expertise, and training to carry out their assignments, and there is documented evidence to support this claim. If not, an isolated quality failure/incident could be an indication of a major systemic quality problem within the organization.

Procedures and Documentation Practices

A review of the SOPs, batch records, analytical procedures, etc., is also required to complete this investigation. This assures that the procedures are detailed enough and easy to follow for the operator; if not, revisions might be needed.

Corrective Action Plan

Quality Assurance management, in collaboration with other appropriate departments within the organization, should develop a corrective action plan with definite time lines for implementation. Such a plan should clearly define the responsibilities and accountability profile of assignments and should include:

Does the incident/failure fall under OOS investigation? If so, is there a need for a separate investigation?

In such cases, the two investigations should complement each other in resolving the issue.

- Identify procedural changes required
- Identify documentation to be revised
- Identify additional training requirements
- Disposition of the drug product(s) involved

Summary, Conclusion, and Final Sign Off

A critical step in the successful conclusion of any investigation is that a summary report and conclusion is written up. Before finalizing such a report, Quality Assurance should verify that all the corrective actions have been (or are being) implemented per their time lines. The effectiveness of completed corrective actions can be evaluated by verification that the procedures and systems were revised, and the employees were retrained by responsible personnel, the new equipment was purchased, or there was a change in a raw material supplier, etc.

Documentation supporting that a given corrective action was completed should be reviewed and referenced or attached to the investigation report, like employee training records, copies of the purchase order, copy of the approved change control, etc.

The report should be reviewed and approved by the appropriate departments within the organization. Quality Assurance and other pertinent departments should sign off on the report and sign-off responsibilities should be delineated in an SOP. The summary report should be used to inform the upper management of any critical quality issues, especially those which would involve capital investments as part of their corrective action plan.

Section II
Water Quality Failure Investigation Procedure

Water purification systems are designed and qualified to assure a consistent supply of purified water of the desired quality. However, despite our best efforts, a water sample may fail to meet its specifications.

Water quality failure/incident has far-reaching implications, as purified water and water-for-injection are widely used in drug product manufacturing and facilities and equipment cleaning. In Section I of this article, quality failure/incident investigation procedure was discussed. Section II of this article, based on the author's personal experiences in handling water system quality failures, will provide a detailed overview of water quality failure investigation procedure, both during validation and routine monitoring of the water purification system.

In order to accomplish a comprehensive investigation of a water quality failure incident, it is important that different aspects of the investigation be assigned to different departments within an organization according to their expertise. This is especially true if the incident happens during validation or major revalidation of a water purification system. The investigation team should include:

- Engineering and Maintenance along with Validation to review the water purification system for physical and functional integrity from an engineering, as well as, a validation point of view.
- Quality Assurance to review the procedural and training issues, as well as the drug product(s) involved from a compliance point of view.
- Quality Control to review the chemical and microbiological testing issues, as well as the

water sampling techniques.
- Drug safety and information to review the safety concerns to decide the disposition of affected drug product(s).

The investigation should be led by Quality Assurance and may also involve Manufacturing if needed. The investigation team should discuss all findings of the investigation before designing a corrective action plan and deciding the disposition of the drug product(s) involved.

Water Quality Failure Investigation

A water quality failure investigation should address the following areas as appropriate (see *Figure 2* for a summarized list).

Define water quality failure/incident

Water quality failure/incident could involve one or more of the following scenarios:

- Purification system malfunction
- Chemical
- Microbiological

In most instances, it is the failure of a water sample for chemical or microbiological specifications which triggers an investigation. Since purified water is being constantly used in production, there is always a chance that the suspect quality water might have been used in equipment cleaning or manufacture of a drug product, thereby putting it at risk.

Define quality significance of the water quality failure/incident

Water quality failure incidents can be classified as critical, major, minor, or for information only, depending on the nature and severity of the incident. For microbiological tests, the quality data is measured against alert and action limits, e.g., total aerobic count for a purified water sample. If the water sample fails pH specification or total organic carbon (TOC), and the purified water was used to manufacture a solid oral dosage, the impact on quality, strength, identity, and safety of the drug product will be much less if the water sample fails for microbiological specifications and is used to manufacture a liquid or sterile drug product. This classification can be a useful tool in determining the extent of the investigation as well as the scope of corrective actions including disposition of drug product(s) involved.

Figure 2

Elements of Water Quality Failure/Incident Investigation

Define water quality failure/incident
- *System malfunction*
- *Chemical*
- *Microbiological*

Define quality significance of the water quality failure/incident

Define the cause of water quality failure/incident
- *Purification system*
- *Sampling*
- *Analytical issues*

Quality failure/incident investigation
- *Purification system*
  - Source water
  - Pretreatment
  - Purification system
  - Storage and distribution
  - Controls, alarms, etc.
  - Sanitization cycle
- *Sampling*
  - Sampling procedure
  - Sampling technique
  - Sample container prep
- *Analytical procedures*
  - Instruments
  - Analytical procedures
  - Analyst training
  - Sample prep
  - Media prep and tracking
- *Drug product/s involved*
- *Personnel*
- *Procedures and documentation practices*

Corrective action plan

Summary, conclusion, and sign off

Define water quality failure/incident

Water quality failure/incident could be caused by one or more of the following; however, try to narrow down this list as much as possible.

Purification system

Each water purification system is designed per individual plant requirements but does have so constants which should be looked into when investigating a water quality failure/incident.

Source Water

Quality of source water as supplied by local water authorities changes with the time of the year and geographic location of the plant. Microbial quality and the total dissolved solids in source water play a vital role in determining the capability of a given water purification system. Source water

test data should be part of the validation file for a given water purification system. Sudden changes in source water quality can cause purified water failure, especially after natural disasters like floods. Source water test data from the local water authority and in-house periodic source water test results should be reviewed to determine any sudden change in source water quality. This review should also indicate any trends that might be developing over recent weeks, especially after heavy rains or floods in the area, as they can affect the composition of natural water reservoirs.

Pretreatment

Source water is pretreated to minimize the level of both organic and inorganic impurities before water is actually processed through the final purification step. If pretreatment steps are not precisely controlled and routinely monitored for performance within preset limits, these could cause quality failure of the water produced.

Chlorination

Chlorine is added to the source water to decrease its bioburden. It also helps to minimize microbial growth in the pipes and storage equipment. Local water authorities usually add a chlorine gas generating chemical to water to produce 1 – 2 PPM of chlorine gas, like sodium hypochlorite. However, there is a downside to the presence of chlorine in water, as it tends to corrode stainless steel surfaces and will deteriorate reverse-osmosis membranes. It is, therefore, very important that chlorine be removed from water before it actually reaches the purification and storage stage.

However, if there is insufficient or no chlorine in the source water, the purification system downstream may not be able to remove all the microbial contaminants, thereby causing a quality failure of the water produced.

Depth Filters

Source water is passed through a series of coarse filters to remove suspended solids. The filtration media could be different grades of sand. However, such filters tend to harbor microbes and should be periodically backwashed to remove all the trapped waste. If left unsanitized, these filters could contaminate the water with microbes, causing failure of the water produced after purification.

Water Softeners or Deionizers

Water softeners or deionizers are used to remove the heavy metal ions from source water to avoid scaling downstream during the purification process. Deionizing resins need to be regenerated periodically, and the regeneration process should be controlled to assure that a deionizer tank does not sit idle for long periods of time after regeneration, as it could promote microbial growth. If such a tank is used in water purification, it might overburden the system and the water produced could fail.

Carbon Filter

Activated carbon filters are used to remove dissolved chlorine and other gases from source water, along with organic materials before water is subjected to the final purification process. However, carbon filters can promote microbial growth and, therefore, foul the downstream components. Frequent monitoring and sanitization of carbon filters should be carried out to prevent this situation. Nonetheless, carbon filters can be a cause of water quality failure.

Purification System

Deionization

Deionization is not considered an acceptable water purification process by FDA to produce water-for-Injection (WFI); however, it is used to produce purified water. Cation, anion, and mixed bed resins are used to remove ionic impurities from source water. The quality of these resin beds can be monitored by determining the conductivity of effluent water. A sudden increase in effluent water conductivity indicates that a resin bed needs to be regenerated. Ion exchange resin tank regeneration should be controlled, and regenerated tanks should not sit idle, as this can promote microbial growth. Also, if there is a leakage of sodium ions from a cation exchange resin, the water produced will have a higher pH, greater than 7.0.

Reverse Osmosis

Reverse osmosis membranes are efficient water purifiers when used in series. However, these can harbor microbial growth, as they are chlorine sensitive and, therefore, can produce water of suspect quality. Also, if the membranes are not periodically backwashed, these would become overloaded and let organic and inorganic impurities pass through.

Distillation

Distillation is the method of choice for producing WFI, assuming it is a continuous process. If, for some reason, the system is idle for a period of time, the feed sections of the still can become dead legs and promote microbial growth. On start up, if used unsanitized, this could produce WFI with high endotoxins.

Storage and Distribution

Storage tank, distribution piping, and associated controls are critical to maintaining the quality of the water being produced. If there are leaks in the system, these could contaminate the entire system. Likewise, the vent filter on the storage tank should be checked for integrity and also to see that it is not harboring any microbes in the condensate, as both could compromise the quality of water. There should be a procedure in place for changing the sterile vent filter on the storage tank. Many times, water quality is compromised by the addition of foreign material during filter changeover. Typically, filter change is followed by a complete sanitization cycle. The heating and cooling system is another critical part of this puzzle, as the water quality is totally dependent on its storage temperature before it is used.

Sanitization process

Water purification systems are periodically sanitized to remove any biofilm and organic build up on different water contact surfaces. If a chemical sanitizing agent is used, there is potential for residual chemicals in the purified water, unless the system is thoroughly flushed and drained.

Sampling

Water samples are drawn during validation and routine monitoring of a water purification system.

This step is very critical and can cause water quality failure if sampling procedure(s) are not strictly adhered to. Details will be discussed in the investigation section of this article.

Analytical issues

Both chemical and microbiological testing have their own set of variables which could cause a water sample to fail. It could be the instrument, sample prep, or the procedure. Details will be discussed in the investigation section of this article.

Water quality failure investigation

Water quality failure/incident investigation should include a review of the following, depending upon the probable cause. Concentrate on those areas believed to have contributed most to a given quality failure/incident.

Source water

Source water test data from the local water authority and in-house periodic source water test results should be reviewed to determine any sudden changes in source water quality. This review should also indicate any trends that might be developing over recent weeks, especially after heavy rains or floods in the area, as they can affect the composition of natural water reservoirs.

Pretreatment

Review all pretreatment steps to see if the quality of source water was compromised at any stage.

Also check for any leaks or malfunction of any alarms, controls, or autoregeneration of deionizing tanks, etc.

Chlorination

Review the source water data to see if there was sufficient chlorine in the water. Also, review the residual chlorine level of pretreated water processed downstream, especially in case of a reverse osmosis water purification system.

Depth Filters

Check the backwash records to see if the depth filters were backwashed and sanitized per requirements, as these can cause both microbial and chemical contamination of the water being purified.

Water Softeners or Deionizers

Review the regeneration procedure and schedule for water softener and deionizing tanks to detect any deviation, especially if the tanks were sitting idle for a long period of time after regeneration, promoting microbial growth and thereby causing contamination of water.

Carbon Filter

Review the monitoring data for post carbon bed to see if there was any proliferation of microbes, which could have contaminated the system downstream.

Purification System

Deionization

Review the regeneration procedure and schedule for cation, anion, and mixed bed resin tanks to detect any deviation, especially if the tanks were

sitting idle for a long period of time after regeneration, thereby causing microbial contamination of water. Also, the conductivity data for effluent water should be reviewed to determine if the tanks were changed as per schedule and not totally exhausted before replacement.

Reverse Osmosis

The reverse osmosis membranes should be checked for integrity if these were exposed to high chlorine source water. Also, the membrane backflushing procedure should be reviewed to determine if it is effective in removing all the build up. The reverse osmosis system sanitization procedure and frequency should be checked to see if they need any revisions, both in procedure and frequency.

Distillation

Ensure that the system was in operation per approved specifications. If there was a shutdown, was the system sanitized before start up? Check that all the alarms and controls are functioning and within calibration. Look for any dead legs in the system as potential breeding grounds for microbes.

Storage and Distribution

Check the storage tank, distribution piping, and all points of use for leaks or other physical defects.

Examine the vent filter on the storage tank for integrity and to see if it is harboring any microbes in the condensate. Check the heat exchanger and chiller controls for proper function to assure the water is maintained at its desired storage and circulation temperature.

If plastic pipes are used, like PVDF, etc., these should be checked, as they tend to sag over time, leading to potential dead legs and, therefore, could promote microbial growth. The drain pipe from the storage tank should have at least a two-inch gap or twice the pipe's diameter, whichever is greater, between the pipe and the floor drain to prevent "back siphon" of floor drain.

Controls, Alarms

Today's water purification systems have a number of controls and alarms to operate the system within specifications while controlling the costs. One should review all the controls and alarms in case of a water quality failure/incident to see if they are functioning properly and are within calibration, where applicable.

Sanitization process

Review the water purification system sanitization procedure and frequency to determine if they could be contributing factors in water quality failure, especially when residual chemicals or high/low pH values are detected.

Sampling

Draw multiple water samples on a daily basis during validation and routine monitoring of a water purification system. The sampling procedure and the individual sampler's technique are key to obtaining uncompromised water samples. While investigating a water quality failure/incident, the sampling process should be scrutinized in detail. Review the following to determine if there is any chance to compromise the integrity of the sample:

Sampling procedure

The sampling procedure should be reviewed to determine the level of detail and clarity of statement for a nontechnical person to understand it. Also review the training requirements spelled out in the SOP and audit training records.

Sampling technique

If sampling is a potential cause for water quality failure, QA should review the sampling technique and perhaps have a microbiologist watch the individual sampler conduct the actual sampling under real-time conditions. This will provide a wealth of information as to the effectiveness of sampling technique as described in the sampling procedure and how people are trained. The sampling procedure should simulate actual practice when the system is used to draw water for manufacturing or cleaning activities, i.e., flush the system for 10 seconds before withdrawing water, etc.

Sample container prep

Water sample containers are specially prepared. Microbiological samples are taken in sterile containers, while chemical samples are taken in containers which have been specially cleaned and rinsed with WFI to minimize contamination. While investigating a water quality failure/incident, one should also review the sample container prep practices. This could involve reviewing cleaning procedures and any studies done on these containers after cleaning to determine the effectiveness of the cleaning procedure. If presterilized containers are

obtained from an outside vendor, obtain access to the vendor's sterilization procedure and supporting validation documents. Nonsterile sample containers have been blamed for false failures of water samples.

Analytical issues

Chemical and microbiological tests are usually performed by the quality control laboratory, and this phase of investigation is best accomplished if a chemist and a microbiologist are asked to review different aspects of the analytical work. In particular, the following should be closely examined:

Analytical instruments

Review analytical instruments to determine if they are within calibration and performance limits.

Also check for any unusual repair or maintenance activity that might have affected the performance of the instrument.

Analytical procedures

Analytical procedures should be reviewed for both chemical and microbiological testing to determine if there are any issues and if the procedures adequately guide the analyst in a step-by-step process to execute the test.

Analyst training

Review training records for the analyst to make sure he/she was qualified to perform the test under review.

Sample storage and preparation

Water samples are usually transported to the quality control laboratory, where they might sit for a while before testing is conducted. Review sample storage conditions as well as the time elapsed before testing was performed. Some companies refrigerate water samples upon receipt and may test them after 24 hours or so. This practice should be discouraged, as it could result in suspect data. Also, review the sample preparation techniques in the laboratory to assure that they do not compromise the integrity of the sample.

Testing time limits

Water samples should be tested as soon as they are received by the quality control laboratory. However, if the company has a practice that allows the samples to be stored for a limited time before analysis, review the records to determine if the samples were tested within the time limit.

Media preparation and storage

For microbiological testing, media preparation, storage, and expiration dating issues are critical in defining the success or failure of a test. Review media preparation procedures as well as the expiration date assigned to a given lot of in-house prepared media to assure that it is used within its expiration date. Other issues to be considered when reviewing microbiological testing should include:

- Incubation conditions
- Qualification status of incubator
- Use of positive/negative controls
- Isolation and speciation of the microbial contaminants

Drug product(s) involved

As part of the investigation, the drug product(s) manufactured with suspect water should be reviewed to determine if the safety, quality, and efficacy of the drug product has been compromised. The following points should be considered in this review:

- Dosage form of the drug product involved
- Route of administration
- Therapeutic class
- Presence or absence of a preservative system in the drug product
- Safety history of the drug product(s)

Personnel

This part of the investigation should determine if there are any deficiencies in the training program and if the people are qualified to perform their assignments.

Procedures and Documentation Practices

All the procedures and documentation involved should be reviewed to see if there is need for revisions, or new procedures should be prepared to supplement ones already in existence. Also, a determination should be made to assess whether all critical data is being reviewed by the appropriate people to make critical decisions (if needed).

Corrective Action Plan

Once all the facts are known, Quality Assurance should develop an appropriate corrective action plan in consultation with other departments. The corrective action plan could involve one or more of the following, depending upon the cause of the water quality failure/incident:

- If the water purification system is operating within specifications, additional water samples should be taken from source water, storage tanks, and all points of use for three to five days and the system released if all samples meet specifications.
- If part(s) of the water purification system need to be replaced, a determination should be made if this change is covered under system parts change program or if it would necessitate a requalification of the system.
- Revise water sampling procedures and retrain employees.
- Revise the analytical procedures.
- Recalibrate the instruments, etc.

Summary, Conclusion, and Sign-Off

A summary report should be prepared detailing the water quality failure/incident, probable or definite cause, corrective action plan, and disposition of the drug product(s) involved. Such a report should be prepared by Quality Assurance and reviewed and approved by appropriate members of management.

The investigation report, along with a summary, should become part of the water purification system file. However, a brief management summary might be prepared to inform upper management if the situation so warrants. ❑

Validating Building Controls Systems

By Jeffrey L. Waters
Landis & Staefa

Why should a company validate its Building Controls System? Today's international competition and wary consumers mandate some kind of quality control in almost every industry. Voluntary compliance with the International Organization for Standardization (ISO) is one of the hallmarks of many successful businesses. The ISO 9000 standard is even recognized by the Food and Drug Administration (FDA) in its internet file (ftp://ftp.fda.gov/CBER/ misc/cgmp.txt). "The principles and practices elucidated in the ISO standards are not in conflict with those provided by the cGMP (current Good Manufacturing Practices) regulations," the FDA states in the file. "Indeed, the voluntary ISO standards share common principles with FDA's cGMP requirements."

"Environmental control in drug manufacturing facilities has drawn increased attention from the FDA in the 1990s."

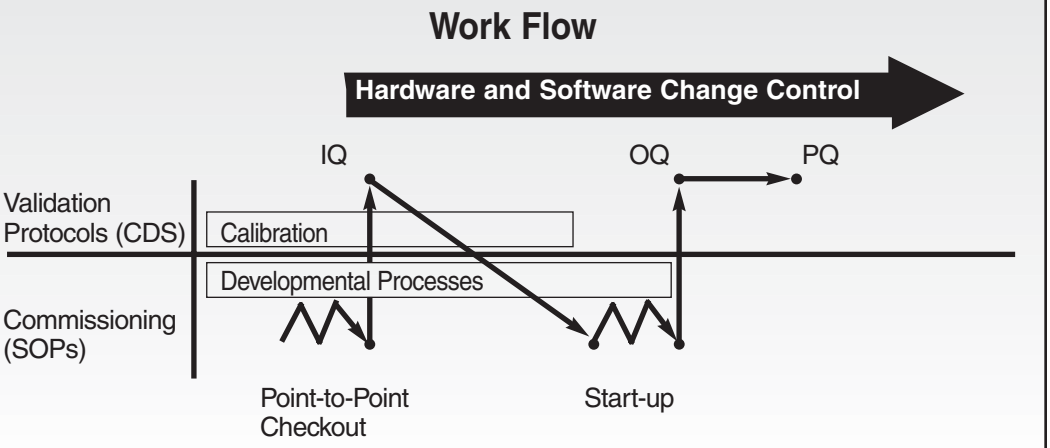
Environmental control in drug manufacturing facilities has drawn increased attention from the FDA in the 1990s. The cGMP (21CFR 211.46), last modified in 1995, says in part:

(a) Adequate ventilation shall be provided.
(b) Equipment for adequate control over air pressure, micro-organisms, dust, humidity and temperature shall be provided when appropriate for the manufacture, processing, packing, or holding of a drug product.
(c) Air filtration systems, including pre-filters and particulate matter air filters, shall be used on air supplies to production areas when appropriate.

These recommendations must be interpreted and implemented by the individual facility operators, but other industry guidelines are more specific. The ASHRAE 1995 Handbook – *HVAC Applications* (pg. 13.8), [for chemical] *Laboratory Ventilation Systems*, states, "Minimum ventilation rates are generally in the range of 6 to 10 air changes per hour [ACPH] when occupied." Actual air change rates may be significantly higher in labs with a high concentration of fume hoods. For example, a 30-by-50-foot lab with 10-foot ceilings (15,000 square feet) containing 10 fume hoods exhausting 1000 cubic feet per minute each (a total of 10,000 CFM) would experience a ventilation rate of 40 ACPH. On the other hand, labs with a single fume hood or bio-safety cabinet may require supplementary general exhaust ducts to provide adequate air changes. Simple mechanical Constant Air Volume (CAV) systems are less expensive to install and start up, but a computerized Building Controls System (BCS) provides dynamic control and monitoring of parameters such as air pressure and humidity. Variable Air Volume (VAV) controls minimize energy usage by reducing supply and exhaust flow when fume hoods are closed or the facility is unoccupied.

Air filtration in most critical applications is provided by High Efficiency Particulate Air (HEPA) filters. Strict specifications (such as Military Standard MIL-F-51079B for fire resistant biological filters)

Figure 1



define the properties of a HEPA filter. The National Sanitation Foundation requires (in its NSF-49 standard for biohazard cabinetry) that aerosol penetration not exceed 0.01% at any point on the filter, so NSF-49 certified HEPAs are at least 99.99% efficient. Pre-filters (to prevent loading the more expensive HEPAs) are simple bag or box filters that trap dust and large particulates such as animal hair. Alternatives for less critical applications include High Efficiency filters (95% efficient), and charcoal filters for organic vapor or odor control.

The cGMPs have governed drug manufacturing facilities since 1963. According to the FDA's World Wide Web site (www.cgmp.com), proposed changes may require construction of separate facilities and control systems for highly toxic agents:

"Penicillin has long been subject to specific cGMP regulations designed to reduce the danger of cross-contamination. Because other substances [cephalosporins, cytotoxic anti-cancer agents, and infectious agents] pose at least as great a risk of toxicity due to cross-contamination, FDA is proposing to expand the contamination control requirements. Section 211.240(b) would require dedicated production, which may include facilities, air handling, or process equipment, in those circumstances in which contaminants pose a special danger to human or animal health."

Fear of FDA intervention certainly is a compelling reason for a company to validate its environmental controls. Accomplishing business goals may be a better reason. According to Landis & Staefa validation consultant Irene Miess, "It just makes good business sense to make sure the facility operates as designed to ensure quality products are consistently produced."

Sean Chuckas, Landis & Staefa's operations manager for validation, explains it this way, "Aside from the risk to the life and health of employees, the cost of product failure due to not meeting quality standards can be very high. Years ago, humidity, pressure, and temperature were not considered part of quality control. Today we realize that production yield is boosted by controlling the environment. It's not just the process (that must be validated)."

Now that we have established the necessity of validating HVAC equipment, it is vital to understand the difference between commissioning environmental controls and validating their performance. A chart will help explain the difference.

The purpose of *Figure 1* is to show the work flow in a linear fashion while separating the Validation Protocols (contained in the Controlled Documents System) from the Commissioning Process. Standard Operating Procedures (SOPs) are used in the commissioning of everyday projects. After the HVAC mechanical equipment and controls are installed, the process should begin with a point-to-point check-out of every component (i.e, verifying that every input and output device is connected to the proper terminals). The jagged line on the chart represents the ups and downs of a typical construction project. A method that reduces cost and time is utilization of commissioning documentation to support validation. For example, commissioning checklists can be referenced in the Installation Qualification (IQ). According to Sean Chuckas, "The alternative is to do them separately and duplicate a lot of paperwork." If calibration is required, the procedures and documentation must be referenced in the validation protocols.

Once Installation Qualification is satisfactorily

completed, start-up of the HVAC system can begin, in accordance with the company's SOPs. The mechanical equipment must be up and running before Operational Qualification (OQ) can begin. This is where verification that the various mechanisms operate as intended must be done (for example, when the room thermostat calls for heat, does the hot water valve open?).

Performance Qualification (PQ) must be carried out by the owner. This is where verification is done to insure that all systems work together under as-used conditions to meet the User Requirement Specification. Do room temperature, humidity, and pressure stay in spec with production under way and people entering and leaving the facility? All systems must be operational to complete PQ.

Cooperation between the various contractors (mechanical, controls, etc.) is vital to completing PQ in a timely and cost-effective manner. Sean Chuckas stresses, "The owner and the designer must sit down at the beginning of the project and determine critical [validated] and non-critical areas. You don't want to waste resources and dollars validating non-critical areas."

To help make this determination, one should ask, "Which areas are critical to the production and storage of the product?" and validate only those areas. If more than one building will be constructed, all processes that must be validated by Good Laboratory Practice (GLP) or Current Good Manufacturing Practice (cGMP) should be segregated to the same building, and non-critical facilities housed in the other. If critical and non-critical areas are mixed within the building, the critical processes should be segregated to one area. Do offices, research-and development-labs, storage areas, and corridors really need to be validated? And finally, are only the rooms critical, or should the HVAC equipment be validated as well (air handling units, filters, temperature sensors, etc.)? One should be sure to coordinate these decisions with the supervisors of each affected area.

Hardware and software change control also must be addressed early on, because it will affect the entire process. If thermistors are specified (they must be replaced when they are out of specification) and then sealed behind drywall during construction, calibration will be a very expensive and time-consuming process. RTDs, which can be calibrated in place and have field replaceable parts, may be more cost effective in the long run even though the initial cost is higher. If the software change control procedure requires re-validation with every minor modification, updates will be very difficult and costly. One should remember that the maintenance staff must live with the change control procedures for the life of the facility. Flexibility should be built in, and subcontractors also must be trained on proper procedures. Change control procedures should address such issues as scheduling and documentation of maintenance, and re-certification of calibrated sensors. How will one insure that a calibrated sensor is available if one fails, or that the control program changes stick to standard formats? This is the nature of Building Control System Change Control.

The following quote from the Proposed Changes file of the cGMP web site emphasizes the FDA's viewpoint: "To preserve the validated status of a process, measures must be taken that will allow any significant process changes to be recognized and addressed promptly. Such change control measures can apply to equipment, standard operating procedures, manufacturing instructions, environmental conditions, or any other aspect of the process system that has an effect on its state of control, and therefore on the state of validation."

"Cooperation between the various contractors (mechanical, controls, etc.) is vital to completing PQ in a timely and cost-effective manner."

An auditor must be able to evaluate the current status of a facility based on the owner's documentation, and compare it to the specifications, but the processes also have to work smoothly and allow improvement. Irene Miess has this advice for anyone responsible for validated processes; "The owner should get involved as early as possible and look at what the desired end result will be, not just the 'cor-

rectness' of the specification. The User Requirement Specification is not always exactly what he wants, and what he wants is not always what he gets."

Some aspects of validation are unique to HVAC control systems. Sean Chuckas elaborates, "Although the controls are one of the last things to go in on new construction, they must not be planned last. The owner must make many decisions before the controls are installed and there should be meetings early in the process. Quality can't be tested into a process. It has to be designed into each system."

The HVAC controls for critical (validated) areas should be grouped in specified field panels. One may want to label these panels, "Critical Process Controls: Please follow Change Control Procedures," or something similar. This will prevent the necessity of having to validate non-critical controls.

Electric and other utilities must also be evaluated. One may need an Uninterrupted Power Supply (UPS) for critical field panels and PC workstations to continuously monitor critical equipment – such as refrigerators, incubators, and particle counters – with the Building Controls System.

When choosing an HVAC controls vendor, one should have experience in the validation process as a prerequisite. A close working relationship can save time and money beyond the initial cost of installation. Irene Miess sums it up thusly, "A primary criterion for choosing a building automation vendor should be the ability to provide support for the life of the facility. Their attitude should be, 'We don't walk away after commissioning.'" ❑

A Pocket Guide to Auditing a Pharmaceutical Water System

Control of water production and its usage are critical in producing a product . . .

by
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Pharmaceutical water may be the only utility from a facility to be administered to a patient. Even if the water is removed in processing the water, it is still regarded as a raw material and has the potential to leave impurities in the product. As with all raw materials of a product, the water must meet predefined specifications but, unlike other raw materials, it may be used as it is produced. Some systems produce water on a batch basis which is tested and released, for use, but others continuously feed water to a storage tank. Water is also used in many different cleaning processes, and, if contaminated, could affect multiple batches. Control of water production and its usage are critical in producing a product that meets predefined specifications and regulatory expectations.

The pocket checklist included with this guide is designed for two audiences. The first is the user of the system and those who have responsibility for maintenance and testing of the system. The list may be used as a proactive tool on a periodic basis to identify and monitor changes which may have occurred but were overlooked for documentation requirements or procedural changes. It should be modified and updated as necessary to support the system and maintain a state of compliance with current Good Manufacturing Practices (cGMPs).[1] The second audience is the auditor, who may use the list as a reference point on which to base an audit while leaving the specific details to the individual.

