Design Concepts for the Validation of a Water for Injection System

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PREFACE

THIS IS THE FOURTH TECHNICAL REPORT dealing with the subject of process validation.[1-3] The QC Subcommittee, under the direction of Frederick Carleton and Robert Kieffer, has outlined methods for evaluating a Water for Injection (WFI) System for use in pharmaceutical manufacturing. The considerations presented in this document are intended solely as a review of factors specific to the design, operation, and evaluation of a system which generally is considered to be capable of consistently delivering WFI. The method herein described is only one of the many possible alternatives for evaluating a system. It should be kept in mind that each installation is unique, and that there are many alternative WFI systems available, each of which may require modification of this methodology. The approach followed in this procedure is limited to the most common method of producing WFI (i.e., by distillation), although other methods are acceptable.

This Technical Report is only intended to provide information to the PDA membership and should not be construed to be a recommendation of the PDA.

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R. M. Enzinger, Ph.D.
Chairman
Research Committee

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[1] "Validation of Steam Sterilization Cycles," Parenteral Drug Association Inc., Technical Monograph #1.

[2] "Validation of Aseptic Filling for Solution Drug Products," Parenteral Drug Association Inc., Technical Monograph #2.

[3] "Validation of Dry Heat Processes Used for Sterilization & Depyrogenation," Parenteral Drug Association Inc., Technical Report #3.

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SCOPE

This document provides design concepts for a Water for Injection (WFI) validation program. Generally recognized procedures are included and an approach for conducting the appropriate qualification tests is outlined. Specific examples are presented to clarify the concepts. It is the judgment of the committee preparing this report that the validation procedure should describe the expected operating and monitoring criteria with limits of acceptability for each component of the system.

A five-step validation system will be discussed in the following order:

  I. System Description, Construction, and Operating Considerations
  II. Installation Qualification
  III. Operational Checks of Equipment and Instruments
  IV. Initial WFI Qualification Sampling and Testing
  V. Documentation and Monitoring Program

INTRODUCTION

Water for injection (as defined by USP XX) is water purified by distillation or reverse osmosis, is pyrogen-free, contains no added substance, and meets the requirements of Purified Water USP except for bacteriological purity. The system to be described will produce, hold, if desired, and deliver to the point of use, water which conforms to the compendial requirements.

Validation often involves the use of an appropriate challenge. In this situation it would be undesirable to introduce micro-organisms into an on-line system; therefore, reliance is placed on periodic testing for microbiological quality and on the installation of monitoring equipment at specific checkpoints to ensure that the total system is operating properly and continuously fulfilling its intended function.

METHODOLOGY

I. System Description, Construction, and Operating Considerations

A. General

Each component of the WFI system needs to have defined quality acceptance and performance criteria for the function it performs in upgrading/maintaining water purity. Starting with the feed water, each successive treatment should enhance the water quality.

In designing the total system, specifications and operational procedures for each subsystem must be developed. Subsystems may include in-plant pretreatment systems, distillation unit, water holding system, and distribution network. The discussions which follow include an outline of construction considerations, validation considerations, and potential problems which may occur in each of these subsystems.

B. Incoming Water

Incoming water may be obtained from a municipal distribution system or from a private supply such as a well. The quality of the water may vary significantly depending on its source, its treatment by municipalities, and other factors such as seasonal temperature and rainfall. The overall quality and variability of the incoming water supply should be determined and a quality target established. This data will allow for the selection of proper pretreatment equipment and will determine the characteristics of incoming water (i.e., solids, hardness, silica, particulates, organic chemicals, etc.) which may require monitoring to ensure proper functioning of the pretreatment system.

C. Pretreatment System

Pretreatment of the distillation unit feedwater is recommended by most manufacturers of distillation equipment to ensure trouble-free operation. As previously pointed out, the incoming feedwater quality may fluctuate during the life of the system, depending upon seasonal variations and other external factors beyond the control of the pharmaceutical facility. The system should be designed to operate within these anticipated extremes. Pretreat-

ment systems for feedwater may be divided into two categories: filtration and primary water treatment. Filtration may include sand filters, charcoal filters, cartridge filters, etc.; primary water treatment may include water softeners, deionizers, and reverse osmosis units. Either filtration or primary water treatment may be used individually or in combination, depending upon the quality of the incoming water. Selection of the size and the type of pretreatment system to be used depends primarily upon the anticipated water volume throughput and the quality of the incoming water. In deionizing systems, the maximum removal of total ionized solids and maximum flow rate are two primary design considerations.

When designing the pretreatment system, typical problem areas that should be considered include:

Sand Filters—They are used for the removal of colloidal materials and extraneous particles.

Channeling—Poor packing of the bed may result in the incoming water passing through "holes or channels" in the bed, thereby allowing unfiltered water to pass to the next stage.

Sand Breakthrough—Sand breakthrough may occur if the retention screen in the filter becomes defective.

Colloidal Build-up—If the incoming water contains colloidal material, build-up of the colloids on the filters may block the water flow.

Charcoal Filters—The primary purpose of the charcoal filter is to remove chlorine in order to prolong the life of the anion bed in the deionizer.

Loss of Adsorptive Capacity—Chemical testing for the chlorine content in the water downstream of the filter is a method used for determining when the filter has lost adsorptive capacity. Once spent, a charcoal filter should be replaced, because it cannot be regenerated.

High Microbial Counts—Bacterial growth in the charcoal filter may result in high microbial counts downstream of the filter and may cause the release of bacterial endotoxin which could overchallenge the ability of the distillation system to remove endotoxins.

Softeners and Deionizers—

Resin Depletion or Contamination—Regeneration is required when conductivity readings significantly increase, or when the microbial counts approach the action limits. As in the case of charcoal filters, high microbial counts may theoretically result in the release of bacterial endotoxin which may overchallenge the ability of the distillation system to remove the endotoxin.

Resin Exhaustion—The need for increased frequency of regeneration indicates that the resin beds are exhausted and should be replaced.

D. Distillation

Stills upgrade the feedwater by vaporizing the liquid water, separating droplets with contaminants from the vapor by means of circular velocity or entrainment separators and condensing the purified vapor in a heat exchanger. The single effect, multiple effect, and vapor compression stills all operate on this principle.

Examples of potential concerns for the distillation unit include:

Feedwater Quality—Most problems occurring in the distillation system are caused by poor feedwater quality as described in section I(C).

Scaling—If the pretreatment system is not designed properly or does not function properly, large quantities of silica may be contained in the feedwater entering the still. This silica will form scale on the heat exchanger surfaces which may result in decreased still capacity or in clogging of the still.

Throughput—In order to ensure the quality of the distillate, the still must be operated within the manufacturer's specified high and low volume water throughput.

Monitoring Equipment—This equipment must be maintained and calibrated so that it always conforms to design specifications.

Weld Integrity—See discussion under section I(E).

Leaching—Metallic ions (especially iron) leaching from internal still surfaces may form metallic oxides and result in particulate contamination.

Entrainment—Contamination may be entrained in the distil-

late if the feedwater is overloaded with contaminants, if the blowdown system is malfunctioning, or if the still is operating outside of its design specifications.

Vent Filter—See discussion in section I(E).

Endotoxin Contamination—See discussion in section I(C).

E.   Holding and Distribution Systems

The holding and distribution systems are the subsystems in which the WFI is collected, held, and distributed to points of use. These subsystems are constructed in such a manner that the WFI is protected from contamination. Holding water over a period of time may result in microbial growth at ambient temperature. A hot, continuously recirculating loop may be employed in order to prevent microbial growth.

A key control is the potentiometric measurement of the distillate coupled with a system which automatically prevents passage of substandard water into the distribution system (automatic dump, see Figure 1).

Examples of potential concerns which may be encountered in the holding and distribution systems include:

Vent Filters—Storage tanks require venting to prevent their collapse when water is withdrawn. Venting systems generally utilize a 0.45-micron hydrophobic bacterial retentive filter to control the microbial quality of the air entering the tank. The filter housing may be equipped with a heated jacket. This will serve two purposes: prevent condensate from entering the filter and blocking it, and prevent microbial growth on the filter.

Welding—A concern associated with handling of high purity water is corrosion. A potential source of corrosion is improper welding. A "smooth finish" weld is important in order to reduce any rough spots where corrosion can start. Furthermore, a rough weld may provide an area where bacteria can lodge and proliferate. During installation of the water distribution system, all welds should be inspected. This may be accomplished by a variety of methods, such as boroscoping, X-ray inspection, or sections with welds may be cut out for visual or microscopic inspection.