Procedures and problems encountered in the microbiology laboratory are outside the scope of this article but can be found in "Guide to the Inspections of Microbiological Pharmaceutical Quality Control Laboratories" (FDA 1993). An introduction to regulatory requirements of water systems can be found in the "Guide to Inspection of High Purity Water Systems" (FDA 1993).

This pocket guide is intended to provide a baseline for auditing water systems. It is not an all-inclusive list of possible items and areas to be examined. The content should be adapted and updated as necessary for individual systems and situations.

Documentation

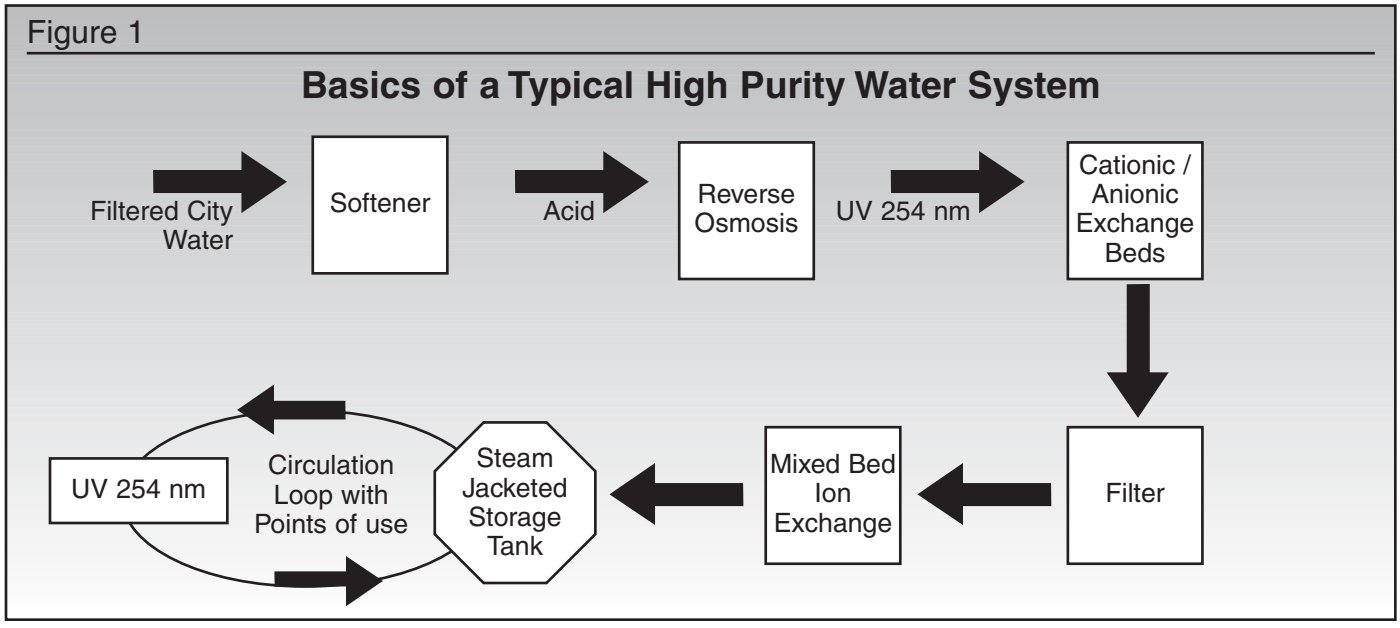
All systems require complete and accurate documentation including qualification, maintenance, change control, investigations, and analytical/microbiological results to provide evidence that the system is in a state of control. Documentation should be checked against the SOP requirements applicable at the time the work was performed and against current industry standards. The current revision of the schematic diagram must accurately reflect the actual system and be authenticated by a suitably qualified person. The auditor can use a copy of the diagram as a checklist during the tour. The date of the diagram should correlate with the last change control if physical changes were made that required changes to the diagram. A typical water system is shown in *Figure 1*.

The following documentation and SOPs can be requested for review in the audit conference room:

- Maintenance records for system components. These must be completed in compliance with the SOP requirements and provide a complete record.
- Qualification documentation (installation, operational, and performance). The qualification must be performed against a suitably approved protocol before the initiation of the work. The results must meet predefined acceptance criteria or be adequately justified.
- Change control log and supporting documentation. The dates that the system was approved for use should be compared to any manufacturing dates in batch records. The water system must be approved for use before it can be used in the manufacturing process. Outstanding requests for change controls may indicate that there are alternative reasons for the delays. If the changes were not performed, the potential impact on the integrity of the system should be assessed.
- Chemical and microbial testing raw data and trend reports. Compare the data against release documents, and check that the trends are being suitably monitored and the necessary people informed of the results.
- Out-of-specification results. The laboratory out-of-specification investigations should be reviewed against the SOP requirements. They must be of a suitable depth, and the conclusions must be supported by adequate data and information. Documentation is required to support any follow-up actions with defined time lines.

Manufacturing requirements will determine the water quality and capacity requirements of the system. Supply of water-for-injection (WFI) to a large manufacturing site will have different physical requirements than the purified water supplying a small solid oral dosage pilot plant. A note should be made of the manufacturer, and model numbers of components of the system for comparison against the validation protocol and change control requests. During the facility tour, the general conditions of the areas should be observed. Excessive water on the

Figure 1



floor and especially from leaking pipes is cause for concern. This is the first indication of the care and attention the area receives from the maintenance staff. Some of these areas are operated and maintained to a high standard. In a larger facility this may be maintained by the dedicated engineering staff compared to the smaller unit, which may be supported by other staff, but cGMP requirements are the same irrespective of the water being produced by the system. Area and equipment log books may be requested at this time, as it is sometimes more useful for the auditor to examine these in situ. This also enables assessment of the individuals responsible for the areas in their own environment. The SOPs applicable to the individual plant areas should be easily accessible so that users can refer to them whenever necessary.

Generation

Resin bed cartridges sent to a contractor for regeneration should be dedicated to the company to minimize any potential for contamination from an unknown user. Any chemicals used in the system for sanitization, regeneration of resins, etc., must be adequately stored, labeled, and as with any component of a pharmaceutical product, quarantined, tested, and released for use by Quality Control. A note of readings on gauges and digital readouts should be made for future reference and checked against operating ranges in the qualification documentation. Any readings that appear to be at the upper or lower end of the ranges or are fluctuating erratically should be investigated further. All major components of the system should be examined for general condition and appearance. Excessive leaking or rusting are an indication of a problem area, which warrants further investigation and explanation.

Distribution and Storage

During the walk-through, the auditor should ask general questions concerning the frequency of changing resins, sanitation, filter changes, integrity testing of vent filters, and general cleaning of areas. The appropriate individuals should be asked how the frequencies were established and what documentation supports the justifications. There must be no place in the distribution pipes where water can remain stagnant and provide the opportunity for microbial growth. These segments of piping, often referred to as “dead-legs,” are found where changes in the distribution have been made or in the removal of a section of the loop. Hard piping of equipment without a non-return valve and drainage of isolated piping back into the system can also cause similar problems.

A suitable number of the points of use and the environment around them should be examined. Points of use requiring tubing must not provide the opportunity for water to be siphoned back into the system and cause contamination. The classic example of this is the tubing reaching into a sink below the overflow level. Equipment joined directly to the water source has the potential to allow water to re-enter the system (back-flushing) and cause possible contamination. One-way flow valves minimize the possibility of this occurring. Air breaks are essential to ensure that there is no possibility that waste water discharged to a drain can possibly be siphoned or forced to enter the system or pieces of equipment from back-flow. All piping in the generation plant must be suitably labeled with a description of the contents and direction of flow.

Points of use must also have clear labeling to ensure there is no confusion in the water quality delivered from the outlet. Multiple outlets labeled “water” are major problem areas, especially when potable and WFI may both be available in an equipment cleaning area.

An explanation of the procedure and any physical controls should be requested when two storage tanks are released individually on a batch system by QC. There must be adequate controls in place to ensure that only water that has been released can be used. This may only administered by QC or by QC providing documentation to another group (engineering). It should be determined if water has ever been released for use before all testing has been complete. If this was allowed, it is defined as manufacturing at risk if the water was used as a component of a product. Manufacturing at risk is not permitted under the cGMPs and has been clearly explained by the Commissioner in the preamble to the cGMPs.[2]

Major maintenance work on the water system may be performed annually when the entire plant is closed for scheduled maintenance. There must be SOPs describing the procedure for decommissioning (i.e., stopping the production of water) and then bringing the system back to its original qualified state again. This must also include the quar-

antine and subsequent testing against an approved protocol with predefined acceptance criteria and ultimately release for use by QA.

Sampling and Testing

At the beginning of the audit, it would be beneficial to inquire if daily water sampling is being performed. If possible, the sampling process should be observed in conjunction with the sampling SOP. The internal auditor is able to request this at relatively short notice in their own facility, as they would have performed background checks to determine the collection times. A contractor should have no problem with the auditor observing the process if they are confident that the sampling is in a state of control and compliance with SOPs. The sampler's name should be noted so that the individual's training records can be requested and verified later.

Procedures used by operators to draw water from the system should be observed where possible, with special attention to the flushing time/volume before usage. The time/volume should be defined in an SOP and concur with those samples taken for chemical and microbial testing. A longer time/larger volume before sampling will create a bias for a more favorable result. This is because any potential contamination is sent to waste in sampling but, in practice, would have been added to the product. The handling process of the water samples should be followed to ensure that it complies with the SOP requirements. The process must be validated and include container type and storage of the samples which are not tested within a set time frame. The container surface must not add anything to or remove any constituents from the water while it is awaiting analysis. The key is to minimize any influences so that they are insignificant and that there is evidence to support this conclusion.

Summary

Water systems are complex and one of the critical components in a sterile manufacturing facility. Failure of any part of the system could cause multiple problems and potentially result in a product recall. Adherence to SOPs, strict maintenance of change control, and clear definition of responsibilities will assist in minimizing potential problems.

Meeting expectations of this guide and checklist

Water Systems Terms

Activated Charcoal: Used to remove odor, chlorine, and some organics.

Adsorption: The process of physical, not chemical, adherence to a surface by particles, colloids, or molecules.

Bactericide: A substance capable of killing bacteria.

Bacteriostat: A substance which inhibits bacterial growth and metabolism but will not necessarily kill the cell.

Chlorination: The addition of chlorine in a concentration of about 0.2 to 2 ppm to render the water bacteriostatic.

Conductivity: The ability of a substance to conduct electricity. Measurements are in microSiemens/cm.

Deionization: The process of removing ionized salts from water using ion exchange resins. Ion exchange is the preferential adsorption of ions from water for equivalently charged ions which are held on resins.

Endotoxin: A lipopolysaccharide found in the cell walls of viable and nonviable bacteria which is a heat-resistant pyrogen.

Hardness: The amount of calcium and magnesium salts.

Limulus Amoebocyte Lysate (LAL): A reagent derived from horseshoe crab blood used for the detection of endotoxins (pyrogens).

Mixed-bed resin: Both cation and anion resins mixed together for the deionization of water. The bed is usually used to polish the water.

Pyrogen: A substance, e.g., endotoxin that will induce fever in mammals.

Resistivity: The ability of a substance to resist the flow of electricity. Measurements are in megaohms/cm.

Reverse osmosis: The application of pressure across a semipermeable membrane so as to produce purer water on one side of the membrane and a more concentrated solution of ionized salts on the other.

Total Organic Carbon (TOC): The concentration of the carbon bound as organic compounds.

UV light: Ultra violet light at 254 nm used to kill bacteria and destroy ozone in the water system.

will not ensure that your facility will not receive an FDA form 483. Auditing is based on education, experience, competency, and instinct. It cannot solely be taught in the classroom but also has to be learned by practical application.

Good luck in passing your next inspection as I may be the auditor at your door. ❑

The opinions expressed in this article are those of the author and are not related in any way to employers, either past or present.

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2. Preamble, 1978 GMPs: *Federal Register*, 29 September 1978 (Vol. 43, No. 190, pp. 45013-45336).

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1. Guide to Inspections of Microbiological Pharmaceutical Quality Control Laboratories. (FDA 1993).
2. USP, current edition.

***The Auditor's Pocket Checklist for Pharmaceutical Water Systems* Follows**

The Auditor's Pocket Checklist for Pharmaceutical Water Systems

Facility:

Address:

Audit Date(s):

Auditor(s):

Product(s):

Water Quality

General Audit Requests

Request the following information from facility management, if applicable:

- ❏ History of business and corporate affiliations.
- ❏ Establishment Registration Number.
- ❏ Organizational chart with names and titles of key management.
- ❏ Facility floor plans.
- ❏ List of products manufactured in the facility.
- ❏ Results of FDA inspections since last audit or, if an initial audit, for the previous two years. Also request company's responses.
- ❏ Master File, if applicable.
- ❏ Quality Manual.
- ❏ Complete SOP list.

	Yes, No, NA or Information
Feed Water ❏ What is the source for the plant water (city or private supply – well ground water, or surface water)? ❏ Is source water entering the facility, whether from a municipal supply or a private well, tested for microbiological contamination, and what are the specifications? ❏ Is coliform bacteria testing performed according to 40 CFR 141.14; 141.21? ❏ Is source water entering the facility tested for chemical contamination, or are municipality reports provided? ❏ Does the water meet the EPA specifications for potable water? ❏ What is the frequency of testing? ❏ If the results are provided by the water supplier, are they reviewed and approved by a suitably qualified user? ❏ What actions are taken if specifications are not met? ❏ If the water is being tested by the user, is a written SOP describing sampling and testing available?	

The Auditor's Pocket Checklist for Pharmaceutical Water Systems

General Water System Requirements

- ❑ What water purification system is used?
- ❑ Is the system a one-way flow (i.e., not recirculating)? These are more problematic and difficult to maintain as they are basically a "dead leg."
- ❑ What is the velocity of the circulating system (6 fps recommended)?
- ❑ What is the temperature range of the water in a recirculating system (normally 65 to 80 ºC), and how is this monitored?
- ❑ What is the temperature of the water in the tank?
- ❑ Is the tank storage time less than or equal to 24 hours for room temperature batch processing?
- ❑ Is there a continuous temperature recorder and controller for each storage tank?
- ❑ How often is the tank vent filter integrity tested and checked for condensate blockage?
- ❑ Is the vent filter a hydrophobic 0.2 um?
- ❑ What type of tubing is used? (316L Stainless Steel piping is common in WFI and purified water. Some plastics (e.g., PVDF can also be used but must be checked for compatibility.)
- ❑ Is there acceptable documentation/video of the stainless steel welding and unique identification of each welded joint?
- ❑ Is there a copy of the welder's certification and the welding procedure on file?
- ❑ Are there any dead legs or potential areas where air can become trapped or where water can stagnate?
- ❑ Does the system contain screw-threaded fittings instead of the required sanitary fittings?
- ❑ Does the system contain ball valves or other fittings that can possibly retain water from the main system and cause potential microbial problems?
- ❑ Does the heat exchanger, with the exception of a double concentric tube or double sheet tube, have a greater pressure on the water system side than the coolant?
- ❑ Do any of the use points in the system have 0.2 um filters (FDA prefers no in-line filters)? Actual water microbial counts may be "masked" by filters.
- ❑ Review water sampling results for at least six months preceding and two months following the manufacture of lots selected during the audit. If specifications were not met, review investigation and corrective actions. Are the results, investigations, and corrective actions acceptable?
- ❑ Are the sampling locations and frequency of testing suitable for the system?
- ❑ Who performs sampling for the chemical and microbial samples?
- ❑ Check that the sampling personnel are adequately trained and the training is appropriately documented.
- ❑ Are chemical and microbial results being trended? Are the results acceptable?
- ❑ Have changes been made to the water system since the last audit? Since the system was initially qualified? If major system changes have occurred, have the changes been evaluated for the need for re-qualification?
- ❑ Are any pumps only used periodically? These can be a source of bacterial contamination from stagnant water.
- ❑ Are thorough and complete records of the system cleaning, passivation, and maintenance maintained? The records should include who performed and supervised the cleaning, date, cleaning agents used, pH, conductivity, and microbial results.

The Auditor's Pocket Checklist for Pharmaceutical Water Systems

- ❑ What chemical sanitization is used, and is it adequate?
- ❑ How often are the reverse osmosis membrane seals checked for integrity to prevent bypass and contamination?
- ❑ Is there a maintenance program for the reverse osmosis to prevent membrane fouling and integrity failure?
- ❑ If resins are regenerated on site, what SOP is followed?
- ❑ Are the ion-exchange beds tested microbiologically and chemically after regeneration?
- ❑ What is the quality of the regenerant chemicals? Are they released by QC before use?
- ❑ Is regeneration of the cation/anion/mixed-bed resins documented?
- ❑ If the resins are regenerated off site, does the manufacturer have written certification that the units have been used for treatment of water in only systems such as this?
- ❑ Are cation/anion/mixed-bed resins regenerated, or are virgin resins always used?
- ❑ Has the correlation between in-line and laboratory testing for conductivity and TOC been established?
- ❑ What is the minimum output of the UV light in the system before replacement is required? (normally 40-50% of original)
- ❑ What wavelength of light is used? (254nm; germicidal, 185nm; TOC reduction)
- ❑ Is there a maintenance program for the UV lamp, especially cleaning of the lens to maintain effectiveness?
- ❑ Are the established specifications and corresponding action and alert levels suitable and based on historical/statistical data?
- ❑ Have any vendors supplying products for the system been qualified?
- ❑ Are any of the components controlled/monitored by a computer or programmed logic controller? If so, has the system been validated?

Water For Injection (WFI)

- ❑ Is the water prepared by distillation or reverse osmosis?
- ❑ Is clean steam (free of additives) used to generate the WFI?
- ❑ How is the feed water treated prior to the distillation? Is the source water chlorinated, carbon treated, deionized?
- ❑ Is endotoxin testing performed on the tank, pre/post-final treatment step and points of use?
- ❑ What is the level of endotoxins from the feed water, and is it appropriate to feed the still or reverse osmosis? (Stills normally only affect a 2.5 to 3 log reduction in endotoxin content.)
- ❑ Is the system in a state of control and producing water of a quality suitable for its intended use?

The Auditor's Pocket Checklist for Pharmaceutical Water Systems

Documentation

Water board testing results at regular intervals according to SOP
 	
Microbial and analytical test results
• Are these acceptable or acceptable with investigations and corrective actions?
• Are sampling plans defined which include a defined purpose and evidence for:
  • Verification of quality attributes in treatment, distribution, and points of use?
  • Supporting the compliance profile?
  • Gathering validation samples?
  • Verifying continued quality of source water supply?
  • Is trending of results done, and does it indicate anything?	

Installation Qualification • Approved protocol? • Meet acceptance criteria? **Operational Qualification** • Approved protocol? • Meet acceptance criteria including daily sampling after each step of the purification process at each point of use for two to four weeks? • Are the operational SOPs approved? • Repeat testing as above. **Performance Qualification** • Approved protocol? • Meet acceptance criteria including: WFI sampling one point of use each day with all points tested weekly. Complete a year of testing and meet specifications?	
Change control requests • Review decision where revalidation of the system was not performed. Were these justifiable? • Does the level of testing relate to the type of change made? • Was water used before the final approval of the documentation? If so, why?	
Quality investigations relating to the system or any water-related problems • Note any open investigations that have not been closed within 30 days. This must be defined in the SOP. Why are they still open, and is senior management aware of the situation? • Are the investigations adequate? • Were the corrective actions suitable and effective in preventing repeat occurrences? • Is trending done and reported to senior management and QA on a regular basis? • Are problems of a similar/same type being reported more than once? (This could indicate a more serious underlying problem.)	

The Auditor's Pocket Checklist for Pharmaceutical Water Systems

Area, equipment, and maintenance log books • Are the SOP requirements being met? • Are the books complete?	
Calibration records • Select equipment and examine the records. Are outside vendor records reviewed and approved by suitably qualified personnel of the company owning the equipment? • What actions are taken when a result is out of calibration?	
SOPs: **Operation and maintenance of the system** **Sampling and handling** **Change control** • Review content and completeness • Do the SOPs reflect actual procedures observed or being documented? **Batch release SOP (if applicable)** • What documentation is required to release the batch? • Who physically releases the batch and how? • Are batches ever used before receiving the quality release documentation? **Shut Down and power failure**	
Current Specifications **WFI** For sample volumes of 100 to 300ml. Microbial > 5CFU/100ml alert level. >10CFU/100ml action level. (Note: These may vary by company). Conductivity Stage 1: Uncorrected for temperature or carbon dioxide. Sample limit is 1.3µS/cm. On-line method. Stage 2: Carbon dioxide and temperature corrected. Sample limit is 2.4µS/cm. Stage 3: Utilizes a sliding pH scale to determine conductivity acceptability. Apparent Total Organic Carbon 500ppb limit response. Endotoxins <0.25EU/ml. **Purified Water** Microbial >50CFU/ml alert level. >100 CFU/ml action limit. (Note: These may vary by company). Conductivity Stage 1: Uncorrected for temperature or carbon dioxide. Sample limit is 1.3µS/cm. On-line method. Stage 2: Carbon dioxide and temperature corrected. Sample limit is 2.4µS/cm. Stage 3: Utilizes a sliding pH scale to determine conductivity acceptability. Apparent Total Organic Carbon 500ppb limit response. Note that water usage may direct the appropriate specification e.g., antacids do not have an effective preservative system and require an action limit commensurate with their formulation.	

Facility Validation

Validating USP Purified Water, Compressed Air and HVAC Systems

By Jean-Pierre Thiesset
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Facility validation is a tremendous task in which many different processes and pieces of equipment must be considered.

The processes addressed within this article include:

- A United States Pharmacopoeia (USP) purified water system that produces USP purified water for use in component and final product cleaning. This water is not used as a constituent of the product itself.
- A compressed air system, which generates oil free air, used in manufacturing processes to blow off components and final products. This system also supplies compressed air to manufacturing equipment.
- A heating, ventilation and air conditioning (HVAC) system that controls temperature, humidity and differential pressure for a class 100,000 controlled manufacturing environment (CME).

"A validation plan does not necessarily need to be an all-encompassing 100-page document."

Successful facility validation requires organization, attention to the different systems and processes one-at-a-time, and patience. It is important not to try to complete the validation before it starts.

The first step is forming a validation team. The importance of assembling a team that includes all interested parties at the beginning of the project is obvious. At a minimum, this team should include, representatives from facilities, manufacturing, quality, validation engineering and information technology. The next important step is developing a validation project plan. This will not decrease the amount of work to perform, but it will significantly contribute to successful validation.

Validation Project Plan

A validation plan does not necessarily need to be an all-encompassing 100-page document. A more concise document, which clearly states the project's purpose, the validation approach, and the overall acceptance criteria may be more useful. A validation project plan should be developed so that it serves as a road map. It ensures that each required task has been executed as planned. Specific qualification protocols, which contain the detailed testing, can be developed separately for each piece of equipment.

An effective validation project plan must contain:

1. Validation project plan number, subject and approval blocks.
2. Project purpose.
3. Project scope.
4. Facility and system: Define what the system does (system description and intended use) and how the system does what it is required to do (design description).
5. Project responsibilities: Define project manager/leader, team members and their respective responsibilities.

6. Planning and organization: project goals, objectives and expected benefits, project organization, constraints, impact on existing systems and operations, proposed time line and major milestones.
7. Validation methodology: broad overview of the validation approach to be taken.
8. Validation responsibilities: consider the supplier's responsibilities as well as those of the validation team.
9. Validation procedure. Installation Qualification (IQ), Operational Qualification (OQ) and Performance Qualification (PQ) requirements. List the specific protocols which must be implemented, (usually one per system, or one for each specific IQ, OQ and PQ). Note: List only major tests that must be included in each qualification. It is not necessary to provide explicit detail within the scope of this document. (The detailed procedure for executing a qualification of a particular system will be specified within a specific protocol for that qualification).
10. Validation deliverables. These might include supplier qualification, operational procedures, process documents, preventive maintenance schedules for each piece of equipment, training plans, and other documentation.
11. Acceptance criteria. List the acceptance criteria for the validation project plan.
12. Attachments. It may be helpful to use a "check sheet" format that contains the list of specific protocols to implement. This section should refer to supporting documentation, such as drawings, flowcharts, and Gantt charts.

After the project plan is approved, the team can begin executing the plan.

USP Purified Water System Validation

This system is described as two stainless steel piping distribution loops which provide continuously recirculating, ambient temperature, USP purified water to manufacturing areas. This system consists of:

■ A supply water (city water) pretreatment system. A multi media depth filter which filters the city water with an automatic backwash system when pressure drop exceeds a predefined value. This filter removes particulate matter greater than 10 microns. A carbon filter removes organic contaminants and chlorine from the water by absorption.

■ A deionized (DI) water production system. A cation/anion unit removes dissolved ions in the water by ion exchange. First, the water passes through a strong acid cation exchanger, (cation exchange resin regenerated with acid HCl). Then, the water flows through a strong base anion exchanger, (anion exchange resin regenerated with caustic soda NaOH). When the resistivity of the water after the cation/anion unit is lower than a predefined value, a regeneration cycle is triggered. A one micron filter completes this DI water production system.

■ A water temperature maintenance and distribution system. This system includes: a sanitary pump, a hot water generator for sanitizing, an ultra violet (UV) disinfecting lamp, a 0.1 micron filter, a bank of three parallel mixed polishing beds, a one micron filter, a second UV disinfecting lamp, a second 0.1 micron filter, and two distribution loops which are connected back to the sanitary pump.

■ A monitoring system. The resistivity of the water is monitored at several points in the system ensuring that the water delivered by the system is greater than a predefined value, and a system of yellow and red indicators alerts maintenance technicians and users if resistivity goes below this predefined value.

USP Purified Water System Installation Qualification (IQ)

The most difficult part of a USP purified water system validation is not the OQ, but the IQ. An important part of a quality USP purified water system resides in its architecture, piping, valves characteristics, and installation method. Knowing that, it becomes evident that the validation must start even before the first pipe is installed by the choice of the right company to perform the soldering, installation and verification.

It is recommended that vendor selection criteria include a requirement for the vendor to provide a quality assurance plan for the project. Their plan

Figure 1

Classic Installation Qualification (IQ) Testing

Test #	Test Designation	Test Description
1	Drawings and schematics review.	Verify that drawings and schematics are available for the following when applicable: major components, connections, wiring, inter-connections, piping.
2	Manuals review.	Verify that a manual is available for each major component.
3	Major components identification.	Record the following for each major component: designation, brand, model, serial number.
4	Major components installation.	Verify that each major component is correctly installed.
5	Connections verification.	Verify that connections conform to drawings and schematics.
6	Wiring verification.	Verify that wiring conforms to drawings and schematics, and wires and cables are identified at both ends.
7	Tagging verification.	Verify that valves, gauges, relays, contractors and fuses are identified and tagged according to drawings and schematics.
8	Utilities verification.	Verify that the following utilities conform to manufacturer specifications when applicable: power supply (voltage), air pressure and quality, water pressure and quality.
9	Plant capacity.	Verify that the plant has the capacity to produce the required utilities without impacting the existing processes.
10	Personal computer software installation (if applicable).	Verify that the computer is in compliance with the minimum software requirements, that the software is available on appropriate medium (e.g., CD-ROM, diskette), that no error message is displayed during the software installation, and the software main menu can be displayed after installation. Verify that the software is compatible Year 2000 (i.e., will continue to operate correctly on January 01, 2000 and the years after).
11	Program review (if applicable).	Verify that program listing (source code) and functional flowchart are available for review, that the program is correctly commented and contains no dead code, and the program has been saved for backup (current and previous versions saved on separate directories or drives).
12	Supplier validation questionnaire review.	This is a questionnaire sent to the supplier of pieces of equipment which contain hardware or software ensuring that the supplier has a software quality assurance system in place. It is used to evaluate the extent of validation testing required.
13	Equipment verification by a safety officer.	A safety officer must verify that the equipment is safe for use in a manufacturing environment.
14	Calibration verification.	A representative from the metrology department must verify that pieces of equipment which required calibration have been calibrated, and that a rationale has been written for the pieces of equipment which do not require calibration.

should address the following:

❶ Material and equipment receipt and acceptance procedures ensuring that materials conform to their specifications. The program should include methods for lot number tracking, review of certificates of conformance and material test reports.

❷ Inspection procedures. These must be detailed, referencing the equipment to use, the technician certification and/or training required, the methods, the sampling plans, and the acceptance criteria for each test. For example, stainless steel welded pipe tests are done in accordance with the appropriate American Society for Testing and Materials (ASTM) specification. The inspections may include verification of outside diameter and wall thickness, inspection of inner diameter surface anomalies (minor pits only, no porosity, no inclusions), cleanliness (e.g., no dirt, grease, grit, oil), and chemistry. Most of these tests require the use of sophisticated instrumentation by certified technicians. Examples of water system tests include: slope verification and pressure testing.

❸ Welders performance qualification procedures and records.

❹ Welding procedures. These may include, but are not limited to, cutting, facing, deburring, cleaning, pipe fitting, purging, and alignment.

❺ Weld documentation. May include a weld numbering system, welder identification, time and date.

Choosing the right company ensures that the water system IQ will be completed practically at the same time of the installation itself. The only part that will be left to organize is a classic IQ (see *Figure 1* Installation Qualification (IQ) testing). During a review of drawings, make sure to verify that your installation has no dead legs. It is not as easy as it seems, because dead legs can be hidden everywhere. (For example, a dead leg can be created when a valve is closed.) Verification that the system has been correctly pasteurized will complete the IQ testing portion of the water system qualification.

USP Purified Water System Operational Qualification (OQ)

The OQ of a USP purified water system is time consuming, but not really complicated, due to the fact that this type of system does not contain a lot of complex pieces of equipment.