Dead Legs—The distribution system should be designed to

eliminate dead legs greater than six pipe diameters. This may be accomplished by locating use point valves only a few inches from the main flow line and minimizing the number of drops to use points.

Monitoring Equipment—Equipment such as level controllers and indicators, temperature controllers and indicators, etc., must be maintained and calibrated so that they always conform to design specifications.

Leaching—See discussion under section I(D).

Passivation—This procedure should be performed on a new system in order to minimize corrosion.

II. Installation Qualification

When the construction of the WFI system has been completed, the next step in the validation process is the development of an accurate blueprint/schematic of the installed system. A physical inspection will ensure agreement of the system with the engineering drawings. An equipment checklist containing critical operating information for each item (pumps, valves, heat exchangers, etc.) in the system should be available. This list should include the name and model number of the item, and the operational characteristics (pressure, temperature ranges, etc.). It should describe the purpose and proper operation of each item listed. This checklist, together with the blueprint/schematic, should enable the development of the operational program described in Section III and become a part of the documentation described in Section V.

At this stage, written procedures may be developed and approved for the cleaning, sanitization, and maintenance of the WFI system. They should include:

1. Methods for the cleaning, sanitization, and maintenance of the system
2. Frequency
3. Documentation

Prior to use, all equipment and pipes should be thoroughly cleansed and rinsed. Stainless steel lines and tanks should be passivated. Upon assembly, the entire unit should be sanitized. These procedures should be documented and become part of the validation file.

Cleaning generally precedes passivation and is usually accomplished by circulating solvents and/or detergents to remove oil and
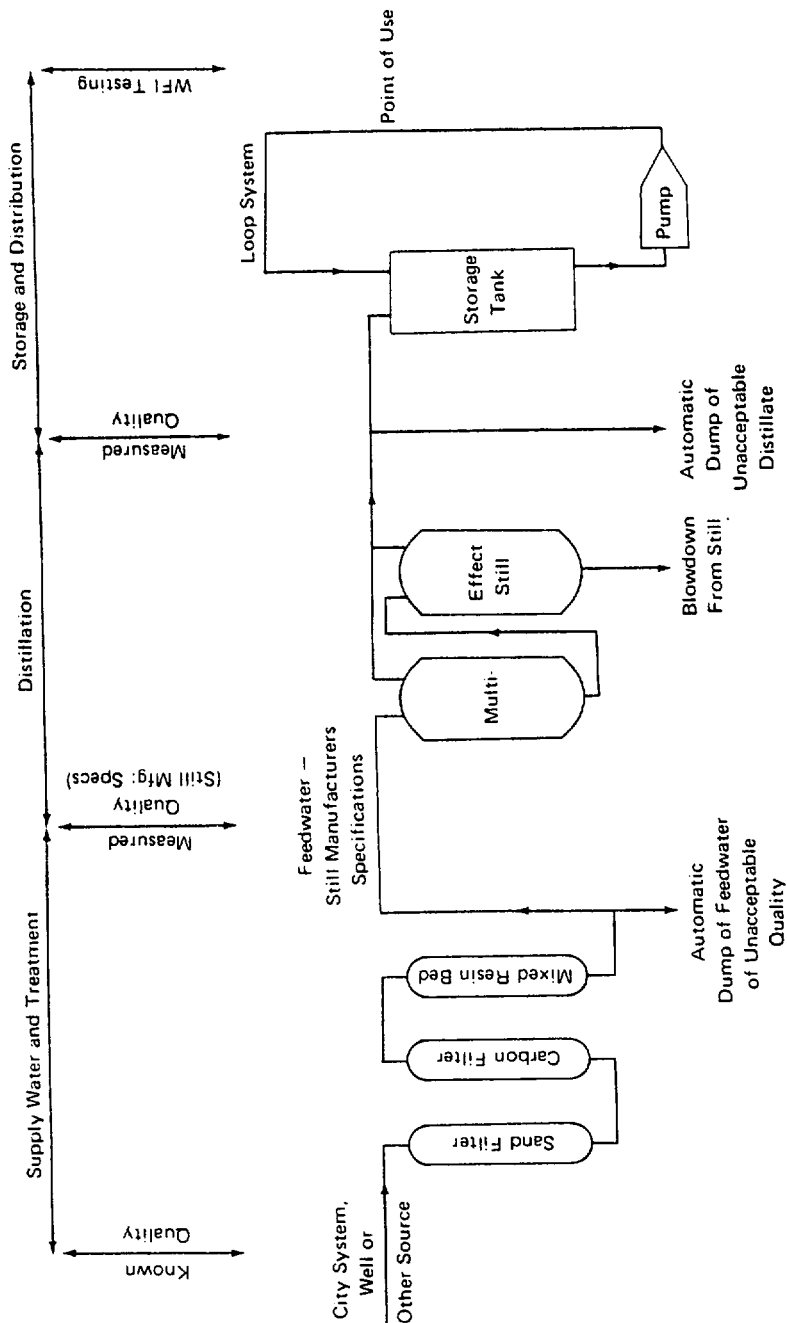
Figure 1.

particulate matter. Rinse water should be monitored to determine the effectiveness of the cleaning. In addition, a removable "test section" of the piping system may be inspected. Final rinse water should be analyzed to confirm the absence of detergent, solvent residues, or particulates generated during cleaning.

III.   Operational Checks of Equipment and Instruments

The schematic (see Figure 1) and the equipment list are two documents used to identify various control system functions. Each identified function should meet established specifications since each part of the system is dependent on the others for production of Water for Injection, which meets current USP criteria.

Operational checks of the total system are performed using calibrated monitoring instruments such as conductivity meters, temperature sensing devices, pressure sensing devices, and flow meters. A calibration program is an integral part of the overall program so that all instruments and equipment will be in a proper state of control to monitor those limits established for the system.

Parameters (flow rates, temperatures, pressures) identified by the manufacturer as the most important indicators of still performance should be checked. This data provides a baseline for the routine checks of still performance. Periodic system checks should be performed to assure that the still operation remains within established limits.

Indicators for determining the performance of the still should be checked and the results recorded. Examples of such indicators include output resistivity, blowdown, distillate temperature, flow as a percent of rated output, and cooling water temperature. One reliable measurement of water quality is resistivity, since it is a prime indicator of still performance.

The flow rates of distillate and blowdown should be checked. A well-designed still uses blowdown as a means of removing the impurities left in the feedwater after distillation. A second indicator of still performance is fluctuation of still capacity. If the capacity falls below 90% of its rating, it could indicate a malfunction.

Water for Injection should be stored in one of two ways: either in a properly constructed tank at a temperature at which bacteria will not grow, or in a tank at ambient temperature and discarded after a specified period of time. The heated storage tank should be

maintained at a specified temperature using a steam jacket or other suitable method and should be equipped with a non-fiber releasing sterilizable hydrophobic vent filter. The water temperature inside the tank should be continuously monitored for compliance with specifications.

The use of a distribution loop requires additional monitoring equipment. The water should be circulated continuously at the specified temperature. The integrity of this system may be maintained by automatic valve setups that dump WFI to drain when it falls below the minimum specified temperature. A temperature measuring device should be installed to monitor this parameter.

IV.   Initial WFI Qualification Testing

The sampling and testing of Water for Injection constitute the final phase of the Qualification Program. This program requires a set of instructions for sampling that covers a range of time and operational conditions. The intent is to cover the range of system operations so that the production and maintenance of the Water for Injection comply with the prescribed specifications. Sampling and testing should be performed at specified locations. Sites that should be considered are: the still outlet, the storage vessel(s), the distribution line, and each of the outlets. The tests performed are usually chemical, microbiological, pyrogen, temperature, conductivity, and non-viable particulate matter. It may not be necessary to perform all tests at all sampling sites at each test interval.

V.   Documentation and Monitoring Program

A.   Equipment

The link between process validation and daily operation is the standard operating procedures and routine system monitoring. Written instructions should describe each monitoring procedure.

A maintenance history log of equipment should be available. Include a description of both the test and calibration equipment such as millivolt potentiometers, certified precision thermometers, pneumatic dead weight testers, a digital electronic stop watch, manometers, ice baths, high temperature reference standards, pressure gauges, etc.