Start by checking each component separately to ensure that it functions as it is supposed to operate:

❶ Verify pump is capable of producing the specified flow rate.
❷ Verify on/off sequence of the UV lights.
❸ Verify the hot water generator is capable of producing the required temperature for the sanitizing cycle.
❹ Verify valves open and close as intended.
❺ Verify alarms are activated as intended.

Once every component has been checked and deemed acceptable, the water system OQ can begin. The system tests consist of the sanitizing cycle test, chemical tests, microbial tests and documentation and training verification. Before conducting any other tests, it is important to check the sanitizing cycle ensuring that the system maintains circulating water at a minimum temperature of 85ºC (185ºF) for 30 minutes. It is critical to ensure that the power supply to the UV lights is shut off during the sanitizing cycle preventing a deterioration of the UV lights. Ideally, the system is designed to automatically cut the power supply to the UV lights when the temperature reaches 50ºC, (122ºF), and turns it back on when the temperature comes back under 40ºC (104ºF). For safety, it is important to install a pressure release valve in order to allow the release of the excess pressure generated during the sanitizing cycle when the temperature increases. This valve must be checked ensuring it is working properly.

The next step is verifying that the control system is operating as necessary. The control of the resistivity, temperature and other parameters are performed by a computerized system. First, it is necessary to verify that the values recorded by the control system conform to the actual values. One method to do this is measuring all the parameters with calibrated instruments. Record the date and time the measurements are taken, along with the values obtained. Compare these manually obtained values to those recorded and saved by the control system during the same period. During the OQ, it is necessary to verify that the control system acts and reacts as it is intended. For example, the system must maintain temperature at an acceptable range, activate correct indicator lights based resistivity readings. The system may also generate customized special reports or exception reports. An important fact to remember is that all computerized systems, including most of today's USP purified water systems, contain software programs which need to be validated.

During the operational qualification, chemical and microbial tests will be performed. It is important to define the testing frequency conducted at each point-of-use. At a minimum, chemical tests consist of the following:

- Description
- Resistivity
- pH
- Total solids
- Chloride
- Sulfate
- Ammonia
- Calcium
- Carbon dioxide
- Heavy metals

Figure 2

Chemical and Microbial Test Matrix

			Operational Qualification				Performance Qualification Phase 1									
Test	Loop	Days	1	2	3		4	5	6		7	8	9	10	11	12
C	N/A	Ctrl	X	X	X		X	X	X		X	X	X	X	X	X
H	A	Begin	X	X	X		X	X	X		X	X	X	X	X	X
E	A	End	X	X	X		X	X	X		X	X	X	X	X	X
M	B	Begin	X	X	X		X	X	X		X	X	X	X	X	X
	B	End	X	X	X		X	X	X		X	X	X	X	X	X
	A	Begin	X	X	X		X	X	X		X	X	X	X	X	X
	A	End	X	X	X		X	X	X		X	X	X	X	X	X
	B	Begin	X	X	X		X	X	X		X	X	X	X	X	X
	B	End	X	X	X		X	X	X		X	X	X	X	X	X
	A	POU-A1	X				X				X			X		
	A	POU-A2		X				X				X			X	
	A	POU-A3			X				X				X			X
M	A	POU-A4	X				X				X			X		
I	A	POU-A5		X				X				X			X	
C	A	POU-A6			X				X				X			X
R	A	POU-A7	X				X				X			X		
O	A	POU-A8		X				X				X			X	
B	A	POU-A9			X				X				X			X
I	A	POU-A10	X				X				X			X		
A	B	POU-B1	X				X				X			X		
L	B	POU-B2		X				X				X			X	
	B	POU-B3			X				X				X			X
	B	POU-B4	X				X				X			X		
	B	POU-B5		X				X				X			X	
	B	POU-B6			X				X				X			X
	B	POU-B7	X				X				X			X		
	B	POU-B8		X				X				X			X	
	B	POU-B9			X				X				X			X
	B	POU-B10	X				X				X			X		

POU	= Point of Use
X	= Test to be performed
	= Sanitizing Cycle to be Performed

■ Oxidizable substances

As the system is stated to be a USP purified water system, the acceptance criteria for these chemical tests must comply with the USP purified water specifications. The chemical tests must be performed at points located as close as possible to the beginning and end of each loop, and at a control point located before the purification system. (This control point should fail the test, as it is located before the purification system). The microbial tests must be performed at each point of use. The validation acceptance level for Colony Forming Units (CFUs) per ml should be below the alert level. For exam-

ple, action levels may be established at 50 CFUs/ml, and alert levels may be 40 CFUs/ml. The acceptance level would then be < 40 CFUs/ml. It may be useful to use a matrix such as the one shown in *Figure 2* to define testing frequency. In the example shown in *Figure 2*, each point of use is tested at least once during the three days of the OQ/chemical and microbial testing and a sanitizing cycle is performed after day three.

The OQ phase will be concluded by verification that appropriate procedures and training are in place. It is important to verify that all required procedures for water system operation, monitoring, and maintenance are applicable and approved (see *Figure 3*, procedures required during facility validation). It is also important that individuals who utilize, and/or maintain the system have been trained appropriately and that this training is documented.

USP Purified Water System Performance Qualification (PQ)

The PQ of a USP purified water system could be conducted in two phases. The first phase consists of an intensive chemical and microbial testing during nine days with a sanitizing cycle between day three and day four. In the example shown in *Figure 2* (chemical and microbial tests matrix) each point of use is tested at least three times during the PQ phase. (Once before the sanitizing cycle and twice after the sanitizing cycle). A recalibration of each piece of equipment calibrated at the end of the IQ must be performed ensuring that the measurement performed during the validation test was valid. If some devices are found to be out of calibration, an investigation of the impact on the validity of the tests performed must be conducted, and a few or all OQ and PQ tests may have to be performed again.

The second phase of the PQ consists of a less intensive, (but more than routine monitoring) of the chemical and microbial conditions during three months to ensure that the system continues to produce the required water quality. Once the second phase of the PQ is completed, routine monitoring starts. Routine monitoring consists of the control of each critical point of use once a week and is used to ensure that the system continues to produce the required water quality. It also allows the assessment of the effect of seasonal changes on source water routinely recommended by industry experts.

Compressed Air System Validation

The compressed air system consists of the following:

Figure 3

Procedures Required During Facility Validation

Procedures	USP Purified Water System	Compressed Air System	Air Handling System
Water Sampling Method	Yes	No	No
Air Sampling Method	No	Yes	Yes
Chemical Test Method	Yes	No	No
Microbial Test Method	Yes	No	No
Hydrocarbon Test Method	No	Yes	No
Viable Particulate Test Method	No	Yes	Yes
Non-Viable Particular Test Method	No	Yes	Yes
Monitoring Procedures	Yes	Yes	Yes
Sanitizing Procedures	Yes	No	No
Excursion Reporting & Investigation	Yes	Yes	Yes
Calibration Procedures	Yes	Yes	Yes
Training Procedures	Yes	Yes	Yes
Standard Operating Procedures	Yes	Yes	Yes
Change Control Procedures	Yes	Yes	Yes
Preventive Maintenance Procedures	Yes	Yes	Yes

■ Oil free air compressor unit. This eliminates hydrocarbon content in the compressed air and eliminates or reduces the need for coalescing type filters.

■ Closed loop cooling system. In order to avoid contamination, the cooling system does not have contact with the compressed air.

■ A dryer. Serves to remove as much water as possible, decreasing the dew point.

■ A copper piping network. This network is oil free and has been cleaned with alcohol. (*Note that the use of galvanized piping, which is porous, is avoided. Such pipe materials will retain moisture.)*

■ Several 0.5 micron Millipore filters at each potential product-contact point of use.

■ A few coalescing type filters may be installed before the Millipore filters at any point of use where particularly high levels of cleanliness may be required due to the nature of product contact at that point.

Compressed Air System Installation Qualification (IQ)

The IQ of a compressed air system is much easier than the IQ of a USP purified water system. It consists of the Installation Qualification (IQ) testing described in Figure 1. The first step is verifying that all components and materials received conform to what was specified. One thing to consider is the installation of "quick disconnects" at each point of use or each monitoring point. This facilitates sample collection that will be necessary during the validation and any future monitoring. It is important to have appropriate instruction manuals and maintenance manuals with a spare parts list for each major component of the system (such as the compressor).

Correct installation of the piping, according to the compressed air network drawings must be verified. During verification, assure that the piping has been efficiently cleaned (flushed) with alcohol to removed any trace of oil, and/or other materials used during manufacturing and installation.

It is also necessary to consider utilities for each piece of equipment. Verify that the utilities comply with manufacturer's requirements. The overall plant capacity must be verified to ensure that it can safely provide the power supply required for each piece of equipment without affecting the functioning of the new and/or existing systems. Compressed air system leak testing followed by verification that all equipment and measurement tools were appropriately calibrated will conclude the IQ.

Compressed Air System Operational Qualification (OQ)

The OQ of a compressed air system consists of two phases:

■ Functional qualification at component and systems-levels.
■ Air quality testing.

During the first phase, each component and each specific piece of equipment must be checked to verify functional operation. Accordingly, it is necessary to design tests that challenge each major function. The ultimate test is one that verifies all functions of a piece of equipment in one unique operation. Unfortunately, this is difficult, and realistically, it will probably be necessary to perform many specific tests to thoroughly challenge each function.

The classic functional tests of compressed air system components might include, but are not limited to, the following:

■ Verification that mechanical moving parts move freely.
■ Verification that all necessary adjustments can be performed.
■ Verification that normal operating adjustments are not at the minimum or the maximum of the range.
■ Low and high alarm testing.
■ On/off sequences testing.
■ Simulation of a power supply shut down and recovery.

Systems-level testing consists of verifying that the compressed air system delivers the required cubic feet per minute (cfm) at the specified working pressure, and is capable of achieving and maintaining the specified dew point.

The air quality testing phase can be planned in the same manner as the water quality testing by generating a matrix of tests to perform. The following tests should be performed on samples taken immediately after the dryer, and at each product-contact point of use:

■ Viable particulates. A typical acceptance level could be less than 0.1 colony forming units per cubic feet (CFUs/ft^3) if the alert level is equal to or greater than 0.1 CFUs/ft^3, and the action level exceeds 0.15 CFUs/ft^3.

■ Non-viable particulates. A typical acceptance level could be less than 9,000 parts per cubic feet (ppcf) for 0.5 micron particulates if the alert level is equal to or greater than 9,000 ppcf for 0.5 micron particulates, and the action level exceeds 10,000 ppcf for 0.5 micron particulates.

■ Hydrocarbon content.

As with any OQ, conclude by verifying that all required operational and maintenance procedures are in place, applicable and approved (see *Figure 3*, procedures required during facility validation). Verify that training of personnel who utilizes, and/or maintain the system has been documented.

Compressed Air System Performance Qualification (PQ)

As with the compressed air system OQ, the PQ is conducted in two phases. The first phase consists of performing the following tests at least one week after the OQ on samples taken just after the dryer, and at each product-contact point of use:

■ Viable particulates.
■ Non-viable particulates.
■ Hydrocarbons content.

The system components should be recalibrated as appropriate in order to ensure that the measurements performed during the validation tests are valid. If some devices are found out of calibration, an investigation of the impact on the validity of the tests performed must be conducted, and a few or all of the OQ and PQ tests may have to be performed again. The second phase of the PQ consists of a less intensive, (but more than routine) monitoring of viable and non-viable particulate levels over at least a three month period ensuring that the system continues to produce the compressed air meeting documented specifications.

HVAC System Validation

The HVAC system considered as part of this validation project supplies conditioned air to a Class 100,000 controlled manufacturing environment (CME) by way of a duct network. Areas are pressurized to achieve the required differential pressures between manufacturing rooms, corridors and gowning rooms.

The system consists of:

■ An air handling unit (AHU). This provides filtered air, and consists of fans and their motors, high efficiency particulate air (HEPA) filters, dampers, a condenser unit with its refrigerant piping, an indirect fired gas heating unit with its gas piping, and an electric panel.

■ A temperature and humidification system. Primary humidifiers inject low pressure steam into the main branches of the duct network in quantities sufficient to produce slightly less than the nominal percent of relative humidity (%RH) required when the air stream temperature is raised to the room's nominal temperatures. Electric duct heaters and terminal trim humidifiers respectively reheat and rehumidify the air prior to being distributed into each area in order to maintain each room's specified temperature and %RH.

■ HEPA filters at the end of the ducts just before the distribution of the air into the room.

■ A sensor system. This consists of temperature and humidity sensors located down-stream from the main stream distributors. Temperature and humidity sensors are located in each room. Differential pressure sensors are located between adjacent manufacturing rooms, between manufacturing rooms and adjacent gowning rooms, between manufacturing rooms and adjacent corridors, and between gowning rooms and adjacent corridors. All these sensors are connected to a computerized control unit.

■ A computerized control unit. This serves to monitor temperature, the %RH and the differential pressure. It also controls the AHU, the primary humidifiers, the trim humidifiers and the heaters. This system is built within a computer-type environment with a lot of hardware components (electronics and printed circuit boards). A complex interconnection network between the unit and the sensors and between the unit and the AHU, the humidifiers and the heaters allows the monitoring and control by this computerized control unit. Of course, the computerized control unit contains several software components which must be validated.

HVAC System Installation Qualification (IQ)

The IQ of a HVAC System may take more than a week, since it involves many different pieces of equipment. However, this does not necessarily mean that the IQ will be difficult to execute. As in any installation qualification, begin by addressing the tests and tasks defined in the installation qualification (IQ) testing described in *Figure 1*. Customize the IQ protocols as necessary for the unique system. It will usually be necessary to add a few tests that are specific for the type of system that has been installed. In the case of the HVAC system described in this article, the system-specific tests consists of, but are not limited to, the following:

■ Duct network verification. Assures the correct duct sections are installed according to drawings and cleaned as defined in cleaning procedure.

■ Room verification. Requires checking that the rooms have been prepared correctly, so that no air leak can compromise the differential pressure that is established by the system.

■ Filter performance. Challenges for leaks and filter integrity. A certified company that is familiar with the appropriate standards, and utilizes only calibrated test equipment must perform testing on all filters. It is critical to use a non-cancerous aerosol agent for HEPA filters integrity testing, Dioctylphthalate (DOP) is questionable, and should not be used.

The validation of a HVAC system, as with any system, could be compromised if scientifically sound measurement principles are not followed. Basic measurement principles require verification and documentation that all measurement instruments utilized have been calibrated, and that the calibration is traceable to National Institute of Standards and Technology (NIST). The calibration must be within the due date. The accuracy of the instrument must be sufficient given the characteristic being measured. The rule of thumb is that the tolerance accuracy ratio (TAR) should ideally be equal to ten. The TAR is the ratio between the total tolerance of the characteristic measured, divided by the accuracy of the instrument utilized. Calibration is a critical part of the IQ, which includes verification that calibration of all components and equipment within the system is calibrated appropriately.

HVAC System Operational Qualification (OQ)

The OQ of a HVAC system will also be very time consuming as it requires that several pieces of equipment be functionally challenged. The OQ of this HVAC System will be conducted in six phases:

❶ Functional challenge of the components and pieces of equipment.
❷ Room balancing.
❸ Testing temperature and %RH monitoring and control systems
❹ Temperature and %RH mapping.
❺ Testing differential pressure monitoring system.
❻ Testing air quality.

The first phase, the functional challenges of components and equipment is unique and specific for each system. The following will outline only a few of the functional tests that are required. As stated in previous sections, each specific function of each component or piece of equipment needs to be challenged. As a guideline, ask the following question: do the tests performed establish confidence that this piece of equipment operates as it is intended to function? It may be very useful to generate a table with two columns. The first column contains the list of all major functions of the system, and the second specifies which test is performed to challenge the function. Special attention must be given to the safety checks, and the alarm's verifications. These aspects must be thoroughly tested ensuring a safe working environment, and establishing confidence that abnormal or unsafe conditions will be detected before they reach critical levels.

Room balancing, the second phase, must be done by specialists. As with HEPA filter performance testing mentioned above, a certified company familiar with the appropriate standards must conduct these tasks, and utilize only traceable calibrated test equipment. Differential pressure specifications depend on the room's usage and the type of product manufac-

tured. The purpose of the operational qualification is not determining whether or not the specifications are correct, but in establishing confidence that the system conforms to the specifications. The PQ demonstrates that there is a high probability that the system will continue to conform to these specifications.

The third phase, testing the temperature and %RH monitoring and control system, consists of a verification that the values of the actual temperature, and %RH in the rooms are:

- Correctly measured.
- Correctly sent to and received by the control system.
- Correctly interpreted by the control system (i.e., control system sent back the appropriate control signal to AHU, humidifiers and heaters.)

The easiest method of verifying that the values are correctly sent and received by the control systems is for one person to record the actual value within the room being tested and another person to record the value registered by the control station at the exact same time. It is helpful if these two persons maintain communication through portable receivers and transmitters or other similar wireless devices. It is extremely important that they record the values at precisely the same time in order to obtain meaningful data. Remember to repeat this procedure for each instrument, and/or sensor that transmits data to the system. Never assume that if the value measured by one temperature sensor, for example, is correctly transmitted, the values measured by the other temperature sensors will also be correctly transmitted. There are many potential causes for a single sensor to fail, thus preventing accurate data transmission (for example, an improper connection, defective output in the transmitting unit, or defective input in the receiving unit).

Verifying that the values are correctly interpreted by the control system can be performed by testing whether the control system responds as defined by the specifications. Events for which a response can be evaluated might include: decrease or increase in the ambient room temperature, change in ambient room %RH; decrease or increase in the room temperature set points, and temperature or %RH reaching predefined alarm limits. It is important to test each room, and verify that each humidifier and heater is turned on and off, when (and only when) it is expected.

The fourth phase, temperature and %RH mapping, requires verifying that the entire room is in compliance with its specifications, not only the specific area where the sensor is physically located. This is performed by measuring the temperature and %RH in various locations throughout the room; for example, the middle of the room, each corner, and at three feet and eight feet points within each location. A data sheet like the one shown in *Figure 4* (temperature and %RH mapping) could be used to record the values measured.

The fifth phase, testing the differential pressure monitoring system, consists of a verification that the differential pressure values are:

- Correctly measured.
- Correctly sent to and received by the control system.
- Correctly interpreted by the control system.

Verifications of correct measurement and receipt by the control system can be performed in a manner similar to that described previously for the temperature and %RH verifications. In order to verify the interpretation of the data received, it is necessary to check that the system generates an exception report. Such reports must correctly document any instance where differential pressure goes above or below the predefined alarm levels, identify the fault, identify the location, and the time of the event (date, time).

In the final phase, air quality testing will be conducted in each room and consists of measuring: viable particulates and non-viable particulates. Typical acceptable parameters for viable particulate might be < 0.1 CFUs/ft^3 if the alert level is equal to or greater than 0.1 CFUs/ft^3, and the action level exceeds 0.15 CFUs/ft^3. Typical acceptable parameters for non-viable particulates might be an acceptance level < 9,000 ppcf for 0.5 micron particulates, if the alert level is equal to or greater than 9,000 ppcf for 0.5 micron particulates, and the action level exceeds 10,000 ppcf for 0.5 micron particulates.

The OQ will conclude, as described in the other OQ sections of this article, with verification that appropriate procedures are in place, applicable,

Figure 4

Temperature and %RH Mapping

%RH at 3': _____.
Temp at 3': _____.
%RH at 8': _____.
Temp at 8': _____.

Room #:_____.
Date: _____.
Performed by:_____.

%RH at 3': _____.
Temp at 3': _____.
%RH at 8': _____.
Temp at 8': _____.

East
North South
West

%RH at 3': _____.
Temp at 3': _____.
%RH at 8': _____.
Temp at 8': _____.

%RH at 3': _____.
Temp at 3': _____.
%RH at 8': _____.
Temp at 8': _____.

Instrument ID #: _____.
Calibration Date:_____.
Calibration Due Date:_____.

%RH at 3': _____.
Temp at 3': _____.
%RH at 8': _____.
Temp at 8': _____.

approved, and personnel who utilize, and/or maintain the system, have been trained appropriately.

HVAC System Performance Qualification (PQ)

The PQ of the HVAC system consists of the monitoring of the following parameters every hour over at least thirty consecutive days:

■ Temperature. A typical acceptance criteria could be > 20ºC (68ºF) and < 25ºC (77ºF).

■ %RH. A typical acceptance criteria could be > 30 %RH, and < 65 %RH.

■ Differential pressures. Acceptance criteria is very specific and based on use and product requirements.

Always assure that all acceptance criteria is consistent with those defined in the approved system specification for each particular case

A temperature and %RH Mapping might be performed for each room at the end of the thirty day testing period to confirm that the entire room is still in compliance with its specifications.

The PQ concludes with verification of calibration status of all equipment, and assuring that all measurements made during the testing phase are acceptable.

Validation of New Systems vs. Existing Systems

The validations described are pertinent to the qualification of new systems; however, the approach to qualifying existing systems will not be significantly different. It is still necessary to form a multidisciplinary team, develop and document validation project plans, and perform IQ, OQ & PQ. The IQ phase will be modified because the systems are already installed. For example, during an IQ of an existing system, it is necessary to verify that the original architectural drawings are consistent with the equipment, as it is currently installed. This is in contrast to an IQ of a newly installed system, in which the equipment is compared to approved drawings.

The OQ and PQ phases will be approached in the same manner for a newly installed system or an existing system. Do not make the mistake of assuming that a review of historical data is a sufficient method of meeting OQ and PQ requirements for an existing system. The only means to competently perform an OQ and a PQ is thoroughly establishing documented evidence that the system operates in accordance with approved specifications and that it will reliably continue to do so. ❑

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Key Aspects of Validating Hydrogen Peroxide Gas Cycles in Isolator Systems

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The application of hydrogen peroxide (H_2O_2) gas to isolators began in the early 1990's with the commercialization of a generator capable of flash vaporizing aqueous H_2O_2 into a flowing air stream in a safe and effective manner. Until recently, the decontamination equipment had primarily been used on isolator systems involved in sterility testing of pharmacopeial products, and papers have been published on validation issues relevant to that topic.[1,3]

"The use of isolators for aseptic processing has gained acceptance in the pharmaceutical industry..."

An isolator has been defined as an enclosure that provides for complete separation of tested or manufactured product from the surrounding environment.[4] The use of isolators for aseptic processing has gained acceptance in the pharmaceutical industry, and the consensus has been to treat these systems with sporicidal germicides prior to manufacturing to reduce viable contamination to below detectable levels.

At the 1998 ISPE Barrier Isolation Technology Conference in Arlington, Virginia, it was reported that H_2O_2 gas was being used for that purpose on 64 of 80 isolated filling lines around the world that are either in production or under validation.[5] Another eight projects were utilizing aqueous H_2O_2 (one in combination with atmospheric steam), while the remaining lines were being exposed to peracetic acid in one form or another prior to use.

Additional validation data on the use of H_2O_2 gas for sophisticated isolator applications are becoming more evident at conferences and in the literature over the last couple of years. In several cases, essential process variables have been overlooked, questions have been raised on the consistency of H_2O_2 gas generators and/or the devices used to qualify them (biological indicators), and difficulties reported in trying to establish a satisfactory, repeatable process.[6,7] These issues may in fact be due to a general lack of experience and/or guidelines on how to properly apply the sterilant to isolators. The purpose of this paper is to revisit some essential validation aspects of sanitizing isolators with H_2O_2 gas in order to assist the industry in demonstrating reproducibility of the process under worst-case conditions.

Equipment Qualification

Please note that most of the discussion in this paper is centered around the testing of an AMSCO VHP®1000 Biodecontamination System (STERIS

Corp., Mentor, OH) since it is the most common sterilant generator in use on isolators. This piece of equipment is a standard product and, as such, the installation qualification (IQ) and operational qualification (OQ) can be easily combined into a single equipment qualification (EQ) protocol and pared to the essentials. Typical IQ lists include equipment and components, drawings, filters, spare parts, consumables, documentation, and required utilities.

All critical components on the commercially available generators, including pressure sensors, temperature sensors, blower controls, and mass measuring devices (electronic balance), need to be calibrated prior to the EQ to assure proper performance. Testing is then performed to verify that their operation is in accordance with the manufacturer's specifications and/or the design and functional requirements of the client.

STERIS Corporation has specified that the sterilant injection rate should be maintained within ±10% and the airflow rate within ±1 ft^3/min after the first minute of phase operation the AMSCO VHP®1000.[8] Control within these tolerance limits is critical since exceeding them can have a negative impact on the sporicidal efficacy of H_2O_2 gas. Each cycle phase should be tested for at least several minutes of "closed loop" operation to confirm the consistency of these critical parameters. The pressure control capabilities of the system will also need to be demonstrated by connecting the generator to each isolator. If included in the isolator design, redundant pressure monitors on independent ports should be tested to confirm that readings are consistent with the pressure control system on the sterilant generator. It is also recommended to test all alarms and aborts, including safety tests, for operator protection.

Sterilization or Sanitization

There has been a great deal of debate on terminology in relation to both isolation technology and on the application of chemical germicides to such systems. The timing couldn't be better for this debate since there are currently no established guidelines (at least domestically) that users of such equipment must adhere to. However, keep in mind that what you claim can and will impact your validation requirements for a system.

Sterilization is a physical or chemical process capable of destroying all microbial life, including bacterial spores, while sanitization refers to a decontamination process which reduces viable contamination to a defined acceptance level. Sanitization can range from a simple cleaning to the application of a sterilant, the choice of which depends upon the type of bioburden present and the intended use of the object being treated.

Hydrogen peroxide gas and other chemical germicides do not possess the physical properties required to accomplish sterilization of every surface in an isolator (crevices, moving parts, etc.); therefore, a sterilization claim is unwise and not even warranted for most applications. Sanitization of the isolator interior is the more appropriate term since difficult-to-sterilize areas such as mentioned above do exist even in the best of isolator designs. The goal should be to eliminate detectable levels of microorganisms. There have been some minimum requirements suggested at conferences and in draft monographs on how best to accomplish that. The consensus at the present time is to treat a precleaned isolator with a sporicidal agent in a quantifiable and reproducible manner and to minimize contact points (glove supports, moving of parts) during the sanitization cycle.[1] This should be the focus of your sanitization validation effort.

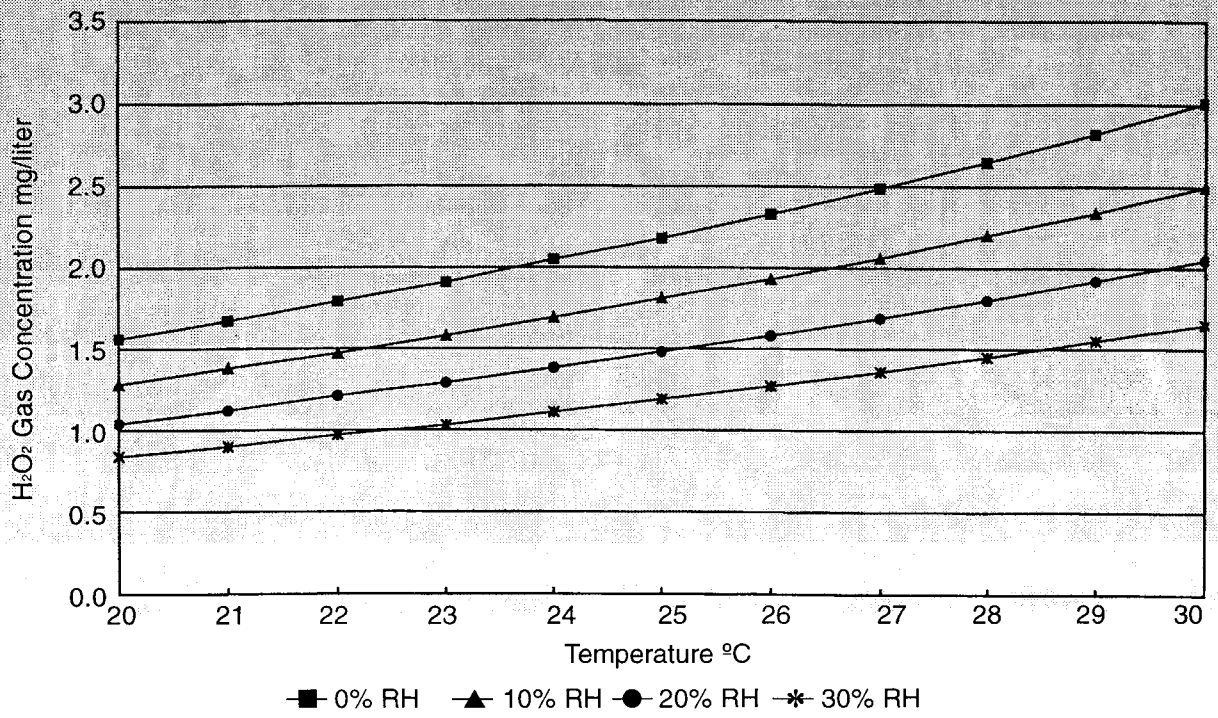
Once an exposure time has been validated, most companies tend to take the conservative approach and double it according to the traditional overkill approach. Since isolator sanitization is not a true sterilization process, the industry may want to look at adding some time to account for potential variables in the process, but doubling the exposure time seems unwarranted.

Cycle Development

Seldom has anyone had the foresight or luck to set base parameters on a H_2O_2 gas generator and arrive at an optimized sanitization cycle on the first attempt. Some equipment vendors have provided useful guides to assist in this endeavor, although the calculations are intended as a starting point for creating custom cycles based on actual validation data.[9] Once properly trained, the end user will become aware that the sterilant is a condensable gas, and temperature and background humidity have a direct relationship

Figure 1

Effect of Temperature and Humidity on Dew Point Gas Concentration for Flash Vaporized 35% H_2O_2 Solution[9]



on the maximum allowable gas concentration (see *Figure 1*). Condensed H_2O_2 does have sporicidal properties, but it will result in lower and inconsistent gas concentrations in warmer areas of an enclosure.[10]

Cycle development calculations utilize known (internal volume including the ductwork) and estimated (minimum surface temperature) isolator variables in determining sterilant injection and airflow rates, which will be optimized experimentally. These studies can be placed in separate protocols to assist in generating acceptance criteria for the actual Performance Qualification (PQ) or included in a separate section of the PQ document if acceptance criteria have already been defined. Thermocouples and chemical indicators should be used to determine the temperature and gas distribution characteristics of the isolator. The actual minimum surface temperature at the end of dehumidification replaces the estimated temperature used for base cycle calculations, and parameters are then optimized if necessary. The chemical indicator data is extremely useful in determining the need for additional recirculating fans and/or a change in sterilant inlet manifolding for multiple isolator systems prior to initiating the PQ.

Recent data also suggest that a real-time gas monitor can be a very useful tool in cycle development by providing quantitative information on H_2O_2 gas and water vapor concentrations.[10] While the use of a monitor can facilitate the setting of optimized gas concentrations within an enclosure, chemical indicators still provide a quick means of verifying that the sterilant is being adequately distributed throughout them. Sterilize phase time still needs to be determined using spore-inoculated test carriers or biological indicators, which is discussed below.

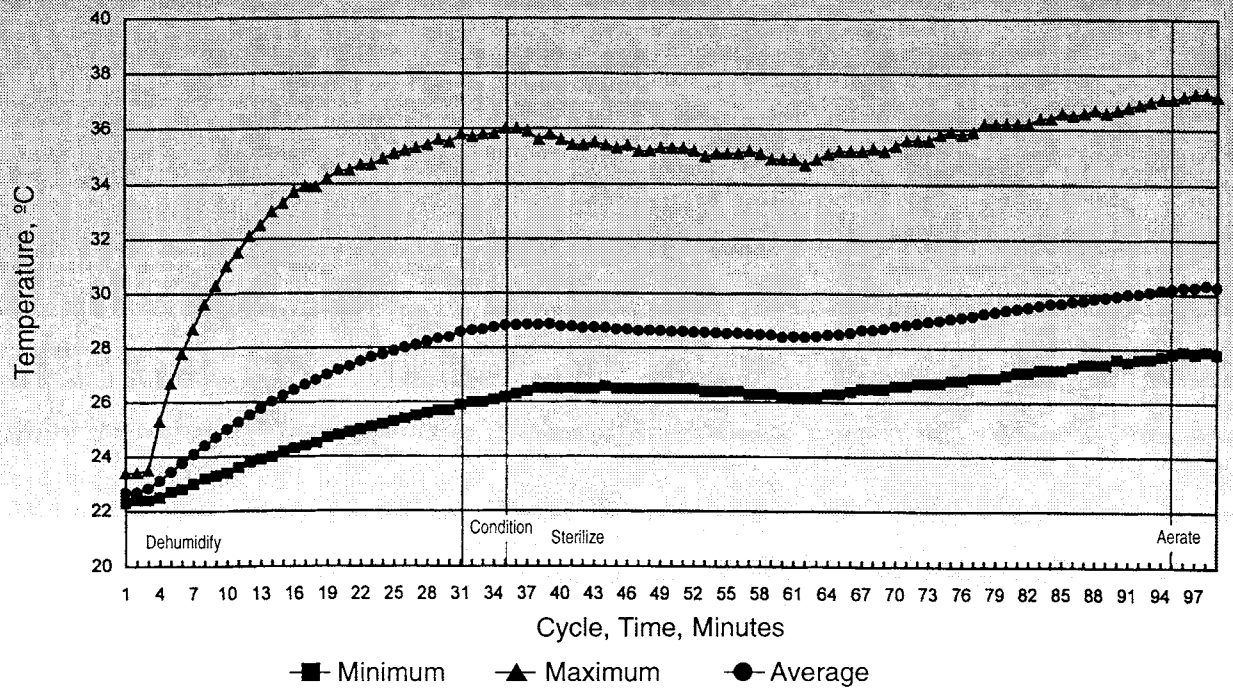
Performance Qualification

Temperature Distribution

The maximum allowable H_2O_2 gas concentration is based upon the humidity level and the minimum surface temperature within an isolator. The humidity is typically reduced to a preset level and then controlled (to some extent) with an internal desiccant or dryer system. The coolest point in an isolator represents the location at which condensation would first

Figure 2

Range of Surface Temperature in a 100 ft³ Isolator During a VHP1000 Sanitization Cycle at Constant Airflow Rate



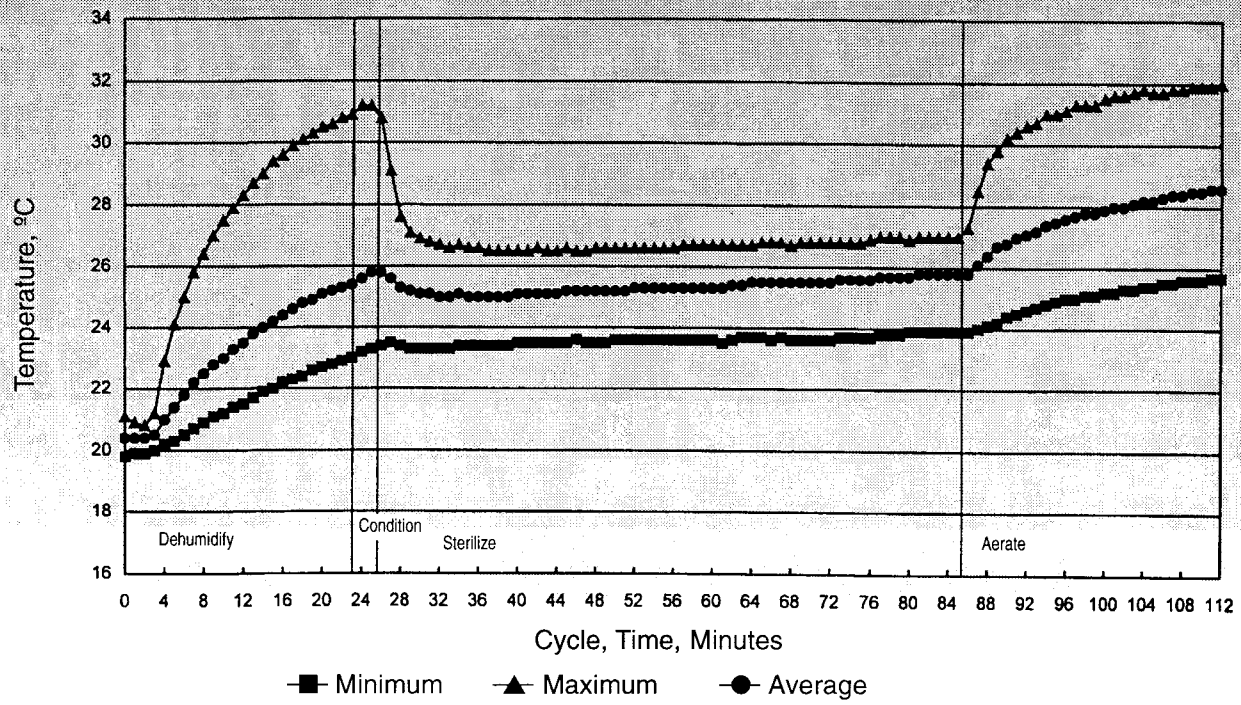
occur when an excessive H_2O_2 gas concentration is used. Temperature has also been shown to indirectly affect sterilization efficacy in that an increase in temperature will lower the percent saturation and the half-life of the gas, both of which can require longer sterilize phase times.[9] With these facts in mind, triplicate studies need to be performed during the PQ to establish a temperature distribution pattern within the isolator and a temperature profile of the surrounding room.

Isolators should be placed in areas designed to control temperature within ±2°C of the set point. This level of control is standard for the industry, and actual data has shown the variance to be typically less than ±1°C in room temperature. From a sanitization cycle perspective, it is more important to demonstrate that day-to-day variability in room temperature stays within some acceptance window, since the room can impact isolator surface temperatures. The sterilant generator itself can also affect isolator temperature at least for enclosures that are less than a few hundred cubic feet in internal volume. Be careful in choosing dehumidify phase times that are too close to theoretical. If a VHP1000's desiccant system is warm, or has less than 10 cycle hours in remaining capacity, there is a chance that the absolute humidity set point will not be reached within the allotted time. Additional dehumidify time may increase isolator temperatures to levels that may affect sterilant efficacy. Choose a conservative dehumidify phase time to avoid such situations. For example, a 20-minute dehumidify phase time should consistently reduce the absolute humidity to <2.3 mg/liter in isolators of 30 ft³ internal volume or less.

If the average daily room temperature varies by no more than ±5%, there shouldn't be a need to validate H_2O_2 gas sanitization cycles at different room temperature set points. The example in *Figure 4* indicates that a 5% increase in isolator temperature (24.0° to 25.2°C) will reduce the saturation level (dew point) of the gas from 85 to 80%. According to the percent saturation chart in the VHP1000 Cycle Development Guide,[9] the H_2O_2 gas D-value would only increase by approximately 23%; however, another 5% rise in temperature would increase the

Figure 3

Reduction in Maximum Surface Temperature by Lowering VHP1000 Airflow Rate During Exposure in a 27 ft³ Transfer Isolator



D-value by approximately 42%. If day-to-day variability in room temperature is greater than ±5%, you may need to establish your noncondensible gas concentration on anticipated cool temperatures, and then base your sterilize phase time on sporicidal data obtained under warm (worst case) temperature conditions. Also, remember to validate the time required to lower isolator temperatures back down to ambient temperature if heat is employed to dry the equipment after cleaning, as most sanitization cycles are validated while under such conditions.

It is equally important to demonstrate consistency in the range of isolator surface temperatures during at least the exposure phases of a sanitization cycle. The temperature plot in *Figure 2* for a 100 ft³ isolator shows that surface temperature gradually rises from the heat of the sterilant generator and/or the isolator's HVAC system. Experience has shown that the average minimum and maximum surface temperature during exposure can also be maintained within ±5% of the average of the triplicate tests. This information will provide further evidence that your sanitization cycle is being performed with the isolator and surrounding room temperatures in some state of control. Record the temperature data on a cycle summary sheet as shown in *Figure 5*.

You can actually lower the required sanitize time for at least small isolators (40 ft³ internal volume or less) by simply lowering the airflow rate of the sterilant generator (*Figure 3*). This will reduce an isolator's surface temperature since the amount of heat being added to the system is less, thereby increasing the efficacy of the gas.

Gas Distribution

The locations selected for the placement of chemical and biological indicators should be based upon the physical configuration and anticipated airflow characteristics of the enclosure. An indication of locations within the isolator that may be difficult to expose to H_2O_2 gas is important, because they could represent areas where microbial kill would occur last. An isolator sanitization process needs to demonstrate that the chemical agent is evenly distributed on a consistent and reproducible basis. For H_2O_2 gas, qualitative chemical indicators are com-

Figure 4

Effect of Temperature on H_2O_2 Gas Saturation and D-Value at 1.35 mg/liter
(24ºC, 30% H_2O_2 Injected at 3.5 gm/min. and 20 ft³/min., 9 min. half-life in 100 ft³ Volume)

Maximum Surface Temperature, ºC	Temperature Increase, %	Dew Point Conc. mg/liter	Saturation Level, %	Est. Increase in D-Value, %[a]
24.0	0	1.58	85	0
25.2	5	1.68	80	23
26.4	10	1.80	75	42

[a]Based upon Figure 1 – 2 in STERIS Cycle Development Guide[9]

Figure 5

Typical VHP1000 Cycle Summary Worksheet

Cycle Phase	Parameter Name	Parameter Values: Validation Test #_____	Validation Test #_____	Validation Test #_____	Parameter Units
	Assumed Min. Temp.				ºC
Dehumidify	Airflow Rate				ft³/min
	Goal A.H.				mg/liter
	Time				minutes
Condition	Airflow Rate				ft³/min
	Injection Rate				grams/min
	Time				minutes
Sterilize	Airflow Rate				ft³/min
	Injection Rate				grams/min
	Time				minutes
Aerate/Exhaust	Airflow Rate				ft³/min
Pressure Control Setting					inches w.c.
No visible condensate					Yes/No
Time of first/last visible CI to violet gray					minutes
CIs change in ≤10 min. of each other					Yes/No
Actual min. surface temp./TC # in exposure					ºC/TC#
Actual max. surface temp./TC # in exposure					ºC/TC#
All non-visible CIs indicate total color change to gray or white by cycle end?					Yes/No
Average room air temp. during cycle					ºC
Average min. surface temp. during exposure					ºC
Average max. surface temp. during exposure					ºC
Test Date					

mercially available to expedite the optimization of an effective mixing system. Their use has been restricted to cycle development by some firms due to their qualitative nature and the need to still use biological indicators to demonstrate adequate gas distribution.

Experience has shown that obtaining a chemical indicator color change window (time from first to last change) of 5-10 minutes in an isolator is indicative of satisfactory gas distribution. This does not imply, however, that the sanitization cycle will be unsuccessful if the color change window is outside of this range. There are means available to optimize gas distribution, but do not expect an isolator's air

Figure 6

Estimated H_2O_2 Gas D-Values Obtained in Various Isolators Using a VHP® 1000 Under Defined Conditions

				Average of Triplicate Tests					D-Value, Minutes		
Project	Carrier Type	Initial Spore Titer, CFU[b]	Approx. Isolator Conc., mg/liter	Inj. Rate, gm/min	Airflow Rate, ft³/min	Isolator Air Temp., ºC	Sterilant Return Temp., ºC	Sterilant Return RH, %	Test #1	Test #2	Test #3
A	Stainless Steel	$1.1x10^6$	1.2 (31%[c])	1.51	10.5	27.9	30.0	20.0	6.2	7.8	7.6
	Spordex-VHP BI	$1.1x10^5$	1.2 (31%)	1.51	10.5	27.9	30.0	20.0	7.0	7.4	7.1
B	Stainless Steel	$1.8x10^6$	1.4 (35%)	1.50	10.5	26.9	32.1	12.0	1.3	1.9	1.4
C	Stainless Steel	$2.6x10^6$	1.5 (31%)	1.70	10.7	28.0	27.2	17.7	7.0	6.6	5.0
	Spordex-VHP BI	$7.8x10^5$	1.5 (35%)	1.70	10.7	28.0	27.2	17.7	10.1	10.2	8.4
D	Spordex-VHP BI[d]	$2.9x10^5$	1.9 (35%)	3.10	20.3	32.6	35.9	10.7	2.7	2.8	3.7
E	Stainless Steel	$1.4x10^6$	1.7 (35%)	2.50	15.9	28.5	34.6	13.4	2.1	1.9	1.1
F	Stainless Steel	$3.5x10^6$	1.2 (35%)	1.80	17.8	30.2	35.3	6.2	12.1	12.1	11.7
G	Stainless Steel	$2.0x10^6$	1.1 (35%)	1.90	18.6	34.8	33.0	9.3	14.1	14.1	12.9

[a]Carriers inoculated with Sporde – VHP™ *Bacillus stearothermophilus* Spore Suspension (STERIS Corp.)
[b]Stumbo, Murphy & Cochran estimation
[c]Aqueous concentration in wt. %H_2O_2
[d]Polyflex instead of Metrigard carrier substrate

recirculation system to accomplish this by itself if numerous pieces of complex equipment are housed within it. Finally, when chemical indicator studies are initiated, you may want to use a "calibrated" set of eyes (same person) for the triplicate tests since the color change from a yellow to violet gray is subjective at best.

Spore Inactivation

Spore suspensions and/or commercially prepared biological indicators for use in validating H_2O_2 gas sanitization cycles need to possess a defined resistance to the gas. Resistance data from the manufacturer should provide at least a kill window (time for all positives/all negatives under defined conditions). It would be preferable to assign a D-value for each lot of product, although manufacturers currently do not provide this information for hydrogen peroxide-based products. Expiration dates should be based on stability in resistance, not solely on spore titer. Unfortunately, there are no monographs on biological indicators for H_2O_2 gas; therefore, the end-user must determine what is acceptable for their particular validation effort. It is advisable to perform on-site D-value testing before and after a validation if you wish to use spore suspensions or biological indicators that have no resistance data established by the manufacturer.

D-values can be estimated if an operator can access an isolator undergoing sanitization without aborting the cycle from pressure control problems. Test parameters have to be consistent from cycle to cycle to generate meaningful data. Maintaining this information can prove quite useful when it comes time to use a new lot of spore suspension or biological indicators for future revalidation efforts. The studies need to be performed under square-wave conditions in triplicate by placing the test carriers in sealed containers until the gas concentration and isolator temperature have stabilized. The recovery media should also be placed in the isolator, but each tube must contain filter-sterilized catalase to neutralize any H_2O_2 that enters the media. Carrier transfer systems have also been used to eliminate the need for placing the recovery media in the isolator and to increase productivity.

The H_2O_2 gas D-value data in *Figure 6* summarizes the results of studies performed over the past several years. Variability in D-values for the individual tests, although relatively small, can be attributed

Figure 7

Sterilization of Spore Inoculated Carriers Distrubuted in Various Isolators Using a VHP® 1000 Under Defined Conditions

Isolator Application	Initial Spore Titer, CFU[a]	Approx. Isolator Conc., mg/liter	Average Min/Max. Surface Temp. During Exposure, °C	Exposure Time, Minutes	Test #1	Test #2	Test #3
Sterility Test Transfer	$1.8x10^6$	1.4	24.3 / 26.0	32	0/23[b]	0/23	0/24
Clinical Interface	$1.4x10^6$	1.5	23.3 / 26.9	48	0/30	0/30	0/30
Clinical Filling	$1.4x10^6$	2.0	31.5 / 44.2	51	0/35	0/35	2/35
				66	0/35	0/35	0/35
Production Filling	$1.0x10^6$	0.8	22.5 / 29.5	75	1/92	1/92	3/176[c]

[a]Stainless Steel carriers inoculated with *Bacillus stearothermophilus* ATCC 12980 spore suspension
[b]Number of carriers positive for growth per number tested
[c]Two carriers placed at each test location for this test (no more than one positive at any location)

to the fact that these isolators were not tightly controlled test vessels. The average H_2O_2 gas D-values between studies, however, ranged between 1.5 and 13.7 minutes. It is impossible to compare these results since the test conditions were not identical for each study. However, it is quite evident that test parameters such as concentration and temperature can affect the kill rate of H_2O_2 gas. If control of either parameter is impossible, remember to test under worst-case conditions when validating the sanitization cycle. Some clients have also requested that D-value studies be performed under anticipated isolator conditions in order to estimate a sterilize phase time. That is why some of the D-value results in *Figure 6* are on the order of 12-14 minutes. Isolator complexity and temperature control issues were primarily responsible for these rather lengthy times, although spore resistance most certainly had a role.

For general PQ studies, the distribution of stainless steel carriers for commercially prepared biological indicators having a known resistance to the gas should be a sufficient challenge. Please note that false positive sterilization results have been attributed to the improper preparation and handling of user-prepared carriers. Once clean and presterilized via dry heat or clean steam, the test carriers should be handled only with sterile forceps. The stock spore suspension should be vortexed for one minute, then an aliquot removed and sonicated in a glass test tube for five minutes prior to carrier inoculation. The latter step breaks apart clumps, which may offer an unrealistic protection from the sterilant. The spore suspension should not be sonicated more than twice to avoid a reduction in resistance.

Spore-inoculated carriers should be distributed throughout an isolator in a manner so that even gas distribution can be demonstrated. There have been instances where over 200 carriers were required due to an isolator's size, complexity, and/or the equipment housed within it. The difficulty in distributing the sanitizing agent should be addressed during factory acceptance or cycle development testing. The test carriers should be placed under equipment as well as in the corners of the enclosure. Carriers that are consistently positive for growth in such locations but negative for growth in directly exposed areas would suggest that a fan, not an increase in exposure time, be recommended.

Testing should be performed in triplicate to demonstrate consistency in gas concentration and distribution. *Figure 7* provides a representative sampling of carrier sterilization data obtained within different isolators and test conditions. The results suggest that consistent isolator sanitization is obtainable using exposure times of around one hour or less. The production application data was obtained during cycle development testing whereby random positives occurred after 75-minute exposures to 0.8 mg/liter. Please note that a random positive carrier when inoculated with $\pm 10^6$ spores is not a rare occurrence when H_2O_2 gas concentrations of less than 1.0 mg/liter need to be utilized. There is currently no proven explana-

Figure 8

H_2O_2 Gas Sterilization of Different Materials in Various Isolators at Exposure Times Established with Stainless Steel Carriers

Project	Approx. Isolator Conc., mg/l	Average Min./Max. Surface Temps. During Exposure, C	Exposure Time, Minutes	Type of Carrier Materials[a]	No. Positive Carriers Per 5 for Each Replicate Test			
A	1.4	24.3 / 26.0	30	Mylar®[b]	1	0	0	0
				Blister Package	0	0	0	
				Butyl Rubber	0	0	0	
				Glass	0	0	0	
				Silicon	0	0	0	
B	1.7	23.8 / 26.8	45	Hypalon®	0	0	0	
				Neoprene®	0	0	0	
				Polycarbonate	0	0	0	
				Polypropylene	0	0	0	
				PVC	0	0	0	
				EPDM Foam[c]	4	5	5	
				Delrin®	0	0	0	
				Silicone	0	0	0	
C	1.2	23.5 / 28.0	60	Glass	0	0	0	
				Polystyrene	0	0	0	
				Polypropylene	0	0	0	
				Polyethylene	0	0	0	
D	1.5	Data Unavailable	80	Polycarbonate[d]	2	0	0	0
				Glass	0	0	0	
				Latex	0	0	0	
				Blister Package[b]	1	0	0	0
				Silicone[b]	3	0	0	0
				Polyethylene	0	0	0	
E	1.2	26.1 / 36.5	120	Polycarbonate	0	0	0	
				EPDM	0	0	0	
				Silicone	0	0	0	
				Hypalon	0	0	0	
F	1.1	22.2 / 27.2	180	Glass	0	0	0	0
				Silicone	0	0	0	0
				Hypalon	0	0	0	0
				Viton®[e]	0	1	0	0
				Teflon®	0	0	0	0
				Polycarbonate	0	0	0	0
				Nickel Plating	0	0	0	0
				Polyethylene[e]	1	0	0	0
				Polyurethane	0	0	0	0

[a]Carriers inoculated with approximately 10^6 *Bacillus stearothermophilus* spores
[b]Samples not thoroughly cleaned for initial testing
[c]Open cell foam gasket (another material suggested)
[d]Positive samples were upside down (spores covered) during exposure
[e]Surface preparation questionable on positive carrier (visible scratch upon microscopic examination)

tion for this anomaly. Longer exposure times may eliminate the positives, but their randomness in the data provided in the figure (all at different locations) could suggest that carrier preparation or handling was suspect. For the third test, two carriers were placed at each location in the production isolator to determine if a positive was location related or an outlier (inconsistency in a user-prepared carrier). The three positives did occur at different locations, which would suggest the latter scenario. For an isolator sanitization process, the placement of duplicate carriers at each location would seem like a valid approach to the elim-

Figure 9

Aeration of Various Isolators Following H_2O_2 Gas Sanitization Under Defined Conditions

Isolator Application	Isolator Construction	Acceptance Criteria	Air Exchanges / Hour	Time, Hours
Sterility Test Transfer	Flexible PVC, Divetex® and Stainless Steel	VHP 1000 Aerate to <3 ppm	44	4
		External Exhaust to <1 ppm	27	16
Sterility Test Workstation	Flexible PVC Divetex and Stainless Steel	VHP 1000 Aerate to <15 ppm	8	2
		External Exhaust to <0.1 ppm	13	30
Clinical Interface	Polycarbonate, Hypalon and Stainless Steel	VHP 1000 Aerate to <21 ppm	20	1
		External Exhaust to <0.1 ppm	32	26.5
Clinical Filling	Polycarbonate, Glass, Hypalon and Stainless Steel	VHP 1000 Aerate to <21 ppm	9	1
		External Exhaust to <0.1 ppm	18	39
Production Filling	Polycarbonate, Glass, Hypalon and Stainless Steel	External Exhaust to <50 ppm	4	0.5
		External Exhaust to <1 ppm	100	14

ination of outliers, although some limit on positives would need to be defined prior to initiating the PQ.

As previously mentioned, every attempt should be made to eliminate obscured surfaces, such as by using glove/sleeve holders and shrouds over complex surfaces, but direct inoculation of suspect areas with spore suspension is not warranted or recommended. There have been statements made in the literature that D-values can vary when different materials are inoculated with spore suspension.[4] Several studies have been undertaken over the past few years to confirm that various materials can be sterilized within a defined exposure time to the sterilant (*Figure 8*). The data suggest that there was not a significant difference in D-value, since the exposures were based on the times required to consistently sterilize stainless steel carriers. Random positives were encountered, but they were attributed to preparation and cleaning issues as mentioned above. There may be applications where certain critical surfaces within an isolator (e.g., stopper bowl) will need to be spot inoculated with spore suspension and exposed to the sterilant under actual use conditions. However, one should question the need for continued testing of Hypalon®, Lexan® (polycarbonate), or glass carriers based on the results shown in *Figure 8*.

Aeration

The amount of generator aeration and/or external exhaust times involved in reducing the H_2O_2 gas concentration to acceptable levels must be determined in triplicate. There has been considerable debate on what is an acceptable level. Naturally, it is going to vary depending on the intended use of the enclosure. In sterility testing operations, a transfer isolator may only be aerated for one to two hours, which typically does not reduce the gas concentration to below 3 ppm. However, sterilant residues in sterility testing or filling isolators pose a potential risk to the test or product involved. A typical response has been to validate the amount of time required to reduce the sterilant concentration to below detectable levels. H_2O_2 gas monitors can typically detect residues as low as 0.1 ppm.

Outgassing of the sterilant from various elastomer and plastic materials can extend the aeration period from several hours to more than a day. The data in *Figure 9* lists the results from several different aerate/exhaust studies on isolators. Product stability testing has been undertaken by some companies to determine if the aerate/exhaust times can be reduced for production isolator applications. Likewise, isolator vendors are investigating new materials of construction that do not absorb H_2O_2 gas, and air exchange rates are being increased or catalytic converters installed in the air recirculation system to lower background levels of the gas.

In terms of validating aerate/exhaust times, the user must be aware of the limitations of commercially available detection devices. Data has been published on the effect that temperature and humidity impart on the accuracy of several different real-time monitoring techniques.[11] The industry has typically relied upon detector tubes containing potassium iodide-coated molecular sieve for measuring low levels of H_2O_2 gas. High temperature and/or low

humidity will significantly affect the color change in these tubes, which will cause false low readings. An isolator environment is typically warm and dry after a generator completes an aerate phase; therefore, you need to introduce cool, humid air to the isolator before taking a gas sample. Also, remember to sample the air under the conditions of use. If the air exchange rate following an external exhaust is lowered prior to production operations, sample the isolator at the lower rate since this will be a worst-case (higher residue) condition. Multiple isolators that are attached to a single exhaust system may need to be sampled with all of the isolators being exhausted, since this will provide the lowest air exchange rate through the isolator under test. Finally, remember to take a negative control sample, as other oxidants will change the color of the detector tubes.

Summary

Information has been provided on how to validate H_2O_2 gas sanitization cycles in isolators under worst-case conditions. New gas generation technologies are being introduced to the industry, which may provide for better process control and subsequently an easier validation. In the interim, confirm that your critical cycle parameters were established under such conditions to ensure that the isolator is consistently sanitized and aerated before use.

Industry's goal is zero-defects testing and manufacturing of sterile dosage forms in a germ-free environment. The use of isolation technology and the application of H_2O_2 gas have certainly contributed to attaining that goal. A significant increase in pharmaceutical applications is anticipated once the learning curve has been reduced and more systems have been successfully validated. It is hoped that this document will assist those who are involved in isolator validation studies and/or the development of regulatory guidelines. ❑

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Validation of Process Gas Systems

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Validation of process gas systems involve documenting the expected system behavior, and verifying that the system performs as expected. This article covers the pertinent aspects of IQ, OQ, and PQ related to process gas systems and many of the potential problem areas. The validation of nitrogen and compressed air systems, including breathing air systems, is used as an example which can be extended to the validation of most other process gas systems.

"This articles covers the pertinent aspects of IQ, OQ, and PQ related to process gas systems and many of the potential problem areas."

Why Validate Process Gases?

Process gas systems may include compressed air, nitrogen, oxygen, helium, or other inert gases. If the gas is used to operate product related system(s), or directly affects the manufacture of drug products, we must demonstrate the system can continuously operate in a state of control.

Inspection agencies require that we demonstrate control over utilities that can potentially impact a product. However, the methods we use to document and demonstrate control of utilities are currently a source of debate in the field of validation. For example,

- Will contractor start-up documents suffice?
- Is commissioning, using "Good Engineering Practices" adequate?
- Are traditional, preapproved validation protocols necessary?

There is no pat answer. Generally, we must demonstrate that the process gas delivered at the point-of-use meets the predetermined user requirements. As long as we demonstrate this, it does not matter what we call the demonstration documents.

Design Considerations

As with any other cGMP system or equipment, we must design nitrogen and compressed air systems so that they can be qualified. The design process begins and ends with documentation of the point-of-use requirements for the system.

A typical compressed air system consists of the air compressor(s), driers (desiccant or refrigerated), distribution piping, and filtration systems. A typical nitrogen system consists of either a liquid nitrogen storage tank and vaporizer or nitrogen bottles, distribution piping and filtration systems.

Breathing air systems are becoming more commonplace as our industry increases the research and production of potent and toxic drugs. The qualification of breathing air systems is generally similar to that of other process gases. However, there are some specific, generally accepted requirements

Figure 1

Minimum Requirements of a Compressed Air or Nitrogen System

Characteristic	*Typical Acceptance Criteria*	*When to be concerned about this characteristic*
Pressure, min. & max.	90-110 psig	Usually to meet equipment needs; max. is important if equipment is not capable of throttling pressure.
Flow, min.	≥ 10 scfm	Usually to meet equipment needs; max. is important if equipment is not capable of throttling flow.
Temperature, max.	≤ 90°F	Seldom important, except for breathing air, unless there is a specific process requirement.
Purity	Meets USP Monograph	Use only if required.
Particulate	Meets particulate class level as defined by Federal Std. 209E	Same requirement as the room in which the gas is introduced, tighter if product contact issues dictate.
Microbial	Meets microbial limits, as defined by your company, for given room classifications	Same requirement as the room in which the gas is introduced, tighter if product contact issues dictate.
Dewpoint	≤ -40°F	Process driven. (Don't claim -40°F if your process doesn't need it).
Hydrocarbon	Non-detectable, (eg ≤ 25ppm as measured with Draeger 10a/P hydrocarbon tubes)	Process driven, generally "non-detectable" for process applications. Specify the lower "non-detectable" limit.
Characteristic	*Typical Breathing Air Acceptance Criteria*	*When to be concerned about this characteristic*
Pressure, min. & max.	20-25 psig	At points-of-use (e.g., hookups to air hoods)
Dewpoint	0-45°F	NFPA 99 guideline
Carbon Monoxide	< 10 ppm	NFPA 99 guideline
Carbon Dioxide	< 500 ppm	NFPA 99 guideline

for breathing air systems.

Figure 1 lists the minimum requirements that should be considered during design of a compressed air or nitrogen system.

Process Gas Standards

Currently, there are no universally recognized standards for the validation of process gases. However, a group within ASTM subcommittee 48.06 is developing validation standards for the process gases, and for the methods used to test the gases. There are several places to go for direction on the requirements of process gas systems. Generally, process gas systems must meet the chemical, microbial, and purity requirements of the products they will potentially contact, and the requirements of the room into which they are exhausted, if applicable.

The USP has developed test monographs for process gases, such as medical air, nitrogen-99%, nitrogen-75%, and oxygen. Care should be taken to consider the particular process application before assuming that conformance to USP specifications is required. Some of these methods are difficult to execute in the field (e.g., Nitrogen-99%), and should not be attempted unless they are required.

For microbial and particulate monitoring, the specific criteria developed in our respective facilities for class 100,000, 10,000, 100 and so on, should be consulted. In general, the process gas must not negatively impact the room into which it is exhausted.

For breathing air systems, the NFPA 99 specifications for breathing air is used as the basis for acceptance criteria. Additional guidance can be found in the journals of the Compressed Gas Association.

Use of Final Filters

The use of the air should always be considered when deciding what type of filter, if any, is required. Compressed air and nitrogen are often used to power

equipment and motors in the process areas. In classified (such as 100,000, 10,000, and 100) areas, where process gases directly contact the product, final filters are advisable.

Point-of-use filters should be in place, or at least considered during PQ of the system. Many companies qualify the system without the point-of-use filters in place to ensure system integrity even if the filter develops a leak during its use.

Filter model numbers should be documented, and controls should be established to ensure the same filters are used over the life of the system. The manufacturer may vary, but critical characteristics, such as filter materials, flow rate, and particulate filtration levels must be maintained. This information can be documented in the system or equipment SOPs, or in the maintenance management system. The filters found in the system two years after the initial qualification must have the same critical characteristics as the filters that were originally designed, specified, and qualified.

Final filters serving class 100, or cleaner areas, should be integrity tested. The frequency of testing should be commensurate with their use. For this reason, it is often advisable to locate the filters outside the process area. A common design approach is using medical grade copper in the distribution system, transitioning to stainless before entering into process areas, with dielectric couplings at the transition. This transition point is usually a good place to locate the system's final filters.

Installation Qualification Issues

As with any cGMP system or equipment, every inch of the system should be checked to verify conformance with as-built drawings, construction materials, valves, cross-connection to other systems, and unused portions of the system. In any large, unused portion of the system, adequate protection preventing fluid buildup during system shutdown, which could compromise the microbial purity of other parts of the system, must be ensured.

All alarms must be tested, including those on the compressors and desiccant driers for the compressed air system, on the storage tanks and vaporizer for nitrogen systems, as well as on the distribution system itself. It is often useful to hire the service representative to conduct these tests. These experienced personnel can test the alarms much faster than someone who is unfamiliar with, and could possibly damage the equipment. Plus, the tests usually take only a few hours with someone familiar with the equipment, versus a few days for someone who does not work regularly with the equipment.

For high purity gas systems, requirements for the material in product contact closely mirror those of a high purity water system. All new high purity systems should be pressure tested, cleaned, and flushed according to preapproved procedures. For stainless steel lines serving aseptic process areas (downstream of final filters), the weld maps should be matched to the weld logs and to the material certifications. If passivation has been specified, its proper execution and flushing should be verified.

Operational Qualification Issues

As with any system, all critical instruments should be calibrated prior to the performance of operational tests. Critical instruments on a process gas system are those instruments used to measure the parameters listed in *Figure 1*. However, an instrument need not be permanently installed for each characteristic. For example, if diversity testing is done well, the permanent installation of flowmeter(s) should not be required. But a pressure switch used in maintaining the minimum system pressure by turning on the lag compressor, should be calibrated.

The instruments used to monitor the critical characteristics of a breathing air system should also be calibrated. These include on-line carbon monoxide (CO), carbon dioxide (CO_2), and dewpoint monitors. CO and CO_2 monitors can be easily calibrated by using standardized test gas canisters which trigger the alarms at the appropriate levels. The manufacturer of the respective monitor can usually provide the certified gas canisters. The gases are typically provided in concentrations that correspond to the alert and action alarm levels. They can be easily input to the monitor, and then flushed from the system.

Sequence of Operation Testing

For complex systems, such as multiple air compressors or multiple liquid nitrogen vaporizers, care should be taken to test, or at least bracket, all oper-

ational scenarios. This includes testing each compressor in a lead and lag position.

Backup compressors or gas cylinders should be tested with the rest of the system. All potential operating scenarios should be explored during the operational qualification process. If an operating scenario affects the quality of the gas produced, it should be incorporated into the hydrocarbon, dewpoint, and microbial testing.

Testing of System Characteristics

The following sections review specific measurement techniques and issues for each system characteristic listed in *Figure 1*.

Each measurement technique should be carried out with calibrated instrumentation. Although Draeger tubes and some accessories will not come with NIST certificates, the flowmeter and timer used to capture the sample should be calibrated. The results obtained from accessories, such as Draeger tubes, should be reported with a corresponding error based on the manufacturer's statement of accuracy. Test results are only as good as the sum of the errors introduced during measurement.

Testing must be performed so that additional error is not introduced into the system. For example, during microbial sampling, an uninformed protocol executor might put the flowmeter between the point-of-use and the agar plate, but this introduces potential additional microbial contamination from the flowmeter. Whenever possible, valves, flowmeters, flow restriction devices and pressure gauges should be placed downstream of the variable being tested. By minimizing introduced errors, the certainty of the final test result is supported.

Test methods should be thoroughly documented, so that qualification can be repeated years after the original tests. For a small start-up company, this may mean simply writing down the test procedure in the comments section of the protocol. For more mature companies that will be routinely performing these tests, the methods should be codified in a company guideline or SOP.

Pressure

Although pressure is probably the simplest characteristic to measure for a large system, a bucket full of fittings may be needed to provide connections to all the points of use. Qualification should not be destructive. If the gas lines are already connected to process equipment, the reading from the instruments on the equipment may be obtained, and the line need not be broken.

Nothing should be taken for granted. If there is a pressure or flow specification at a point-of-use, that point-of-use should be tested. One cannot assume that because the correct pressure appears at one drop in a room, it applies to all drops in the room.

Pressure considerations during diversity testing are discussed in the following section.

Flow

The flow rate of each point-of-use should be measured to verify that user requirements are met. However, for many drops, there may be no predetermined user requirement. Typically, a baseline flow measurement is taken for each drop, whether or not it has a predetermined specification. By obtaining a flow rate measurement for each use point, a comprehensive document is established, which can be used in the future to help make decisions about whether the system can support a new piece of equipment. For example, if on initial test, only 10 scfm could be obtained, it is clear that the line size or supply pressure will need to be increased to support equipment that requires 25 scfm.

Performing the flow test at each drop also provides a visual check for large pockets of stagnate water in the pipeline. This can be important because dewpoint measurements may not be performed at all locations. Condensate may form in the lines during the initial installation of a system, or after an old portion of an existing system has not been used for an extended period. If water is found in the line, the system may not have been adequately cleaned and flushed.

Flow rate diversity tests should also be performed to identify how many (and which) points-of-use can be operated simultaneously. For a new system, diversity values should be predefined in the design documents. For existing systems, a few interviews with the equipment users should provide sufficient information for educated assumptions about simultaneous use of equipment. Simultaneous recording of flow rate and supply pressure at critical points-of-

use provides very useful information about the ability of the system to perform as designed.

Flowmeters can be found in most process equipment and instrumentation catalogues. A good contract calibration company should be able to calibrate the flowmeter, and provide a standardization table for each process gas.

Purity

If claims are made about the purity of the process gas, then testing should be performed to demonstrate that the appropriate specifications are met. A sample is typically obtained into a vacuum container or bag that can be transported to a laboratory. The methods used to obtain the sample, and to demonstrate purity should be carefully documented and reproducible.

"For more reliable, precise data, a gas sample can be obtained for laboratory analysis."

Hydrocarbon

Among the many ways that hydrocarbon tests can be performed, the most common is the use of Draeger, or equivalent, tubes to indicate the approximate level of contamination. These indications are generally not traceable to a standards bureau, such as NIST, but they are a reliable, repeatable, and commonly accepted method for discerning system contamination.

For more reliable, precise data, a gas sample can be obtained for laboratory analysis. This is usually necessary for demonstrating compliance with breathing air standards. Most large contract environmental testing laboratories provide the vacuum containers used to obtain and transport the sample.

Hydrocarbon measurements should be taken near the source during maximum load conditions to ensure that minimum system requirements are met. They should be tested at points-of-use where product will be contacted. Bracketing should be used on large systems to keep the number of tests to a manageable level. For example, in a room with three compressed air drops, a sample from location one on day one, from location two on day two, and location three on day three should be adequate to ensure that portion of the line is hydrocarbon free.

Dewpoint

Dewpoint can be a difficult characteristic to measure. The equipment used to measure dewpoint include chilled mirror, moisture level conversions, and others. The chilled mirror method is usually accurate enough to meet the process requirements. Alternatively, Draeger tubes (or their equivalent) can be used to measure moisture levels in ppm, which can be converted to dewpoint. Additionally, there are handheld measurement instruments that can be submerged in the process gas to provide dynamic measurements.

It is important that the dewpoint measurement be taken at the correct temperature and pressure. The dewpoint conversion information provided by manufacturers is often only applicable at atmospheric pressure and standard temperature. Measurements taken at other pressures and temperatures must be converted to ensure that the system specifications are met. Measurements taken at high pressure can also damage the measurement equipment.

Particulate

Most standard particle counters can be used to measure particulate levels in process gases. The same caution with respect to pressure also applies to particle monitors. The supply gas is limited to very low pressure thresholds. The monitors usually contain their own pump because they are mainly used for collecting samples from room air.

Flow must also be carefully controlled during particulate measurement. Particle counters are usually designed to pull the sample at 0.1 or 1.0 cfm. Most particle counter manufacturers can provide a dispersion tube that can be used to bring the gas down to the required flow and pressure.

The calculations provided in Federal Standard 209E can be used to translate the sample measure-

ment to a specific confidence level for the room classification being tested. Again, the particulate level should correspond to the particulate level of the room into which the process gas is being exhausted.

Microbial

Microbial air samples can also be difficult to obtain. A variety of sampling devices, such as slit-to-agar, centrifugal, and direct impact, can be used. The best method will closely mirror the sampling technique used for open air measurements in your facility.

In recent years, sampling devices have been designed specifically for process gas sampling. A sampling atrium can be used to pull samples directly from the process gas line. The sampling atrium can be sterilized between uses to ensure that it does not add to the microbial load of the sample. An agar plate, such as that used for room air sampling, can be easily and aseptically placed into the atrium for sample capture. The amount of air that passes over the agar plate should match that of a typical room air sample, usually at least 40 liters.

Post Validation

After the initial qualification, process gas systems should be maintained in a qualified state. To accomplish this, the following actions should be taken:

- Utilize change control.
- Develop preventive maintenance (PM) and operational SOP's.
- Calibrate any critical instruments.
- Train mechanics and operators on the SOPs.

Point-of-use filters should be included in a PM program. All point-of-use filters can be changed by maintenance personnel at a specified frequency, such as semiannual. Alternatively, point-of-use filters are considered part of the process equipment that it serves. In this method, production operators are responsible for checking and replacing the filter as part of the equipment setup. The main benefit of this approach is that filters are maintained with the same frequency as the equipment. If equipment is not used, money is not wasted on filters, but if equipment is used frequently, the filters receive a corresponding level of attention.

Summary

If it is approached methodically, validation of process gas systems should not be an overwhelming task. The potential impact of the specific system on the product and the process must be considered. Execution of a well-developed plan that demonstrates conformance to the predefined criteria should be simply a milestone on the way to a validated facility. ❑

Purified Water Systems: A System Perspective Under the New USP Quality Requirements

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Editor's Note: Figure 1 has been included to define specific terms appearing in this article.

"The days of simple table top, color chemistry are definitely over."

A reliable, consistent supply of high-purity process water is essential in the regulated health care industry. Concepts of quality assurance and sound system management, including a rigorous monitoring program, should be applied to the operation of all in-house, high-purity water production systems.

The issuance of the Eighth Supplement to USP 23 (official as of May 15, 1998) will complete the process of radically changing how a large portion, if not all, of the regulated health care industry monitors and tests for basic purified water quality. The days of simple tabletop, color chemistry are definitely over. Now we will be utilizing selective testing for discretely measurable quality attributes. In addition to the current pH and bioburden requirements, Purified Water (PW) and Water for Injection (WFI) requirements will now include conductivity and Total Organic Carbon (TOC) testing to replace the panel of testing that has been in place almost since the inception of the official compendia for water quality.

Design, Installation, and Operation of a Water Treatment System

Purity of process water is critical to product integrity. The proper design, installation, and operation of a high-purity water system is the primary consideration. The first challenge is to define high-purity water as it relates to the process in question. There are a series of very comprehensive flow charts on pages 7542–7544 of the May–June 1994 *Pharmacopoeial Forum* that includes a scheme for the Water System Validation Life Cycle. The charts show the logical steps to be taken during a high-purity water system definition and validation effort.

The many phases for the qualification of a water system has been extensively covered in previous issues of the *Journal of Validation Technology*, as well as many other professional publications. I will not regurgitate any of that information in this article. Suffice it to say that this process is well characterized.

Review of the Water System Monitoring Program

So what's first? In reviewing the current water system monitoring program here at Sanofi Diagnostics Pasteur (Sanofi), we observed that the major changes were considerations for conductivity requirements and the establishment of TOC analysis as part of our ongoing testing capability program. We already have in-line resistivity monitoring of our Deionized Water (DIW) loops at our two primary production facility locations. This information has been historically used to trigger change out of the deionization and activated charcoal beds. Up until this point, it was not effectively used as one of the key quality release criteria for our DIW.

Figure 1

Terms and Definitions

Refer to the *The Validation Dictionary* published by the **Institute of Validation Technology** for sources of most terminology used in this article and for the specific terms that follow.

Conductivity (in water) – Electrical conductivity in water is a measure of the ion-facilitated electron flow through it. Water molecules disassociate into ions as a function of pH and temperature and result in a very predictable conductivity. Some gasses, notably CO_2, readily dissolve to form ions which predictably affect conductivity as well as pH. These ions and their resulting conductivity can be considered intrinsic to the water. The units of measure of conductivity are µS/cm (or µmho/cm or $\mu\Omega^{-1}$). The reciprocal of conductivity is resistivity. The unit of measure of resistivity is megohm centimeters or MegOhm cm (or MΩ*cm or MΩ cm or MΩ-cm).

Deionized Water (DI Water or DIW) – Water produced by passing treated water through either a mixed-bed or two-bed ionic (cation/anion) exchange resin system. Also see Purified Water and Reagent Grade Water.

Distillation – A purification process involving phase changes (from liquid to vapor to liquid) leaving behind certain impurities.

Purified Water – Water obtained by distillation, ion-exchange, reverse osmosis, or any other suitable process. It is prepared from water complying with the regulations of the EPA for Potable Water and contains no added substances. Purified Water meets all criteria specified in the USP 23, Official Monographs of Water also described in Section <1231> "Water for Pharmaceutical Purposes." Purified Water meets criteria for High-Purity Water as defined in Containers USP<661>:

TOC: USP<643>, of ≤500 ppb or µg/L [≤0.5 mg/L (ppm)]; and

Conductivity: USP<645>, of 1.3 to 1.5 µS/cm @ 25-35ºC (See USP Supplement 5, Stage 1 Table).

Potable Water – Water that is safe to drink, meets EPA Standard for Drinking Water; 40 CFR 141.14; 141.21. The grade of water that should be supplied for the manufacture of Purified Water or DIW.

Reagent Grade Water – Water purified for general laboratory uses and broken down into various levels of purity as specified by several professional societies (College of American Pathologists [CAP], National Committee for Clinical Laboratory Standards [NCCLS], American Society for Testing and Materials [ASTM] and American Chemical Society [ACS]. Type I (HPLC grade, similar to USP WFI), Type II, Type III (Similar to USP Purified Water), and Special Reagent Water. Incidence of microbiological contamination is however not well defined; stated as "Minimum Growth." No specific recommendations for pyrogen testing. Also see: Purified Water and Deionized Water.

Reverse Osmosis Water (RO) – Water produced by a process which uses a membrane under pressure to separate relatively pure (or other solvent) from a less pure solution.

Total Organic Carbon (TOC) – An indirect measurement of organic molecules present in pharmaceutical waters measured as carbon. Organic molecules are introduced into the water from the source water, from purification and distribution system materials, and from biofilm growing in the system. TOC can also be used as a process control attribute to monitor the performance of unit operations comprising the purification and distribution system.

Water for Injection (WFI) – Water purified by distillation or by reverse osmosis (double pass) and containing no added substance. WFI must also meet criteria specified in USP 23 Official Monograph of Water.

Comparison of the acceptable resistivity ranges to USP Conductivity requirements appeared not to be problematic. It was a non-issue as far as we were concerned.

The decision of how to handle the TOC analysis was the main issue we faced. The two obvious choices were to either do it in-house or send the samples out to a local, reputable laboratory. I will address each of these three considerations in following sections.

A question that we also had to face: Is our current DIW system capable of consistently achieving ≤500 ppb TOC? Up to this point in our cleaning process qualification efforts, our DIW had only been tested to a limit of detection of <1 ppm. Some literature has referred to instances where the WFI water tested in a particular facility was not able to meet the specification of ≤500 ppb TOC. This was because of a malfunction (TOC crossover or TOC breakthrough) of the distillation system.[1] What unknown situation might we also be facing? We know that our resistivity readings indicate that we produce very high purity water. However, TOC is largely a non-ionic contaminant that does not correspond to conductivity/resistivity measurements. We might be facing expensive upgrades to our current DIW systems.

Conductivity vs. Resistivity: An Adequate Measurement of Water Quality

Regulatory Agencies that our company has been in contact with over the last couple of years have experienced some level of difficulty dealing with more than one reference scale. We have had to prove

Figure 2

Table of Laboratory, Reagent and Electronic Grade Waters

Type	TOC	Conductivity	Resistivity	pH
USP Purified Water [4,5,6,7]	<.05 ppm	1.3 @25ºC	NS	5.0–7.0
NCCLS Type I	NS	NS	*10 @ 25ºC	NS
NCCLS Type II	NS	NS	1.0	NS
NCCLS Type III	NS	NS	0.1	5.0–8.0
CAP Type I	NS	0.1	10	NS
CAP Type II	NS	0.5	2.0	NS
CAP Type III	NS	10	0.1	5.0–8.0
ASTM Type I	NS	0.06	16.6	NS
ASTM Type II	NS	1.0	1.0	NS
ASTM Type II	NS	1.0	1.0	6.2–7.5
ASTM E-1	0.075 ppm	NS	17 @ 25ºC	NS
ASTM E-2	0.5 ppm	NS	10 @ 25ºC	NS
ASTM E-3	1 ppm	NS	1.0 @ 25ºC	NS

NS = Not specified in resource material *Specifies an in-line measurement

on a number of occasions that the method that we employ as an indicator of water quality is comparable to the method that has found its way into the latest revision of the USP 23. Measurement of this particular aspect of water quality is appropriate using either method.

It is clearly stated in the Fifth Supplement of USP 23, Conductivity expressed in µS/cm (or µmoh/cm) is the reciprocal of Resistivity, expressed in MegOhm*cm. Therefore, the higher the quality the water, the higher the resistance or the lower the conductivity. DIW should fall in a resistivity range of 4-10 MegOhm*cm because of the carbon adsorption.[2] The in-line measurement of the DIW resistivity at Sanofi runs between 10 and 18 MegOhm*cm, which translates to 0.1 and ≈0 µS/cm Conductivity. The Stage 1 Conductivity Requirements for USP Purified Water between the temperatures of 30–35ºC (average system operating temperature at Sanofi's Redmond Main Facility) is 1.4–1.5 µS/cm. The USP requirement is a relatively less stringent quality than the standards already maintained at Sanofi.

In comparison to other previously recognized standards, the DIW at Sanofi conforms to various grades of Laboratory, Reagent, and Electronics Waters. National Committee for Clinical Laboratory Standards (NCCLS) Type I Water is very similar to USP Purified Water, with a slightly higher resistivity requirement; NCCLS Type II Water is of lesser quality, but is generally good quality DIW; NCCLS Type III Water is deionized water that is primarily required for glassware rinsing functions.[3] (See *Figure 2*).

Selection of a TOC Analyzer

To send the samples away to an outside testing laboratory seemed at first blush to be the easiest approach. There were a couple of items that presented themselves that weighed against this option. The first was the expense. We have approximately 30 sites we sample every month at only one of our two facility sites. Cost of analysis by an outside laboratory comes to over $1,000.00/month for that one facility alone. At this rate, we figured that we would be able to pay for an in-house analyzer in approximately a year, processing all samples from all facilities.

The next consideration was the timeliness of the reporting. We are already tied to a three-day lag for bioburden analysis. The outside lab results can take a week or more to come back for review. We could have all the samples put on a special high priority test schedule, but that service could potentially double the cost of the analysis. If the TOC analyzer were part of our in-house QC laboratory services, we could in effect have results within 24 hours of initial sampling.

On the other hand, on-line or in-line sampling provides instantaneous readouts. We are then limited to possibly just a few monitoring sites, like we are with our resistivity measurement. Is that adequate? We opted for the multiple site, off-line analysis for our TOC, because we felt it was a higher priority quality aspect to monitor on a continuous basis.

To bring a new analysis system in-house was still an awesome task. It is no small chunk of change to first qualify the analyzer in association with all the peripheral accouterments, then maintain the system over each ensuing year. Even with all that, for our particular company, an in-house system was clearly the preferred alternative.

Selecting the TOC analyzer was really a very straightforward approach. There have been a plethora of articles that specified a number of specific manufacturers. Along with that basic source information, many of these same manufacturers were saturating the trade journals with advertising touting their ability to meet the new USP standards and offering a wide variety of different styles of analyzers, methods of analysis, and installation formats.

The basic techniques for the determination of TOC in water samples have remained well understood and stable for nearly two decades. Organic compounds are converted to carbon dioxide (CO_2) utilizing a number of methods either singly or in some combination that may include chemical oxidizers, UV radiation, or combustion. The CO_2 is in turn measured by conductometric, microcoulometric, or IR absorption techniques as total carbon (TC). Through other methods, total inorganic carbon (TIC) is removed, the effluent measured, and the resulting difference yields a value for TOC in the sample (i.e., TOC = TC - TIC).

Performance Considerations: The measurement of TOC in high-purity waters is of particular importance. TOC assays are used to evaluate the level of contamination in a wide variety of water, from feed water to high- and ultra-high purity water. Characteristic TOC concentrations can range from 1 microgram per liter and lower (<1 ppb TOC) to well over 1,000 milligrams per liter (>1,000 ppm TOC), depending upon the type of water in use. Generally in the regulated health care industry, we are looking for water that has a contamination level ≤500 ppb TOC.[5,6,7] Other types or sources of samples may be processed, so the upper end of the capability range is equally as important.

Vendor selection was a snap. We contacted the top three vendors to obtain as much promotional material as possible. This was reviewed by a select panel of people from our cross-functional Validation Committee. We selected two systems to be more closely scrutinized and invited vendor representatives in to demonstrate their systems. These in-house demonstrations gave us a snap-shot of our in-house water quality and also answered the nagging question about our ability to produce water that was ≤500 ppb TOC.

We reviewed the demonstration sessions and invited our primary candidate back again for a more rigorous on-site trial with a variety of samples from all around our facility. We again reviewed the two top contenders and processed the request for funding. The selection process took far less time than the funding process, but we finally received our shiny new TOC Analyzer System.

In-line Sampling vs. Auto-Sampler vs. Grab Sample

The choice is really yours. For our particular set of needs, an in-line system just was not a practical consideration. We were looking for the greatest level of versatility and flexibility possible for our TOC analyzer system. To be able to stretch our limited budget as far as possible and be able to use the system for as many different functions as possible, we selected an analyzer with the autosampler option. With the autosampler, it is possible to set up a full set of samples, start the machine at the end of the day and collect the finished analysis reports the next morning when you return to work. Proper set up of the series of samples is the primary consideration. It is a good idea to run your "lowest" expected TOC/contamination levels first, then graduate to samples with a higher potential for contamination. This potential to walk away and allow the machine to carry out its programming assumes that you have that level of confidence in the machine and its capability to perform as it is intended, with minimal human intervention. This may not happen initially, but will come with time and experience with your particular system.

We also wanted to have the capability to process cleaning process qualification samples, cleaning process monitoring program samples, and perform our regular DIW analysis, all on the same test platform. The system that we chose has the widest range possible and still maintains the capability to achieve accuracies below the 100 ppb level.

Validation of the Analyzer System

Several vendors offer a "validation package." Depending upon the level of expertise within an individual company, the amount of value your company places on the time and effort it would take to replicate a comparable qualification package and the availability of resources within your company, these packages can be very valuable, despite the sometimes outrageous price that is attached to them. Since this is a relatively new technology for us, we face time and resource limitations. We chose to purchase the vendor validation package. However, we did not use all of the information made available to us in the validation package. We instead prepared a protocol that directed which sections we would be using and how each section would be used to complete our qualification effort. We attached copies of the appropriate vendor test sections and data collection sheets to our protocol and approved it for execution.

Editorial Advisory Board Reviewer's Commentary: There is a need to evaluate the TOC vendor's ability to supply a compliant and usable protocol. Part of the selection/purchase process should be an assessment of the vendor's "validation" capabilities. If the vendor understands the cGMPs and has a good track record, then their supplied protocols or validation services will probably be adequate for your needs. Many vendor protocols concentrate on validating of the functionality of their system, which should already be established, as the system is in wide distribution. The intent of validation should be to assess the compliance and reliability of the system as it is installed at the customer site.

Instituting Changes to the Current Monitoring Program

If you already have a water system monitoring program established, it will be a relatively straightforward revision of your current documentation. To swap one method of quality determination for another should be directed by your in-house Document Change Control Program. The industry has had a year to get this new program into place and possibly exercise the new procedures for a month or two. Be sure that your organization establishes a clear cut-over date that is as close to the official initiation of the newest revision of the regulation. It should, of course, follow the validation of the new analyzer system and personnel training on any change to sampling techniques and on the new instrument(s) as well.

Since Sanofi currently (at the time of this writing), does not have a crystal-clear understanding of the performance of the entire system under this new method of testing at all its points of use, and system monitoring locations, we have chosen to approach the implementation much like we did during a relatively recent system qualification following the expansion of one of the DIW distribution loops. Bioburden, pH, and resistivity will remain as we have previously established in our program. We will use the ≤500 ppb TOC as our Action Limit, but wait to establish a meaningful Alert Limit based on a time intensified system sampling plan. The entire system will be sampled for 20 consecutive workdays. From this data population we will establish our Preliminary Alert Limit. The normal monitoring program will kick in at that point, and the Environmental Monitoring Committee will review the results as part of the regular monthly environmental review schedule. At the end of the first year, the Preliminary Alert Limit will be reviewed and adjusted if necessary to more accurately reflect the actual system performance over the previous year's sampling period.

If your company does not already have a water system monitoring program established, get one started.

Editorial Advisory Board Reviewer's Commentary: Look carefully at implementation schedules. Validation and related programs using water quality monitoring might end up with remnants of the old methods in addition to the new TOC methods. That means SOPs, training, and records might exist for both methods at the same time. This would be very difficult to document and defend in a final validation report. It may also be necessary to implement the TOC program early in some evaluations to assure continuity of the program.

Summary

A reliable, consistent supply of high-purity process water is essential in the regulated health care industry. In an attempt to bring more concise definition to the quality aspects of high-purity process waters, new regulations were made official by the USP on May 15, 1998. This change makes it necessary to alter the current approach most organizations have previously employed to define the quality of the high-purity water that they produce as part of the fabrication of their final product.

A logical and systematic approach is recommended for the implementation of the changes to the new water quality monitoring system. Ensure the measurement of either conductivity or resistivity is conducted and yields results in a manner that is compatible with the guidelines that are provided by the USP or other recognized standards applicable to your particular sector of the industry.

Examine the capabilities of the various makes and models of TOC analyzers that are currently available on the market. Make sure the range of performance capabilities meets or exceeds the demands for accuracy and precision for its intended use. The effort of validating the new system can be eased by extensive communications with the vendor's Technical Service Group, or purchase the vendor's validation package, if one is available. Upon completing the validation of the new system, change your procedures to incorporate the latest change to the USPquality requirements. Don't forget to train the technical staff in any changes to their routine because of the demands of the new test methods.

Finally, no matter what standard it is that you use, it is usually just the minimum or baseline quality measurement for your process water. If your particular product has any specific water quality demands other than those outlined in the new USP regulations, those should continue to be met as well. ❑

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Disclaimer

Management Considerations in Water Purification Systems Validation

By Shahid T. Dara
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Validation is a multidisciplinary effort, especially for a complicated system like water purification. In order to accomplish a successful water system validation, it is essential that the validation manager or professional assigned to head up this project must understand the complexity of this endeavor from concept to commissioning. This article is an overview of water purification systems with a life cycle approach to its validation and highlights the importance of a validation team concept in achieving the ultimate goal, i.e., the consistent supply of purified water of desired quality.

"In 1996, 27.5% of all warning letters issued to the pharmaceutical manufacturers involved citations for water systems deficiencies."

Introduction

Water is the source of life on this planet. For the pharmaceutical industry, the importance of water is unmatched, as it is used in huge quantities in everyday operations, both in manufacturing and cleaning (see *Figure 1*). Water quality determines the ultimate quality of drug products manufactured.

Each water purification system is unique for a given manufacturing facility, and the process itself is a complex operation consisting of a series of elaborate, multistep purification processes. The design of a water system depends on the quality of water desired and is influenced by the physiochemical and microbiological characteristics of source water. (See *Figure 2* for Water Quality Designations). A water purification system is a living, breathing system, and the validation cycle never ends with the initial qualification of the system. As a matter of fact, between routine monitoring and periodic revalidation efforts, it is one of the most resource-consuming projects within a pharmaceutical manufacturing operation. However, it is critical that a water system must be validated prior to its commissioning and then be maintained in a qualified state for its life. In 1996, 27.5% of all warning letters issued to pharmaceutical manufac-

Figure 1

- Cleaning Agent:
  Universal rinsing agent for equipment, solvent for detergents/sanitizers.
- Solvent:
  Base for all aqueous liquids, injectables, suspensions, ointments.
- Granulating Agent:
  For wet granulation preparation.
- Diluent:
  For lyophilized powders, reconstitution of suspensions.

Figure 2

- Potable Drinking Water: Meets EPA specifications for drinking water (40 CFR 141).
- USP Purified Water: USP 23, 1995, pp 1637.
- USP Water-for-Injection: USP 23, 1995, pp 1635-1636,
- USP Bacteriostatic Water-for-Injection: USP 23, 1995. pp 1636.
- USP Sterile Water-for-Injection: USP 23, 1995, pp 1636-1637.
- USP Sterile Water for Inhalation: USP 23, 1995, pp 1636.
- USP Sterile Water for Irrigation: USP 23, 1995, pp 1636.

turers involved citations for water system deficiencies. It is therefore prudent, both for regulatory compliance and business profitability, to have a team of experts to manage and conduct this validation.

Management of Water Purification System Validation

If and when a pharmaceutical manufacturer decides to install a new water system or to upgrade an existing system, the validation department should be involved from the earliest possible stage to avoid undue delays caused by poor execution of any phase of this mammoth project. A team approach is the most effective way to accomplish this very complicated undertaking, with clear lines of communication and areas of responsibility and accountability defined up front for each member of the team. Basic project management assures that the task will be finished on time per organizational requirements and within budgetary limits. The validation team should be in place as soon as the project is given a go ahead and there must be a back up designated for each member of the team.

Validation Team

Who should be part of the Water System Validation Team?

Considering the technical aspects of the project, the following disciplines should be represented along with their primary areas of responsibility:

Engineering:
- Concept and design of water system
- Water system drawings per design
- Installation, operation, and performance qualification of the system
- Instrument calibration
- Preventive maintenance schedules and procedures
- Water system drawings as built

Manufacturing:
- End user of the product
- System capabilities and limitations vs. plant manufacturing needs
- Operation of the system and usage criteria, i.e., flushing before use, etc.
- Sampling of water

Quality Assurance:
- Define SOP requirements for each phase of validation
- Change control procedures
- Water sampling procedures
- Employee training requirements

Quality Control Laboratories:
- Chemical and microbiological testing
- Test methods
- Alert and action limits

Validation:
- Project supervision
- Prepare the protocols
- Coordinate all validation activities
- Collect all documents
- Manage validation change control
- Compile final reports
- Coordinate review and approval of protocols and final reports
- Commissioning of the water system

Once the water system validation team is assembled, the project should be defined in detail, with timelines established for completion and review/approval of all critical phases. Also, it should be established who will be responsible for final review and approval of the water system validation before the system is commissioned for use.

Life Cycle Approach

Water system validation is best accomplished via a life cycle approach. Once the quality of water to be produced is established, the project should be divided into the following phases:

- Concept
- System design
- Vendor/s selection
- Water system drawings
- Sampling plan
- Installation qualification (IQ)
- Operation qualification (OQ)
- Performance qualification (PQ)
- Final reports, reviews, and approvals
- Ongoing monitoring
- Revalidation

Concept:

The quality of water produced and the manufacturing needs of the plant determine the purification technology to be used. While defining the desired water quality and the manufacturing needs, one must consider current requirements, as well as any future expansion possibilities, thereby building flexibility in the system to expand if needed. Validation should have a thorough understanding of the purification technology, as it will help in preparing effective validation protocols.

> **"A team approach is the most effective way to accomplish this very complicated undertaking."**

Water Purification System Design

In designing a water purification system, the quality of the source water must be considered. Local water authorities can provide some vital information as to the historical data on source water quality as well as any seasonal variations in the water quality. Also, periodic water test reports should be obtained routinely from the local water authority to ensure the source water meets the compendial requirements for drinking water. During the design phase, the team should consider the initial cost of the system components as well as their long-term maintenance costs. The design team should consider the following when defining the design specifications:

Pretreatment of Feed Water:

This is especially true for reverse osmosis membrane systems and is also needed to account for seasonal variation in source water quality. Pretreatment is intended to minimize maintenance of the actual purification system and could include the use of dechlorination, depth filters, carbon filters, and water softeners. Each step of pretreatment should be duly documented along with operating procedures for cleaning and sanitization to comply with validation requirements.

Purification of Water:

Source water can be purified by deionization, reverse osmosis, or distillation. Each purification technique has its merits and demerits. However, the selection should be based on eventual use of the purified water and the compliance benefit/risk analysis, as there could be a substantial cost difference in switching from one purification technology to another. Generally, USP Purified Water is water obtained by deionization, reverse osmosis, or distillation, while USP Water-for-Injection is water purified by distillation or by reverse osmosis.

Deionization:

Deionizers remove solids that are ionic in nature from source water. Cation exchangers replace positively charged ions, like calcium and magnesium, with hydrogen ions. Anion exchangers replace negatively charged ions, such as phosphate and sulfate, with hydroxide ions. When used in series, a cation exchanger and an anion exchanger combine to deliver nearly pure water. Use of mixed bed deionizers, containing both cation and anion resins, generally generate the best quality water. In deioniza-

tion based water purification systems, the purified water is passed through a UV lamp and a 0.2 micron filter to reduce the microbial count. Deionization can be used as the primary purification technique when the USP Purified Water is to be produced in limited quantity and is therefore cost effective compared with reverse osmosis or distillation. However, deionization is usually the first step in the purification process and is either followed by reverse osmosis or distillation to obtain water of desired purity.

Ion exchange resins regeneration schedules can be defined by measuring the conductivity of feed water vs. conductivity of effluent. By trending these values, one can predict the regeneration cycles with reasonable accuracy.

Deionization has its limitations:

- Limited capacity based on the ion exchange resin volume and type
- Regeneration of ion exchange resin
- Hazards of handling caustic regeneration chemicals
- Potential of idle resins to harbor microbial growth
- Need for a close monitoring of automatic regenerating cycles

Reverse Osmosis:

The principle of reverse osmosis is pretty simple: Under pressure certain membranes pass water molecules while rejecting others. It is filtration under pressure and leads to separation of suspended and dissolved solids from water. Flow across the membrane is tangential, and large quantities of the feed water are rejected. To make it feasible, a very large filtration surface area is required, and that is accomplished by rolling into alternate layers of inert porous material and filtration membrane. A single pass RO filter can remove more than 95% of dissolved solids from feed water. Usually a multi-pass filtration schematic is used so that initially rejected water is refiltered. Using conductivity measurements of the feed water and the effluent, the rate of water purification can be determined, and a trending of these values can also be used to establish cleaning schedules for RO systems. When used in series, RO systems can produce very high quality water, meeting the USP Water-for-Injection monograph. However, reverse osmosis has its own limitations:

- High pressure of feed water can damage the filter membrane.
- Reverse osmosis filter membranes are not absolute and can let microbes pass through.
- Fine contaminants, like silica, can pass through these membranes.
- Most reverse osmosis filter membranes are not resistant to chlorine. Therefore, the feed water has to be dechlorinated, leading to a high bioload for the membrane to handle. This could cause microbial contamination of the filter membrane and would require periodic sanitization.
- Scale formation at the filter membrane surface is another problem which could limit the effective filtration area.

Distillation:

Distillation is the most popular method of water purification and can produce both USP Purified Water as well as USP Water-for-Injection. Feed water is boiled to make steam, leaving behind the contaminants in a liquid state. The steam is removed from the boiler and condensed into water, either using a cooling heat exchanger or compression. Distillation can purify up to 95% of feed water and the efficiency can be increased by using multiple stills. The liquid concentrate of the contaminants is removed from the still by a process referred to as "Blowdown." Distillation does reduce the endotoxins level of feed water: however, the feed water must be reasonably free of microbes and endotoxins to produce Water-for-Injection.

Initial cost of a distillation unit and attendant controls along with ongoing maintenance is a major investment and can run into hundreds of thousands of dollars. Inappropriate design or operation of a distillation unit can be very costly. If the system is idle for any reason (routine maintenance) for a period of time, the feed sections of stills become dead legs and could harbor microbes. The still must be cleaned and sanitized before restarting, otherwise a mixture of water and microbes can enter the still and contaminate the whole system.

Heat Exchangers:

If purified water is to be stored after production and has to be recirculated, then there will be a need for heat exchangers to maintain the water temperature above 80ºC – 85ºC during storage. Also, there will be a need for heat exchangers (with adequate chill water flow), to cool the hot water to ambient temperatures before it is used. For a facility working eight to ten hours a day, the system should be designed to operate in a thermal cycling mode. At the beginning of a work day, the heat exchanger with adequate flow of chill water will decrease the temperature of stored and recirculating water to 25ºC. The inlet temperature for the chill water should be about 12 – 13ºC and the outlet temperature would be about 18ºC. The flow rate of the chill water is determined by the volume of water to be cooled. At the end of a work day, the recirculating loop operating at 25ºC is heated to 80 – 85ºC, using facility maintenance steam which also maintains the temperature of water in the storage tank. All heating and cooling operations are performed and controlled by a dedicated heat transfer and control system associated with the jacketed and insulated water storage tank.

For continuous-use operations, the water in the storage tank and the recirculation loop is maintained at 80-85ºC, and it is at the point of use drops where the water is cooled down to 25ºC using chiller water.

Storage Tank:

The purified water storage tank's material of construction should be such that it does not compromise the integrity of the purified water stored inside. Preferably, it should be constructed from stainless steel and should be equipped with vent filter attachments which allow for easy replacement of the filter.

Distribution Piping:

Purified water is distributed over varying distances in a manufacturing facility. The piping could be made of stainless steel or PVDF. Both materials are inert and easy to sanitize. One should be aware of the dead legs in the piping system and should keep these to a minimum. System sanitization could be a routine activity based on the data gathered during validation and daily operation of the system.

Sanitization might also be required in response to a contamination of the system with microbes. Steam sanitization is the best way, as it will not leave any residue but could cause problems by removing the biofilm built up on the inner surface of distribution piping. Also, it may not remove all the microbes either.

A number of chemical agents have been used alone or in combination for water system sanitization. However, chemicals can have adverse reactions with stainless steel or PVDF, generating chemical impurities while removing microbes. Also, the chemical sanitizers could leave residues in the water stream which could have an adverse effect on the drug product stability, especially if it is a highly potent oxidizing agent. Hydrogen peroxide has been used successfully in varying concentrations (0.2% – 10.0%) in sanitizing water purification systems, as it is an effective biocide and degrades into water and oxygen.

Other chemicals mentioned in literature include sodium hydroxide, mineral acids, sodium hypochlorite, peracetic acid, etc. Sanitizer selection and frequency of sanitization should be established during validation of the water system.

Vendor Selection

Selecting vendors of a water system components should be based on a vendor's reputation in the pharmaceutical industry, and consideration should be given to the following:

- Prior experience in pharmaceutical industry water system design, installation, and operation
- Knowledge of pertinent regulatory requirements
- Ability to provide documentation when required
- Training capabilities
- On-site technical support

The design team should develop a standardized questionnaire for prospective vendors. Also, it should ensure that each vendor has the ability to document the work performed per validation protocols. Suppliers/vendors should be paid only when

validation certifies that all necessary services, documents, etc., have been provided and meet the validation requirements.

Water System Drawings Per Design

Once the water system design is finalized, the vendor must provide detailed drawings of the system before starting the installation. This drawing per design should be used as a blueprint to compare the actual installation of all the components to the design specifications and should be redlined whenever necessary to reflect any deviations from approved design. Once the installation is complete, a final "as built" water system drawing should be provided by the vendor and become part of the validation package as a required document.

Sampling Plan

Sampling plans should be critically evaluated before adoption in validating a water purification system. "The FDA Guide to Inspection of High Purity Water Systems" details the Agency's expectations. The initial sampling plans during OQ are meant to assess the system's ability to perform as a unit and produce water of desired quality. The samples should be taken daily (seven days a week) and analyzed for both microbial and chemical contents. If the system is equipped with heat exchangers/water chillers, the water temperature profile should also be determined at this point.

During PQ, sampling and testing can be divided into two phases. Initially, the samples should be taken seven days in a row. During this time, multiple samples might be pulled from each site each day. If the results are satisfactory, the sampling could be reduced to five days a week for the next four weeks. This will mimic the routine operational activities, when there is no activity over the weekend and holidays. The samples are again tested for chemical and microbial contents. The water temperature profile is also established during this period, measuring the water temperature distribution within the storage tank, distribution loop, and at the points of use drops.

Installation Qualification

As the design is finalized, validation personnel should start developing the qualification protocols. This will enable the engineering personnel to obtain all necessary documents from the different vendors as the components are being purchased. Also, this will help technicians to verify that the water system components are being installed per design and each component meets its specifications. If the vendor is involved in the installation of the equipment, a copy of the IQ protocol should be provided to their technical staff. This ensures that the vendors' engineers and technicians understand the validation requirements and are familiar with the documentation.

The IQ protocol should detail the following:

- System description
- Scope of qualification
- Responsibilities
- Incoming components specifications and inspection
- Installation verification
- Utilities installation
- Critical instrumentation calibration
- Software qualification, if needed
- Preventive maintenance procedures
- Documentation
- System drawings as installed
- SOPs
- Summary report and conclusions

Operational Qualification

Following successful installation of all the components, the water system should be commissioned for operation after testing each component (and the water system as a whole), assuring that it operates per manufacturers' instructions and specifications. All the controls should be operating within limits, and critical instruments should be within their calibration period. The IQ must be completed before starting the OQ.

The OQ protocol should detail the following:

- System description
- Scope of qualification

- Responsibilities
- Critical instrumentation calibration
- System cleaning/sanitization procedures and frequency
- Sampling plan
  - Daily for two weeks
- Sampling points
  - Source water
  - After each critical step in the purification process
  - Storage tank (temperature profile and water quality)
  - Circulation loop (temperature profile only)
  - At each point of use (temperature profile and water quality)
- Sampling procedures
- Testing requirements
- Testing methodologies
- Acceptance criteria
- Documentation
- SOPs
- Summary report and conclusions

Performance Qualification

Once the IQ and OQ are completed, the water system should be qualified to prove that it is capable of producing water of desired quality consistently over a period of time under varying seasonal conditions.

The OQ protocol should detail the following:

- System description
- Scope of qualification
- Responsibilities
- Critical instrumentation calibration
- Sampling plan
  - Initially one week
  - Daily for four weeks
- Sampling points
  - Source water, initially and every week thereafter
  - After each critical step in the purification process
  - Storage tank (temperature profile and water quality)
  - Recirculation loop (temperature profile only)
  - At each point of use (temperature profile and water quality)
- Sampling procedures
- Testing requirements
- Testing methodologies
- Acceptance criteria
- Documentation
- SOPs
- Summary report and conclusions

Commissioning of Water System

Following a successful campaign of IQ, OQ, and PQ, the water system can be commissioned for routine production of water of desired quality. However, all the validation protocols must be completed and the summary reports with conclusions be reviewed and approved by all the pertinent organizational units before the water is used in manufacturing.

Ongoing Monitoring:

In order to complete the validation cycle, the sampling and testing of water should continue after the water system has been qualified and commissioned to produce water of known quality. This is necessary to account for any seasonal variation in the quality of feed water.

- Sampling plan
  - Routine sampling frequency
- Sampling points
  - Source water once a month
  - For Water-for-Injection, one point of use daily and all points of use once a week

Revalidation

Water systems are periodically revalidated. However, revalidation might be called for if there is a critical change in equipment or there are persistent water quality issues. In such cases, depending on the cause, the revalidation effort might be a repeat of the PQ alone or could involve IQ/OQ also. Each case should be duly investigated and system requalification be performed per company policies. ❑

Related Articles From The *Journal of Validation Technology*

1. Elms, B., and Green, C., "Water Systems: The Basics – Part 1, Design as a Prelude to Validation," Vol. 1, No. 2, February 1995.
2. Elms, B., and Green, C., "Water Systems: The Basics – Part 2, Validation and Maintenance," Vol. 1, No.3, May 1995.
3. Collentro, W. V., "Proper Validation of a Water Purification System; An Inherently Flawed Process?" Vol. 1, No.3, May 1995.
4. Fessenden B., "A Guide to Water for the Pharmaceutical Industry: Part 1 – Basic Chemical, Physical & Dynamic Concepts," Vol. 1, No. 4, August 1995.

Suggested Reading

1. "The FDA Guide to Inspections of High Purity Water Systems Inspections," July, 1993.

The Study of the Design of Production Systems of Purified Water for the Pharmaceutical Industry

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Part I

Water used in the pharmaceutical industry, especially water used to manufacture drug products (purified water and water-for-injection) is vital to the manufacture of these products and, therefore, should be considered as a raw material that needs to comply, at a minimum, with specifications set out in Pharmacopeia.

Presently, validation is essential to ensure the reliability of any system to produce water of pharmaceutical quality. The first step to ensure the correct functioning of the system is that each instrument, each component, all the building materials, and all other considerations in the design of these systems should comply with ruling Pharmacopeias and the current Good Manufacturing Practice (cGMP).

This study examines the design of the production systems of purified water for the pharmaceutical industry in three pharmaceutical plants where a study on the design (description of functioning) is carried out for each of them, together with a report on the design.

"...validation is essential to ensure the reliability of any system to produce water of pharmaceutical quality."

General Considerations

The chosen pharmaceutical plants have been labeled Pharmaceutical Plant A, Pharmaceutical Plant B, and Pharmaceutical Plant C.

The study for each of the three plants has been separated into two distinct sections:

1. Study of the design: A description of the functioning of the system. To examine the design of each production system of Purified Water, the study has been divided into two phases:

❶ Production and storage of purified water
❷ Distribution of purified water to points of use

2. Report on design: Contains recommendations for each point of improvement* (both critical and noncritical) detected by the study in the design.

Pharmaceutical Plant A

In *Figure 1*, the fundamental stages to carry out a systematic follow up on the flow of the water have been numbered, from the moment it enters the system as feed water to the moment the purified water enters the distribution loop where the different points of use are found.

Study of the Design

Description of the functioning of the system

Production of Purified Water

Chlorination – flocculation – filtration – decalcification – adding sodium hypochlorite – carbon filter – 2 μm filtration – reverse osmosis – Osmotic water storage tank – ionic exchange – 2 μm filtration – UV lamp – 0.22 μm filtration – Purified Water storage tank.

• Water purification is carried out in two fundamental stages, a first stage of purification by means of reverse osmosis and a second stage of polishing by means of ionic exchange resins.

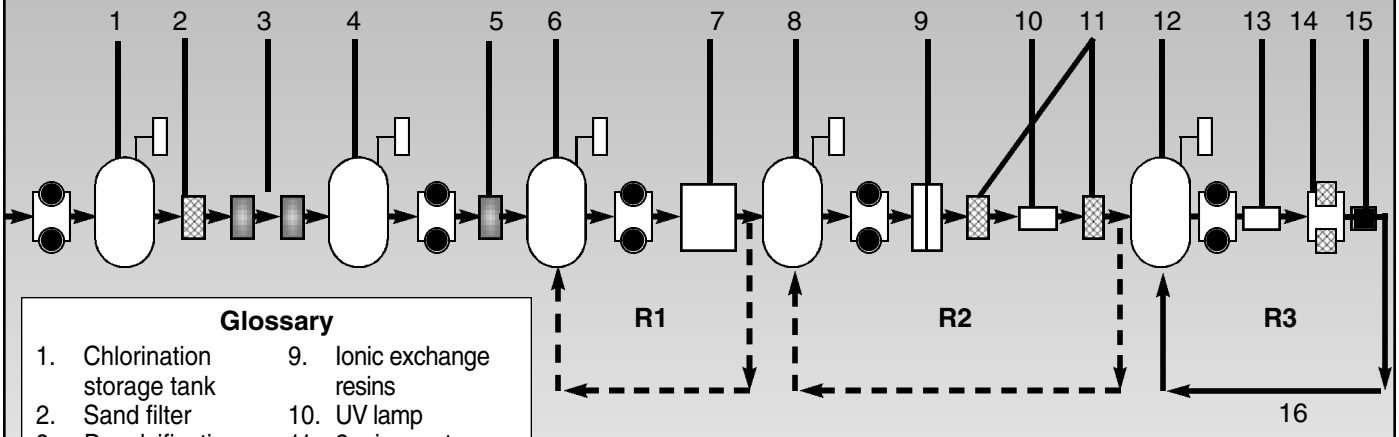
• The dechlorination of the water prior to the reverse osmosis step is carried out through the action of a carbon filter.

• Note that in the system there are two recirculations: R1 and R2. These recirculations prevent the water from remaining stagnant in critical equipment, such as reverse osmosis membranes and the ionic exchange resins, during periods when production is stopped.

R1: The R1 water recirculation refers to the recirculation from the exit of reverse osmosis to the intermediate storage tank. This recirculation is put into operation if the osmotic water tank is full, which occurs when there is no consumption of purified water, i.e., during the night, at weekends, and holiday periods. At the same time, this recirculation is also put into operation in case the conduc-

Figure 1

Production System for Purified Water Design Diagram: Pharmaceutical Plant A



Glossary

1. Chlorination storage tank
2. Sand filter
3. Decalcification equipment
4. Intermediate storage tank (adding of sodium hipochloride)
5. Carbon filter
6. Intermediate storage tank
7. Reverse Osmosis
8. Osmotic water storage tanks
9. Ionic exchange resins
10. UV lamp
11. 2 micrometer and 0,22 micrometer filters
12. Purified storage tank
13. UV lamp
14. 0,22 micrometer filters
15. Heat exchanger
16. Distribution ring to points of use

R1: Recirculation 1
R2: Recirculation 2
R3: Recirculation 3 (Distribution loop)

tivity values of the water when leaving the reverse osmosis are higher than those of the established limit.

R2: R2 water recirculation refers to the access to the purified water tank to the osmotic water storage tank. This recirculation is put into operation when the purified water tank is full, which occurs when there is no consumption of purified water.

• With the aim to avoid excessive loss of water due to the rejection of the reverse osmosis, this goes into operation cyclically for 15 minutes every 120 minutes, recirculating through the R1 recirculation to the storage tank.

Storage and Distribution of Purified Water to Points of Use

Purified Water storage tank – UV lamp – 0.22 μm filtration – heat exchanger – distribution loop – Purified Water storage tank

The microbiological quality of both the purified water from the storage tank and that of the water flowing through the distribution loop is assured by the UV lamp and the two high efficiency filters of 0.22 μm installed in parallel before the water enters into the distribution loop where, except during holiday periods, the water is constantly recirculating. After any holiday period, sterilization with clean steam is carried out at 121ºC for one hour. In addition, the loop is cleaned for sanitary purposes every 15 days with purified water heated to 80 – 85ºC for 90 minutes.

Report on the Design of Plant "A" Conclusions

Having studied the detailed description of the functioning of the system, some points of improvement are proposed, and a series of recommendations for each are set down.

Recommendations

1. Carbon filter: Although carbon filters are a technological option for water dechlorination, they invite a high risk of microbiological contamination in the system. It is then advisable to eliminate such filters and obtain dechlorinated water by means of a system of bisulfite dosifications together with the corresponding controls. It is advisable in the actual situation to:

a) Strictly control cleaning and sanitization procedures, which should occur at least once a week in the beginning, then using experience to indicate the necessary frequency to ensure that microbiological levels are within limits.
b) Control water leaving the carbon filter twice a week to establish the microbiological level.

2. Stainless steel tanks: These cannot be sterilized with clean steam, so it is recommended that they be replaced with storage tanks that can be. Considering the possibility of the intermediate tank, an alternative solution is to install a UV lamp at the entrance to the reverse osmosis. This would achieve a much lower microbiological contamination and provide greater safety for the system.

3. Return of the distribution loop to the purified water storage tank: Installing a UV lamp will avoid accidental contamination which might arise at any points of use. In this way, the correct microbiological quality of the water entering the purified water tank coming from the return of the distribution loop could be ensured.

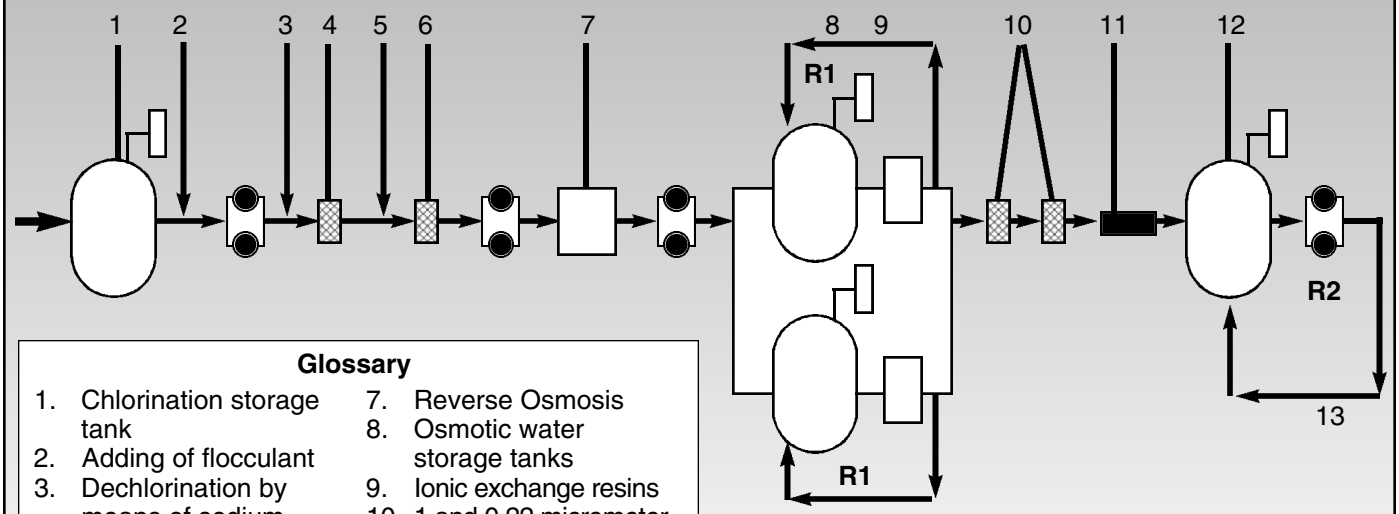
4. The 0.22 μm filters: Can be eliminated, which would represent an economy, as the UV lamps are considered to be enough to assure microbiological quality. Keep in mind that although applying the high efficiency filters is a technologically correct option to ensure microbiological quality of the water in the last stages, these filters represent a high-maintenance cost (sterilizing and regular changing). The use of ultraviolet technology along the pretreatment phase and at distribution is considered an adequate technology, as it maintains the microbiological quality level at lower maintenance costs.

Pharmaceutical Plant B

The study carried out is similar to that for Plant A. See *Figure 2*.

Figure 2

Production System for Purified Water Design Diagram: Pharmaceutical Plant B



Glossary

1. Chlorination storage tank
2. Adding of flocculant
3. Dechlorination by means of sodium bisulfate
4. 10 micrometer filter
5. Adding of chelating agent
6. 5 micrometer filter
7. Reverse Osmosis
8. Osmotic water storage tanks
9. Ionic exchange resins
10. 1 and 0.22 micrometer filters
11. Heat exchanger
12. Purified storage tank
13. Distribution loop to points of use

R1: Recirculation 1
R2: Recirculation 2 (Distribution loops)

Study of the Design:
Description of the functioning of the system

Production of Purified Water

Sand filter – decalcification equipment – chlorination – Flocculation – adding of bisulfite – 10 μm filtration – adding of abductor – 5 μm filtration – reverse osmosis – intermediate storage tanks – ionic exchange resins – 1 μm filtration – 0.22 μm filtration – Heat exchanger – Purified Water storage tank.

• As in Plant A, purification of water is carried in two stages, first, by a reverse osmosis unit and second, refining by means of ionic exchange mixed bed resins.

• Water dechlorination prior to reverse osmosis is carried out by adding sodium bisulfite. At the same time, note the addition of the chelating agent, which avoids the precipitation of carbonates and calcium sulphate on the membranes of reverse osmosis due to a possible excess of sodium bisulfate.

• There is a double recirculation, R1, which includes the two storage tanks of osmotic water and the two installations for demineralizing. In this way, possible microbiological contamination in the inner layers of resin is diminished when the equipment does not produce water, whether there is no need for consumption or simply because it is in reserve.

• The microbiological quality of the water that goes into the purified water tank and comes from the ionic exchange resins is ensured first by a 0.22 μm filter and later by the heat exchanger. The water is stored at 80ºC in the heat-resistant storage tank, which is made of AISI 316 L stainless steel.

Storage and Distribution of Purified Water to Points of Use

Purified Water storage tank – distribution loop – Purified Water storage tank

• It should be noted that the microbiological quality of both the water in the purified water tank and that of the water flowing through the distribution loop in this plant is assured by increasing the temperature of the water carried out by the heat exchanger to 80ºC. Starting from the stainless steel storage tank the water is pumped to the entire plant, flowing at 80ºC in a closed

loop so as to ensure that the water is sterile in practice. To maintain the temperature, the storage tank for the purified water and the distribution loop are insulated.

As the flow of water is thermostatically controlled at 80ºC through the loop, no stoppages in the recirculation of the distribution loop are forecasted for its sanitization as supported by the microbiological data of this plant. In practice, the distribution loop is sterilized by means of clean steam at 121ºC for an hour after holiday periods.

Report on the Design of Plant "B" Conclusions

Having carried out and studied the detailed description of the system according to the design diagrams, the design can be considered to be correct.

In this design, the microbiological quality of the water in the distribution loop and the purified water storage tank is assured by heating the water to 80ºC, in contrast to the design of Plant A, where quality was ensured by the combined use of sterilizing filters and ultraviolet technology.

Keep in mind that the FDA(Guideline 1993) considers that heat, as an assurance of microbiological quality in the distribution loop, can turn out to be more expensive than other systems. At the same time, it states that maintenance and control costs, together with the potential problems that other systems might incur, could be higher than the cost of power saved.

Some points that could be improved upon have been detected. A series of recommendations are set out for each of them.

Recommendations

1. Dechlorination by means of bisulfite: Dechlorination using bisulfite after the flocculation and prior to the entry of the water into the modules of reverse osmosis could entail a risk of microbiological contamination by use, as it is considered that the dechlorination is carried out at a stage excessively distant from the reverse osmosis. It is advisable for the chlorination to be carried out prior to the entry of the water into the reverse osmosis or, otherwise, for a UV lamp to be installed at the point where the water enters into the osmosis module in such a way that any possibility of microbiological contamination of the water entering the osmosis module is avoided.

2. Regarding the R1 recirculation: Recirculation of water through the reverse osmosis module during periods when production is stopped is not contemplated. This implies the risk that the membranes in such modules could be microbiologically contaminated. Install two UV lamps-one at the entrance of the reverse osmosis modules and one at the exit-to ensure the microbiological quality of the water entering and leaving.

3. Section of the pipe in which water could remain stagnant while the R1 is functioning: If the R1 recirculation is started up, there is a section of pipe between the beginning of said recirculation (after the ionic exchange resins module) and the purified water storage tank where water could remain stagnant. One possible solution calls for not starting the water recirculation exactly as it has been designed (immediately after the exit of the ionic exchange resins module), but at the point where the water enters the purified water tank. In this way, the dead leg can be avoided.

4. 0.22 micrometer filter at the entrance to the purified water storage tank: Its elimination is recommended. Despite being an option to ensure the final microbiological quality of the water coming into the tank of purified water, the thermostatic control of the water by means of the heat exchanger is considered to be sufficient assurance. It should be kept in mind that the water at the entrance to the purified water storage tank must comply with the microbiological limits of Pharmacopoeia.

Pharmaceutical Plant C (*Figure 3*)

Study of the Design:

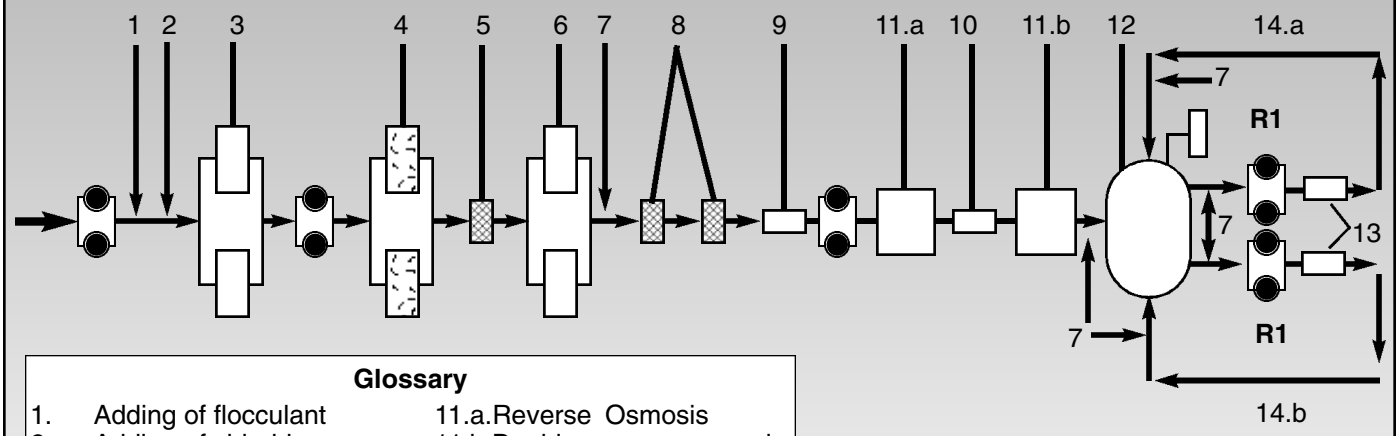
Description of the functioning of the system

Production of Purified Water

Flocculation – chlorination – filtration – carbon filters – 5 μm filtration – decalcification – ozonation – 5 μm and 1 μm filtration – UV lamp – 1ST reverse osmosis – UV lamp – 2ND reverse osmosis – ozonation – Purified Water storage tank.

Figure 3

Production System for Purified Water Design Diagram: Pharmaceutical Plant C



Glossary

1. Adding of flocculant
2. Adding of chloride
3. Silex – anthracite filter
4. Carbon filters
5. 5 micrometer filter
6. Decalcification equipment
7. Ozonation
8. 5 and 1 micrometer filters
9. UV lamp
10. UV lamp
11.a. Reverse Osmosis
11.b. Double reverse osmosis
12. Purified water storage tank
13. UV lamps
14.a. Distribution loop 1: Production
14.b. Distribution loop 2: Laboratory

R1: Recirculation 1: Distribution loops

• In this plant, water is also purified in two stages, but differently from the other plants and, because of the low conductivity of feed water, it is carried out through double reverse osmosis.

• Dechlorination of the water is carried out using two carbon filters in a parallel installation.

• Note that from the moment the decalcified water is obtained, its microbiological quality is ensured by the combined treatment of ozone (bactericidal and oxidizing agent) and of ultraviolet technology.

• Throughout the system, the water is ozonated several times, specifically at the entry points to the purified water storage tank, at the entry point coming from the production plant, and in all the returns in the two distribution loops. Water is also ozonated when it leaves the tank of purified water before the water enters each of the two loops, just prior to the last treatment with ultraviolet lamps.

Keep in mind that the use of ozone as a bactericidal agent is far more convenient than treatment with chloride; the effect of the ozone is not influenced by the pH in the medium. On the other hand, it does not leave residual compounds, add odor or flavor, nor does it attack the membranes in the ionic exchange nor those in the osmosis stage. In this sense there should be no concern regarding the elimination of ozone after treating the water. However, it does have a drawback when compared to chloride: Its effect is not as lasting, which implies that the water should be treated later with chloride at a smaller dose (as a result of the prior treatment with ozone) or, as in this case, repeat treatment along the entire system to ensure the bacteriological quality of water thus treated. Nevertheless, it is well known that UV wavelengths employed in water treatment are 254 nm and 185 nm; 254 nm UV light is employed in disinfection and ozone destruction applications.

Storage and Distribution of Purified Water to Points of Use

Purified Water storage tank – ozonation – UV lamp – distribution loop – ozonation – Purified Water storage tank

The design shows two independent distribution loops from a sole tank of purified water. The micro-

biological quality of the water in the purified water storage tank and the water flowing through each of the two loops is ensured by the joint action of ozonation and UV lamps. At the same time, in each of the returns of the two loops and before the water enters the tank of purified water, the water is again ozonated. A flow of ozone also goes to the tank for its sterilization. After holiday periods, sterilization of the two distribution loops is carried out by means of clean steam at 121ºC for one hour.

Report on the Design of Plant "C" Conclusion

After studying the design of Pharmaceutical Plant C, it can be said that it is correct to achieve water of microbiological and chemical quality as set out in the norms for purified water to be used in the pharmaceutical industry.

Note that there are two differences between the design of the Pharmaceutical Plant C and that of the Pharmaceutical Plants A and B.

The first difference is that once the water has been decalcified, ozone is used together with ultraviolet technology to assure microbiological quality. The other difference lies in the double-sequenced reverse osmosis treatment, which enables correct conductivity of the water. The high quality level of the water obtained by double osmosis makes the ionic exchange resins in the system unnecessary, thus avoiding the drawbacks they represent in the regeneration of same.

Keep in mind that the application of double-reverse osmosis is recommended only for water with low conductivity (under 600 (s/cm), as an increase of concentration will overcome the retention capacity of the reverse-osmosis, thus causing the water leaving the osmosis modules to have a conductivity over the limits.

Should the water have a high conductivity (600–1500 (s/cm), employ ionic exchange resins or electrodeionization equipment (CDI), as these methods have a greater power of retention than that of reverse osmosis.

There are several points where improvements can be made.

Recommendations

1. Recirculation between the purified water storage tank and the modules of reverse osmosis: There is no recirculation of water between the purified water tank and the modules of reverse osmosis in case of stoppage, whether caused by the tank of purified water being full or by stoppages at weekends or holiday periods. In both cases, the water will remain stagnant in the pipes and equipment from the entry of feed water to the modules of reverse osmosis (inclusive), with all the dangers of microbiological contamination that this entails.

A system for water recirculation should be placed between the tank of purified water and the two modules of reverse osmosis, like the one in Pharmaceutical Plant A.

2. Carbon filters: To avoid the problems of microbiological contamination and maintenance these systems require, it is preferable to remove them and obtain dechlorinated water by means of a system of bisulfite dosage with its corresponding controls. It is advisable to:

a) Strictly record the cleaning and sanitization processes, which should be carried out at least once a week. Experience will suggest the most adequate frequency to ensure that the microbiological levels are within limits.
b) Check the microbiological level of the water twice a week at the point it leaves the carbon filter.

3. Ozonation: Bear in mind that, in this plant, the ozone and UV treatments are used consecutively. Although apparently this is contradictory to previous statements; as a general rule, a UV dosage of 90,000 (W-s/cm2 is required to completely destroy 1 ppm (1 mg/l) of residual ozone.

The bactericidal treatment of water by using ozone is a technologically correct option, but it is far too expensive. Therefore, it is recommended to replace this treatment with one less expensive, such as ultraviolet lamps, as these represent much lower maintenance costs.

Points of improvement are understood to be those points where the final quality of the product as well as the productivity of the process might be affected. These points of improvement are divided into critical and noncritical points.

Critical points are those which affect or might

affect the quality of the final product and the optimization of which ensure the final quality and consequently allow for greater productivity.

Noncritical points are those which do not affect the final quality but the optimization of which implies an increase of the productivity of the process and the decrease in costs this implies.

Part II – Optimizing a Design

The design of the production systems for purified water in three European pharmaceutical plants was covered in the first part of this study. This second part continues with the study, from a theoretical-experimental standpoint, of a production design for purified water, not only optimized from the point of view of obtaining better chemical and microbiological quality water, but achieving the most economical and simplified production system possible.

Introduction

Designing a system depends on different factors, such as the quality of the feed water or the different methods to treat or obtain the water to be introduced into the system. At the same time, it depends on the forecasted consumption of water in the pharmaceutical plant, which in turn, depends on the pharmaceutical formulations to be prepared and the plant's production capacity.

The goal is a design to produce purified water in which all the factors that affect the quality of the water have been taken into account, including overall cost; and keeping maintenance costs as low as possible.

This study includes: the study of the design (diagram and description of functioning); chemical and microbiological specifications in accordance with the European Pharmacopoeia (1997 Edition) and the USP 23; critical sampling points; a report on the design qualification; and, lastly, a recommended sampling schedule carried out to validate the system (PQ: Performance Qualification).

Chemical and Microbiological Specifications of Purified Water, According to European Pharmacopoeia (1997) and USP 23:

The European Pharmacopoeia (1997) and the USP 23 relate those chemical and microbiological characteristics that water must possess to be within purified water specifications. *Figure 4* compares the specifications of the European Pharmacopoeia with those of the USP 23.

It must be pointed out that with the publication of the fifth supplement of USP 23 on November 1996, some chemical determinations were revised. In this way, the determination of the salts and the oxidizable substances were eliminated and two new determinations introduced:

a. Total Organic Carbon (TOC)
b. Conductivity

Figure 4

Purified Water: Comparison of the Determinations and Their Specifications, Between European Pharmacopoeia (1997) and USP 23

Determinations	European pH 1997	USP 23
pH	5,0-7,0	_____
Chloride (mg/l)	Nc(*)	_____
Sulfate (mg/l)	Nc	_____
Ammonia (ppm)	0,2	_____
Calcium (mg/l)	Nc	_____
Heavy metals (ppm)	0,01	_____
Oxidizable substances	Nc	_____
Total Solids (%)	0,001	_____
Conductivity, µs/cm (a 25°c)	_____	1,3
TOC (ppb)	_____	< 500
Total aerobic count (CFU/ml)	10^2	10^2(**)

(*) Nc: Any physical or chemical change is produced by the reaction specified in European Ph. (1997)

(**) Defined in USP 23 as action limit

Likewise, the publication of the eighth supplement of USP 23 in 1998 eliminated the pH determination. Therefore, according to the eighth supplement, the chemical determinations required at present is:

Total Organic Carbon (< 500 ppb) Conductivity (< 1,3 ~s/cm at T=25ºC).

The European Pharmacopoeia still requires the determination of salts, oxidizable substances, and pH.

Microbiological specifications for purified water determined by the European Pharmacopoeia and the USP 23 are very similar. The only difference between them is that the USP 23 establishes two kinds of limits-alert and action limits-and the European Pharmacopoeia establishes only one, which coincides with the USP 23 action limit.

Study of the Design: Diagram and description of the functioning of the system

Figures 5, 6, and *7* show the design of each system.

Description of the Functioning

Two clearly distinct phases were set:

Phase 1: Production of purified water
Phase 2: Storage and distribution of purified water to points of use

Phase 1: Production of Purified Water (see *Figure 5*).

Production of Osmotic Water

Chlorination – flocculation – filtration – decalcification – dechlorination (by bisulfite) – 5 rim filtration – W lamp – reverse osmosis.

Feed water (drinking water or from the well) is submitted to chlorination in tank. From this tank, water is driven along the circuit by two alternative pumps.

Figure 5

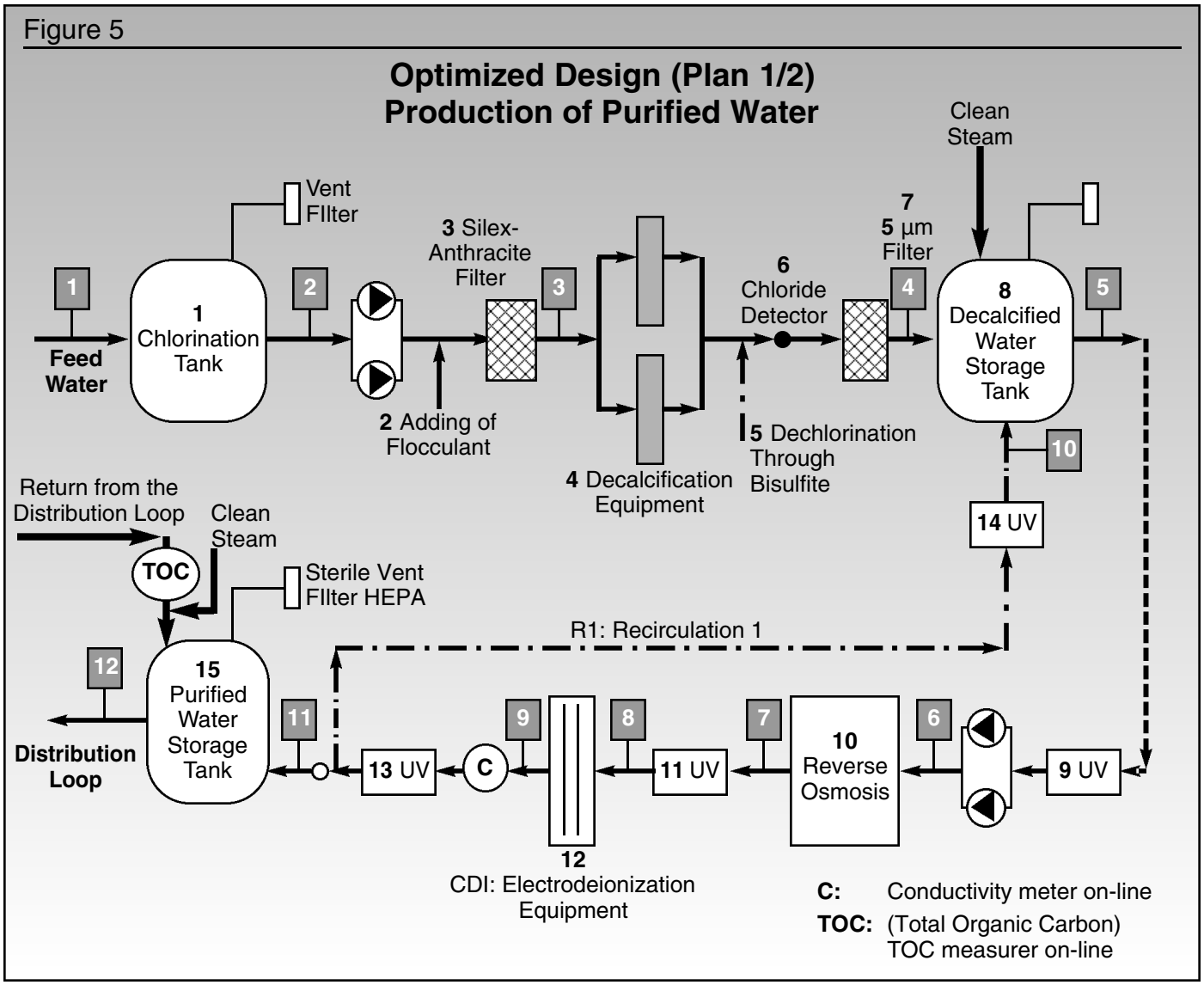
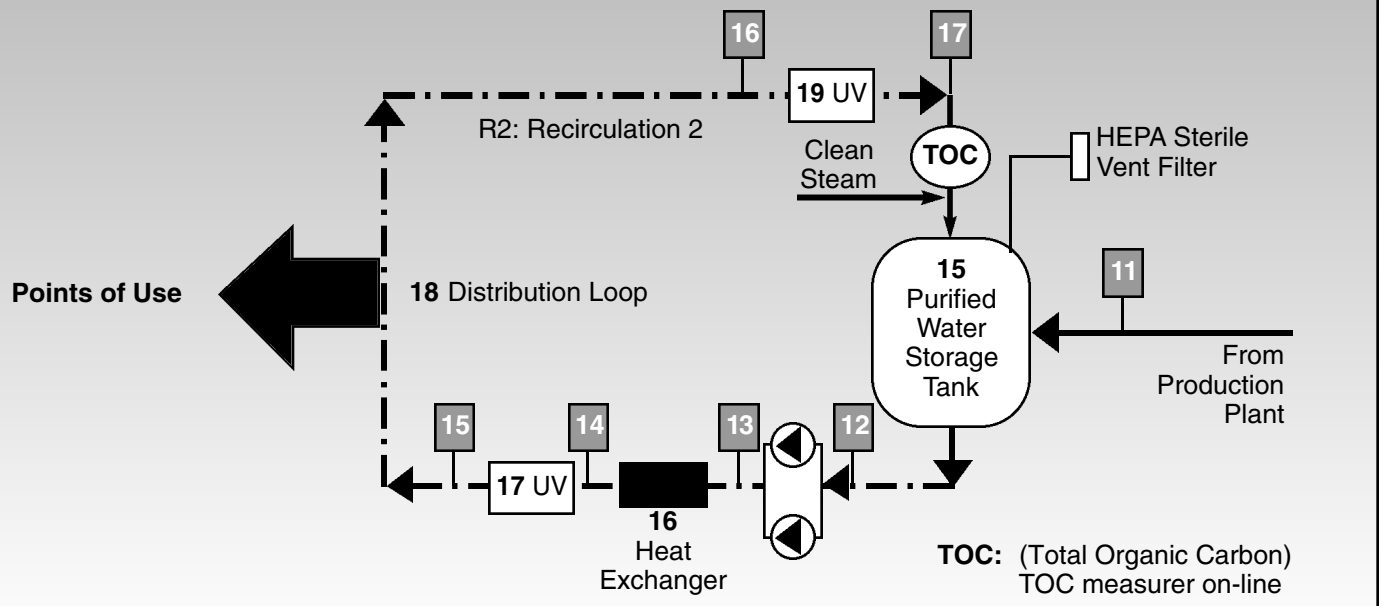


Figure 6



When leaving the tank, the flocculant is added to cause a flocculation of solid matter, easing its elimination through filtration by silex-anthracite, the function of which is to retain suspended solids.

The water, once filtered, goes through decalcification equipment, which retains calcium and magnesium in the water. The equipment is made up of a double cationic resin in sodium cycle, with the aim of carrying out an automatic regeneration of resins, i.e., when one of these goes into a regeneration period, the other column starts functioning. This means that it is not necessary to stop the production of purified water to allow for the regeneration of these resins.

Once the water has gone through the decalcification equipment and just before it enters the decalcified water storage tank, dechlorination of the water takes place by injecting bisulfite into the system, avoiding the chloride attacking the membranes of the reverse osmosis.

As chloride, even at low concentrations, could damage the membranes of the reverse osmosis module, there is a chloride detector after the dechlorination module and just before the entry of water into the decalcified water storage tank. This ensures that the process is stopped should there be a high level of chloride in the water and thus preventing it from entering the tank.

Prior to the water entering the decalcified water tank, it flows through a 5 μm filter to retain particles which might break away from the decalcification equipment.

The water enters the decalcified water storage tank, which is sterilized by clean steam.

After the water leaves the decalcified water tank and prior to it flowing into the reverse osmosis, the water flows through an ultraviolet lamp to ensure its microbiological quality before entering the reverse osmosis modules.

Water is driven by two autonomous high-pressure sanitary pumps (15/20 atmospheres) into the polyamide membranes of the reverse osmosis modules to carry out the first stage of deionization, eliminating 95 – 97% of the salts in the water, thus allowing the desired quality to be attained in an economical way.

Purification of Osmotic Water Into Purified Water

Reverse osmosis – W lamp – electrodeionization (CDI) – Wlamp – Purified Water storage tank.

Once it has gone through the reverse osmosis, the water passes the ultraviolet lamp, ensuring its micro-

biological quality before it enters the electrodeionization equipment (CDI) This eliminates salts which may remain in the water after going through the reverse osmosis modules. It should be noted that there is a conductivity meter installed on-line at the exit of the CDI equipment which stops the production of purified water should the specified values of conductivity be surpassed as specified by the USP 23 (1 – 3 μs/cm at T=25ºC).

Once it has left the electrodeionization equipment, the water flows through an ultraviolet lamp to ensure its microbiological quality before it enters the purified water tank.

Phase 2: Storage and Distribution of Purified Water to Points of Use
(See *Figures 6* and *7*)

Purified Water storage tank – Heat exchanger – W lamp – distribution loop – UV lamp – Purified Water storage tank

The water leaves the purified water storage tank and passes through a heat exchanger before it reaches the points of use in the distribution loop. The heat exchanger sanitizes the loop. Later, the water is driven by two independent pumps to a UV unit and, finally, to the distribution loop.

In the return of the distribution loop to the purified water tank and before it enters the tank, the water is again treated by a UV unit to ensure its microbiological quality before arriving at the storage tank. Before the water enters the purified water tank, there is an on-line TOC (Total Organic Carbon) measurer that allows control of the level of organic substances present in the purified water.

Another possibility to ensure the microbiological quality of the purified water to points of use consists of changing the ultraviolet treatment units by water heating to 80ºC by means of a heat exchanger.

Keep in mind that, in this sense, the FDA (Guideline 1993) considers that although the use of heat could turn out to be more expensive than other systems, it does lower control and maintenance costs and reduces potential problems in the production system for purified water.

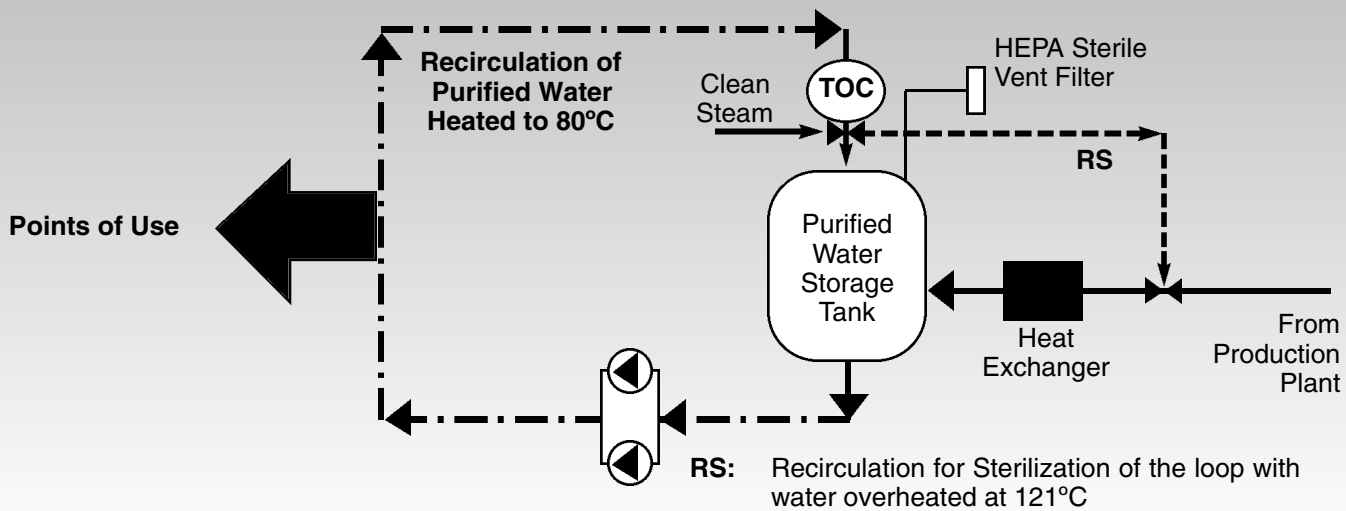
Recirculation

This design in *Figure 8* shows the recirculations which ensure the quality of the water in case of stoppage in the production of purified water.

R1 recirculation: R1 recirculation starts after the ultraviolet lamp and before the purified water storage tank (and creates a closed circuit.)

Figure 7

Optimized Design (Plan 2/2) Storage and Distribution of Purified Water to Points of Use – Heated Water to 80ºC



The installation of the ultraviolet lamp. Located in the recirculation circuit at the entry to the storage tank, it ensures the microbiological quality of the water entering the tank.

Rl recirculation functions during periods of non-production, i.e., when the purified water tank is full, during holiday periods, and during stoppages for sanitization of the distribution loop

The recirculation is continuous to avoid the risk of the contamination of the water when there is no production. So, when there is no demand for purified water, the water does not remain stagnant in the membranes of the reverse osmosis modules and in the resins of electrodeionization.

Another way to avoid water remaining stagnant in the membranes of the reverse osmosis module and the resins in the electrodeionization equipment during periods of production stoppage is to have the reverse osmosis module function cyclically for short periods of time. For example, reverse osmosis would start to function every two hours and do so for 10 minutes. In this way, there could be power and water saving as a result of the losses caused by the recoils in the reverse osmosis and electrodeionization equipment.

It should also be noted that the functioning of the R1 recirculation decreases the water level in the tank. When the tank reaches its minimum level, it causes the system to start, filling the tank till it reaches its maximum level.

It should be pointed out that some industrial plants that utilize recoils coming from the reverse osmosis module and electrodeionization (CDI), collects and recycles them. In fact, this practice is presently being studied by the pharmaceutical industry for application in those cases where there is a water shortage or in which the cost of water is very high.

R2 recirculation: Recirculation in the distribution loop. The water is constantly recirculating within the distribution loop, from the points of use to the purified water storage tank. Stoppage of recirculation in this distribution loop is only contemplated during holiday periods and for sanitization purposes. Before starting the recirculation after stoppages in the system after holiday periods, the distribution loop should be sterilized by clean steam at 121ºC for 60 minutes. Sanitization of the distribution loop should be carried out once a month by means of purified water at 80ºC for 120 minutes using the heat exchanger.

The data collected during routine use will con-

Figure 8

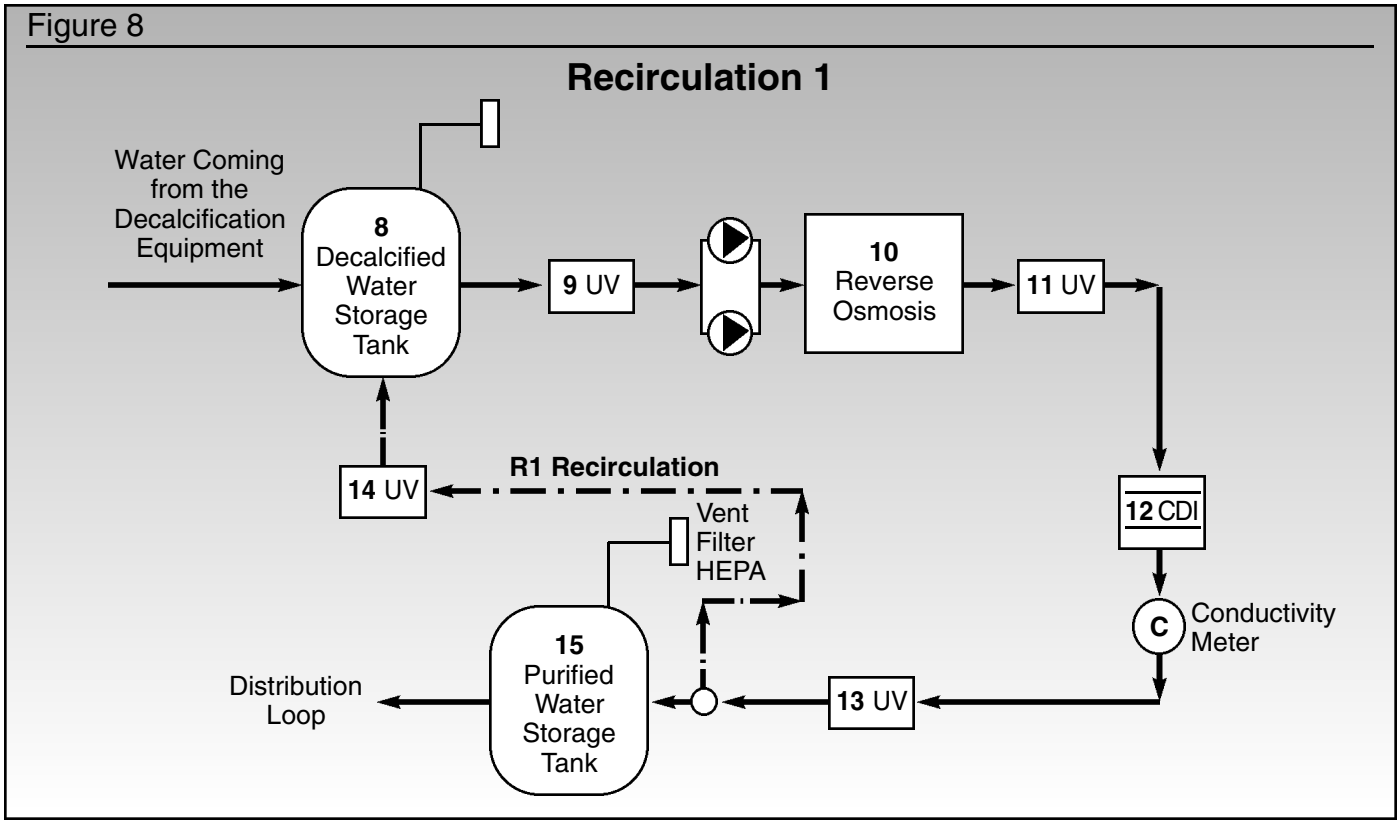


Figure 9

Index to Optimized Design Diagram

Reference Number on Diagram	Description
1	Tank: Chlorination
2	Flocculation: Electrolyte dosifying valve
3	Silex / Anthracite filter
4	Decalcification equipment
5	Dechlorination: Bisulfite dosifying valve
6	Chloride detector
7	5 µm filter
8	Decalcified water storage tank
9	Ultraviolet lamp
10	Reverse Osmosis
11	Ultraviolet lamp
12	Electrodeionization equipment (CDI)
13	Ultraviolet lamp
14	Ultraviolet lamp
15	Purified Water storage tank
16	Heat exchanger
17	Ultraviolet lamp
18	Distribution loop to points of use
19	Ultraviolet lamp

Key Symbols

R1: Recirculation 1 (Stages: 13-14-8-9-10-11-12-13)

R2: Recirculation 2 Distribution loop

Sanitary pump

Sampling point

firm if the frequency of sanitization can be decreased.

Should the microbiological treatment chosen for the water distribution be that of heating the water to 80ºC, there is no need for stoppages in recirculation in the loop for sanitization, as water circulating at 80ºC is a sanitization by itself.

Another possibility is to sterilize the loop with water heated to 121ºC for 60 minutes. Note in Plan 2/2 (see *Figure 7*) that to reach to sterilization of the distribution loop, in this design exists a recirculation (RS) which allow the pass of the Purified Water from the distribution loop through the heat exchanger to overheat it.

Figure 10

Specifications

Microbiological Specifications for Purified Water

Determinations	Limit
Total Aerobic Count (at 32ºC)	10-20 UFC/ml(*)
E. coli	No traces in 100 ml
Ps. aeruginosa	No traces in 100 ml

Chemical Specifications for Purified Water

Determinations	Limit
Aspect	Transparent
Color	Colorless
Odor	Odorless
TOC(**)	350-500(*) ppb
Conductivity(**)	0.5-1.3(**) µs/cm at T=25ºC

* *Limits of alert/limits of action: Surpassing the alert limit shows that the normal conditions of the process have undergone some change. It is a warning but does not require the corrective measures to lead the process back to its normal conditions.*

** *According to the fifth supplement of the USP 23, determining the conductivity replaces the determination of the different salts, and the determination of oxidizable substances. Determination of the pH is also eliminated according to the eighth supplement.*

Report on the Qualification of the Design

The design has been conceived to attain purified water in accordance with the specifications of the European Pharmacopoeia and the USP 23, together with the recommendations of the FDA ("Guide to inspections of high purity water systems," July 1993).

To carry out this optimized design, the following factors have been taken into account: quality of purified water obtained; reduction of possible incidences and maintenance costs to a minimum; factors which could be engulfed in a fundamental criterion: Quality Production.

Optimization of this design presents a series of advantages, which are detailed as follows:

1. Water dechlorination by bisulfite avoids using carbon filters for water dechlorination, thus avoiding the risk of microbiological contamination that the use of such filters entails. At the same time, it represents less expensive maintenance of the system, as

carbon filters need a strict and continuous maintenance program.

2. Using electrodeionization equipment (CDI) to replace the ionic exchange resins presents economic, safety, and environmental advantages, as electrodeionization avoids the use of the chemical solutions employed to regenerate the resins of ionic exchange.

3. The combined use of reverse osmosis and electrodeionization technology fully ensures the chemical and microbiological quality of purified water obtained in an operative and inexpensive way.

4. The use of ultraviolet lamps as disinfectant along the system assures the microbiological quality of the water at all times. In addition, this method creates an advantage over the use of high-efficiency filters for this purpose when it comes to maintenance, cleaning, and sanitization. High-efficiency filters have to be sterilized periodically to avoid possible microbiological contamination; therefore their maintenance makes the production of purified water more expensive.

5. Regarding the recirculations in the system:

The general recirculation R1, which includes reverse osmosis and the electrodeionization equipment, helps ensure that, should there be a stoppage, the possibility of problems as a result of microbiological contamination are reduced to a minimum in the osmosis membranes and electrodeionization resins, as the water is recirculating through this equipment.

Constant recirculation of the water in R2 prevents water from becoming stagnant in the distribution loop, avoiding the possible risk of microbiological contamination.

6. Chlorine is eliminated before the water enters the tank of decalcified water because of R1 recirculation. In this way, when recirculation is started after a stoppage of the system, there is no need to dechlorinate constantly.

7. The heat exchanger has two functions: periodical sanitizations and regulating the water temperature (not higher than 22ºC).

8. Note the on-line control of the conductivity of the water when it leaves the electrodeionization equipment. If the conductivity is over the limit set by the USP 23, it stops the system.

Figure 11

Microbiological Critical Points 1, 4, 5, 6, 7, 8, 9, 10, 11, 12, 15, 16, 17 and Points of Use

Point	Situation	Determinations and Specifications
1	Entry of feed water into system	Total aerobic at 32ºC (<200 CFU/ml) and no traces of total fecal colifoms in 100 ml
4	Entry to decalcified water storage tank (8)	Total aerobic 50-100 CFU/ml. No traces in 100 ml of E. coli and Ps. aeruginosa
5	Exit of decalcified water storage tank (8)	
6	Entry to reverse osmosis	
7	Exit from reverse osmosis	
8	Entry into the electrodeionization equipment (CDI)	
9	Exit from electrodeionization equipment	
10	Entry into tank (8) from recirculation R1	
11	Entry into purified water storage tank (15)	Total aerobic 10-20 CFU/ml. No traces in 100 ml of E. coli and Ps. aeruginosa
12	Exit from purified water tank (15), prior to UV lamp (17)	
15	Entry into distribution loop, after UV lamp (17)	
16	Return of distribution loop, prior to UV lamp (19)	
17	Return to purified water tank (15), after UV lamp (19)	

Note: The lower limit is the alert limit and the higher one is the action limit.

Figure 12

Chemical Critical Points 1, 4, 7, 11, 15, and 17

Point	Situation	Determinations and Specifications
1	Entry of feed water into system	All controls: Drinking water
4	Entry to decalcified water storage tank (8)	Total chloride (0.0 ppm)
7	Exit from reverse osmosis	Conductivity < 150 µs/cm
11	Entry into purified water storage tank (15)	All those determinations for Purified Water
15	Entry into distribution loop, after UV lamp (17)	
17	Return to purified water tank (15), after UV lamp (19)	

Figure 13

Weekly Sampling Criterion (Microbiological)

Points in the System	Total Points	Monday	Tuesday	Wednesday	Thursday	Friday	Total Points Sampled
A. Pre-Treatment	11	2	2	2	2	3	11
B. Points in Loop:							
B.1 Control Points	6	1	1	1	1	2	6
B.2 Points of Use	40	8	8	8	8	8	40

In such a way that:

- Every week all the pre-treatment points and all points in the distribution ring are sampled.
- At the end of the 4 week's validation period, four samples from each point will have been taken

9. An on-line TOC measuring apparatus is placed in the return of the distribution loop, before the entry of water into the purified water storage tank. It ensures that the organic substances in the water do not exceed the specifications.

10. R1 recirculation function:. It is convenient and economical to program a 10-minute recirculation every two hours at weekend stoppages instead of having the water circulating constantly. This would recoil the minimum amount of water caused by the functioning of the reverse osmosis module and in the electrodeionization equipment.

Recommended Sampling Plan for the Validation

- Introduction
- Sampling points
- Microbiological sampling plan and specifications
- Chemical sampling plan and specifications

Introduction

The FDA, in its 1993 Guideline, recommends that the validation of the system (PQ) is carried out in three phases. In the first and second, samples are obtained every day, for two/four weeks at each pretreatment point and at the distribution loop. The third phase consists of compiling the data attained from the routinary control plan over one year.

Because of the great number of points of use and pretreatment points (before the distribution loop) found in pharmaceutical plants, it is very difficult to comply with this FDA recommendation. Therefore, develop a sampling plan which does not totally correspond with this recommendation but which is considered to be enough to prove that the system operates in accordance with the established standard operating procedures (SOPs).

Sampling Points

The sampling points in the system are divided into two groups:

Figure 14

Points in the System Prior to the Distribution Loop: Determination and Specifications

Determination	Sampling Points: Specifications					
	1 Entry of Feed Water	2 Exit Tank (1)	3 Entry Decalcification	4 Entry to Decalcified Water Tank	5 Exit Decalcified Water Tank	6 Entry Reverse Osmosis
Total Aerobic at 32ºC (in CFU/ml)	<200	<100	<100	50-100	50-100	50-100
Total Coliforms	No traces in 100 ml					
Faecal Coliforms	No traces in 100 ml					
E. coli		No traces in 100 ml	No traces in 100 ml	No traces in 100 ml	No traces in 100 ml	No traces in 100 ml
Ps. aeruginosa		No traces in 100 ml	No traces in 100 ml	No traces in 100 ml	No traces in 100 ml	No traces in 100 ml

(*) *When two values are shown in the specifications, the first one is the alert limit and the second one is the action limit.*

Figure 15

Points in the System Prior to the Distribution Loop: Determination and Specifications

Determination	Sampling Points: Specifications				
	7 Exit Reverse Osmosis	8 Entry to CDI Equipment	9 Exit CDI Equipment	10 Entry to Decalcified Water Tank (from R1*)	11 Entry to Purified Water Tank
Total Aerobic at 32ºC (in CFU/ml)	50-100	50-100	50-100	50-100	10-20
E. coli	No traces in 100 ml	No traces in 100 ml	No traces in 100 ml	No traces in 100 ml	No traces in 100 ml
Ps. aeruginosa	No traces in 100 ml	No traces in 100 ml	No traces in 100 ml	No traces in 100 ml	No traces in 100 ml

(*) *From R1 = Coming from R1 recirculation.*

A. Points in the system prior to the distribution loop (pretreatment)
B. Points in the distribution loop
   B. 1 Control sampling points
   B. 2 Points of use
A. Points in the system prior to the distribution loop: (Total = 11 points)

1. Entrance of water into the system
2. Exit from tank
3. Entrance to the decalcification equipment
4. Entrance to the decalcified water storage tank
5. Exit from the decalcified water storage tank
6. Entry into reverse osmosis
7. Exit from reverse osmosis
8. Entry into the electrodeionization equipment
9. Exit from the electrodeionization equipment
10. Entry into the decalcified water storage tank

from Rl recirculation
11. Entry into the purified storage tank

B. Points in the distribution loop:

(6 control sampling points + 40 points of use. Total = 46 points)

B. 1. Control sampling points:

12. Exit from the purified water storage tank prior to heat exchanger
13. Entry into the heat exchanger
14. Exit from the heat exchanger, prior to UV lamp
15. Exit from the UV lamp, entry into distribution loop
16. Return of the distribution loop prior to UV lamp
17. Entry into the purified water storage tank after UV lamp

B.2. Points of use (sampling points)

As the design being introduced is a theoretical-

Figure 16

Points of Use of the Distribution Loop: Determination and Specifications

B.1 – Control Sampling Points

Determination	Sampling Points: Specifications					
	12 Entry from Purified Water Tank	13 Entry into Heat Exchanger	14 Exit from Heat Exchanger	15 Entry into Distribution Loop	16 Loop Return Prior to UV (19)	17 Entry into Purified Water Tank (from return)
Total Aerobic at 32ºC (in CFU/ml)	10-20	10-20	10-20	10-20	10-20	10-20
E. coli	No traces in 100 ml	No traces in 100 ml	No traces in 100 ml	No traces in 100 ml	No traces in 100 ml	No traces in 100 ml
Ps. aeruginosa	No traces in 100 ml	No traces in 100 ml	No traces in 100 ml	No traces in 100 ml	No traces in 100 ml	No traces in 100 ml

B.2 – Points of Use

Determination	Points of Use: Specifications
Total Aerobic at 32ºC (in CFU/ml)	10-20
E. coli	No traces in 100 ml
Ps. Aeruginosa	No traces in 100 ml

Figure 17

Weekly Sampling Criterion (Chemical)

Points in the System	Total Points	Monday	Tuesday	Wednesday	Thursday	Friday	Total Points Sampled
A. Pre-Treatment	4	1	1	1	1		4
B. Points in Loop:							
B.1 Control Points	2	1	1				2
B.2 Points of Use	40	8	8	8	8	8	40

In such a way that:
- Each week all the critical pre-treatment points and all the critical points in the distribution loop will be sampled.
- At the end of the 4 weeks of the validation, 4 samples will have been taken at each point.

Figure 19

Points of Use of the Distribution Loop: Determinations and Specifications

B.1. – Control Sampling Points

Determinations	Sampling Points: Specifications	
	15 Entry into Distribution Loop	17 Entry into Purified Water Tank (from return)
Aspect	Transparent	Transparent
Color	Colorless	Colorless
Odor	Odorless	Odorless
TOC	350–500 ppb	350–500 ppb
Conductivity	0.5–1.3 µs/cm	0.5–1.3 µs/cm

B.2. – Points of Use

Determinations	Points of Use: Specifications
Aspect	Transparent
Color	Colorless
Odor	Odorless
TOC	350–500 ppb
Conductivity	0.5–1.3 µs/cm

11. Entry into the purified water storage tank

B. Points along the distribution loop

B.1. Control sampling points: (2)

15. Entry into the distribution loop, after UV lamp
17. Return to the Purified Water storage tank, after UV lamp

B.2. Points of use: All (40)

Sampling is to be earned out according to the criterion set out in the following table:

- Each week all critical pretreatment points and all critical points in the distribution loop are sampled.
- At the end of the four weeks of validation, four samples will have been taken at each point.

A. Points in the system prior to the distribution loop: Determinations and specifications

B. Points of use of the distribution loop: Determinations and specifications.

B.1 Control sampling points

Discussion

The novelties presented in this optimized design are:

Elimination of sterilizing filters, which are very efficient but expensive to maintain, can sometimes cause "accidents" by blockage, raising the microbiological level of the water (bioburden).

Introduction of a decalcified and dechlorinated water storage tank, which ensures that water entering the reverse osmosis equipment will always be chlorine-free and have a very low microbial level.

R1 recirculation circuit: The decalcified water tank is the center of the R1 recirculation circuit, which ensures that water in pretreatment will constantly have a very low microbial level, which in practice means obtaining purified water with a microbial level under 5 CFU/ml.

Presently, the functioning and control of water production systems are regulated on-line by means of specific software through a PLC (Programmable Logic Controller).

Conclusion

The proposed design is easy, economical to maintain, and ecological because it has no high-efficiency filters, eliminating the constant regeneration of the ionic exchange resins. It should also be pointed out that stainless steel tanks for decalcified and purified water can be sterilized easily and regularly by means of clean steam.

Therefore, validation of the system will ensure the production of water will be dependable and within the specified limits. In this case it will be easy to prove that the price of the purified water will be competitive and, in practice, less expensive then other water-producing systems. ❑

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Autoclave Qualification: Some Practical Advice

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Despite the fact that the subject of autoclave qualification has been the topic of numerous articles, books, and symposia in the past decade, autoclave qualification shortcomings are among the leading source of FDA 483 citations reported for the biotech industry. This article attempts to present a hands-on approach to efficiently and reliably qualify autoclaves. This article assumes that the reader is somewhat familiar with the basic theoretical development of steam sterilization and equipment qualification.

"This article assumes that the reader is somewhat familiar with the basic theoretical development of steam sterilization and equipment qualification."

Autoclave qualification, or for that matter qualification of any piece of equipment, should begin after the equipment is installed and fully commissioned. Designing the Installation and Operational Qualification (IQ/OQ) to also serve as the commissioning and start-up document is a practice that has recently gained popularity, but is not recommended. Such thinking arose because organizations believe that it will lead to time as well as resource saving. However, when qualification serves as the commissioning and start-up function, failures and deviations from protocol acceptance criteria will most likely result thus increasing cost. A better approach for saving time and money would be to consider all the operational requirements for the autoclave prior to ordering and commissioning the autoclave with qualification expected to verify these functional requirements. Such an approach would also avoid duplication of effort and lead to a smooth qualification. A factory acceptance test, prior to receiving the autoclave at the facility, should be performed. Once the autoclave is installed, it should be rigorously commissioned and then started. In other words, the autoclave should be thoroughly tested during the commissioning and start-up phase. All bugs must be fixed, and the autoclave must be in proper working condition before the qualification phase can proceed.

Prior to beginning the qualification effort, assessments of the material being autoclaved should be made for cycle development. Some parameters to consider are susceptibility of the load to the heating conditions, maintenance of sterility after autoclaving, differences in solids and liquids heating, and the effect of trapped air. Load patterns should be established, assigned to cycles, and tested. These tests should verify, at a minimum, that the load was not affected by the heat profile, the container integrity has not been compromised, and the sterility of the load has been achieved. This is typically done by a combination of heat penetration studies and biological testing.

Installation Qualification (IQ)

Upon completion of the load and cycle development, the IQ phase is initiated. Equipment IQs are generally similar and vary little from one kind of equipment to another. Therefore, the IQ portion of the qualification will not be emphasized in this discussion. In general, the IQ may verify the following information:

1. Equipment specifications: verification of primary system components.
2. Component/Auxiliary equipment specifications: verification of secondary system components.
3. Instrument specifications and calibration: verification of associated critical and non-critical instruments.
4. Materials of construction: verification of product and non-product contacting surfaces.
5. Filter schedules: verification of system filters with associated replacement procedures.
6. Control systems: verification of system control type and necessity for individual control system qualification.
7. Utility connections: verification that required utilities are installed as required.
8. Design specifications and drawings: verification of system specifications and associated diagrams.
9. Installation documentation and drawings: verification of system schematics and as-built diagrams.
10. Standard Operating Procedures (SOPs) and related programs: verification of approved SOPs for start-up, shutdown, operation, preventive maintenance, cleaning, calibration, and change control.
11. Certification documents: verification of all certifications resulting from the installation of the system.
12. Required training documents and procedures: verification of the establishment and implementation of approved training procedures.

Documents and manuals should be reviewed thoroughly to confirm and assure that the information collected during the IQ phase of the qualification effort is accurate and contradictions do not occur.

Operational Qualification (OQ)

Depending on the complexity of the autoclave control system, a variety of different tests should be performed during the OQ portion of the qualification effort. The most important issue to keep in mind when conducting the OQ is temperature mapping of the empty chamber.

Empty chamber tests, which should be performed to verify the proper operation of the autoclave, are normally designed to test and determine the hot and cold spots for thermocouple placement. During an empty chamber run, a sufficient number of thermocouples, depending on the volume of the chamber, should be distributed to establish the temperature profile within the chamber and verify that there is a minimum of temperature differential and fluctuation during a cycle. The thermocouples should be:

- positioned throughout the chamber and within the anticipated hot and cold regions, the steam inlet, and condensate drain.
- held in position with heat resistant tape, or a similar material that will not affect the temperature sensing capabilities of the thermocouples.
- positioned at the extremities of the chamber, but slightly off the surface of the inside chamber; two to four inches, depending on the size of the autoclave, is usually sufficient.

Other important factors to consider when developing tests for an autoclave OQ include:

- Control system setup: Is the system set up to operate by recording the F_0 value of a control thermocouple or by ramping and holding a temperature for a period of time?
- System safety features: Are there locks on the autoclave doors during pressurization cycles? Should the system enter a slow exhaust mode if shut down during a run? Does the system sound an audible alarm when the cycle is complete?
- Quality of cooling water or air injects: Any medium that comes in contact with the sterilized load should be shown to contain a low bioburden and be part of a monitoring program.
- Vacuum and/or relative pressurization: Chamber

operation while running loaded chambers and assessing the minimum lethality levels. In addition, these tests should be developed to verify the heat penetration throughout the load and the sterility level reached. Tests conducted during a PQ are normally comprised of two components; heat penetration studies and biological challenge tests. The heat penetration studies are performed to verify that each position within the load is exposed to sufficient heat for proper sterilization. These tests are conducted in a manner similar to the OQ empty chamber tests, except that the thermocouples are positioned within the load instead of the chamber extremities.

Thermocouples should be strategically distributed within the load with the purpose of measuring the temperature and lethality at the locations that may represent the most difficult heat penetration situation. Special care should be taken to monitor large thermal masses, highly insulated components, and all product-contacting surfaces. Once these locations have been identified, the actual placement of the thermocouple wires should ensure that the thermal center of the component is measured and that no harm comes to the thermocouples. Load carts and metal covers can easily damage thermocouple wires and ruin tests if allowed.

The biological challenge tests are conducted at the same time as the penetration studies by means of Biological Indicators (BIs). These BIs can be obtained in a variety of different types, including ampoules, spore strips, discs, and suspensions. Regardless of the type chosen, positive controls should be collected for each test performed. Special care should be taken to record the organism's name, the BI supplier, spore population, lot number, expiration date, and specific resistance information. Typically in autoclave qualification, *B. stearothermophilus* BIs with a spore population of 10^6 are used. However, other commercial BIs are available for moist heat sterilization studies that are comprised of other organisms such as *B. subtilus*, *B. coagulans*, and *C. sporogenes* with populations from 10^3 to 10^9 and possibly higher. BI requirements depend on the particular load and sterilization requirements. However, justification should be provided at the time of qualification. When conducting the studies, the BIs should, at a minimum, be placed in the components adjacent to the thermocouples, but ideally as close as possible to the thermal areas, which are being measured by the thermocouples. Tests are typically conducted multiple times and with worst-case scenarios in mind. However, it is strongly recommended that tests be conducted at a minimum in triplicate for each load pattern.

Final Reports

Final reports, summarizing the results of the studies, should be generated after completion of each qualification step. All raw data generated, including biological indicator growth results, should be attached to the executed protocol. Autoclave re-qualification should occur periodically, according to established change control procedures and with associated test protocols, to verify that the autoclave has remained in a validated state.

Summary

In summary, autoclave qualification is a fact of life in the pharmaceutical and biotechnology industries, but doesn't have to be a source of stress if the system qualification is carefully thought out and approached logically. The confirmatory nature of validation suggests that the system's operation should be known prior to conducting qualification tests. Once installed, load development tests should be run to establish a baseline for the system. Once established, the system qualification can start. The system should be installed according to manufacturer specifications, calibrated, connected to appropriate utilities, and have associated diagrams and SOPs established and available. The autoclave control system should be tested by means of logical system tests to verify proper system operation and temperature distribution. Furthermore, temperature penetration tests and biological challenge tests should be performed to confirm the sterility of the materials after undergoing an established cycle. ❑

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Qualification of Purified Water Systems

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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.

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

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 diffi-

cult 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 moni-

tors, 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

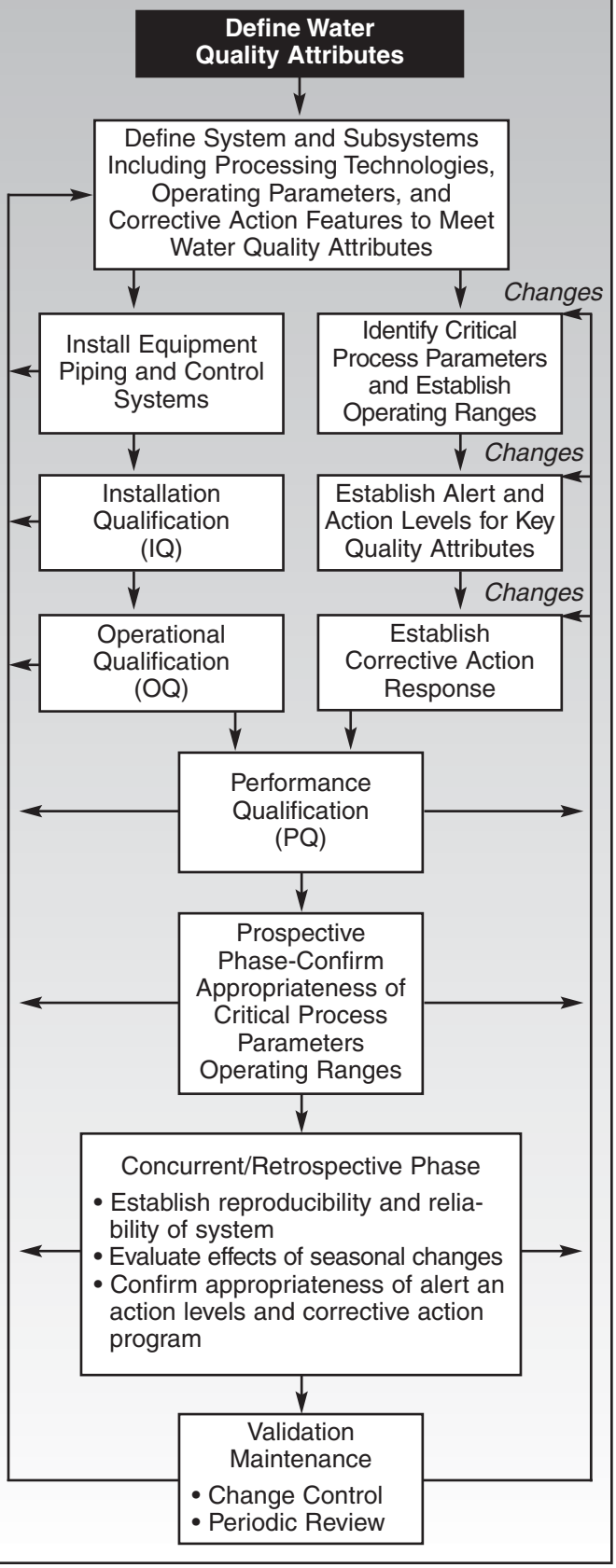
There are many ways of qualifying a water system. The following is one typical method:

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 method-

ologies 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

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

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. ❑

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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