B.   System Components

Each of the system's major components-circulating pumps, stainless steel piping, holding tanks, heat exchanger, still, pretreatment components, filter and filter housing, etc., should be documented. For instance, the holding tank should be numbered or coded and should have the following information recorded:

1. Description
2. Manufacturer
3. Model number, if available
4. Serial number, if available
5. Date of purchase
6. Date of installation
7. Building in which it was installed
8. Room in which it was installed
9. Approved replacement parts list

A separate section should be developed in which the control instrumentation is identified. Information for each control device should include the manufacturer, the model number, the serial number, and an identifying code number such as a tag number. Examples of devices that should be identified in this section are:

Thermometers
Thermocouples
Low temperature switches
Timers
Shutdown alarms
Cool WFI temperature control valves
Nitrogen, pressure regulators
High-level switches and alarms
Low-level switches and alarms

C.   WFI Sampling and Test Records

The last item in the validation program documentation should be the location and identification of the sampling sites. Samples are identified by site, time, and date. Sampling frequency and methodology should be described in an operating procedure. Finally, all test results should be recorded, dated, and signed by an authorized individual.

Examples of tests which may be performed are:

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

The result of the data accumulated from a series of test runs can serve as a profile for normal working conditions of the entire WFI system. Deviations from this profile can easily be detected during routine operation and corrective action taken to ensure the continued production of Water for Injection.

Requalification of the system is generally unnecessary as long as a state-of-control exists. One should determine if a given change in the system could affect the state-of-control—such as a change in equipment, utilities, and/or facilities. An ongoing program of preventive maintenance should aid in maintaining the state-of-control.

ADDENDUM
Glossary—Water for Injection System

Air Vent Filters on Storage Vessels: 0.45-micron or finer, hydrophobic filters. Vent filters should be sized for maximum pump in/out rates from the storage vessel and should be protected to prevent moisture condensation inside the filter. The vent filter must prevent a pressure or vacuum buildup.

Blowdown: The bleeding-off of fixed quantities of accumulated feed water to reduce concentrated impurities. If these impurities are permitted to accumulate, they may pass through the distillation process and contaminate the distillate.

Chemical Treatment: The most common type of chemical treatment, chlorination, is performed for the control of microbial populations. *Warning:* The chlorine must be removed prior to entering the still.

Conductivity: The reciprocal of resistivity (see "Resistivity").

Deionization: Filtered potable water passes through the deionizer column(s) which contain cation and anion resins. The cations such as magnesium, calcium, and sodium are bound by the cation exchanger in exchange for hydrogen ions (H^+): chloride, sulfate, and bicarbonate anions are bound by the anion exchanger in exchange for hydroxyl ions (OH^-). The released hydrogen and hydroxyl ions will combine to form water. By this method, deionizer column(s) will continuously produce high purity water until their resins become exhausted and require regeneration.

Resistivity: Measurement of the specific resistance (of water). This measurement determines the suitability of the water by measuring its resistance to the passage of electricity. The electical resistance of water is proportional to the quantity of ionizable impurities, for example, the resistivity will decrease as the quality of the water decreases.

Reverse Osmosis: The reverse osmosis system is designed to provide purified water by forcing the water molecules from a high solids solution through the barrier into a low solids solution. The build-up of osmotic pressure is avoided by discarding the water containing the highly concentrated solids.

Validation/Qualification: As used in this article, the terms "Validation" and "Qualification" are interchangeable. Validation/Qualification is providing documentation that each step of the process does what it is purported to do.

Water Distribution System: The distribution system piping should have the following features: (*a*) minimum dead legs (maximum dead leg length of six pipe diameters), (*b*) lines should be sloped to permit free drainage, (*c*) low points should be drainable, (*d*) compatible with proposed sanitization procedures, (*e*) piping should be constructed of welded or sanitary connected stainless steel (non-rusting grade) similar to low carbon grade "L" to minimize corrosion of welds, and (*f*) welded uniformly and free of burrs to prevent corrosion and microbial deposition.

Chemical Passivity: The stainless steel in the distribution system may be rendered chemically passive by introducing concentrated nitric acid or other appropriate chemicals. There is an im-

mediate reaction of dissolving some of the metal, but it does not continue. The metal is then rendered passive to chemical reactions.

BIBLIOGRAPHY

1. Artiss, D. H., "Pharmaceutical Water Systems—Design Concepts," *J. Parenter. Drug Assoc.*, **32** (2), 89 (1978).
2. Artiss, D. H., "Materials, Surface Finishes and Components for Sanitary Applications," PMA Water Seminar, Atlanta, GA February, 1982.
2a. Artiss D. H., "Materials, Surfaces, and Components For WFI and Other Sanitary Piping Systems," *Pharm. Technol.*, **6** (8), 37 (1982).
3. Disessa, P., "The Generation of Pharmaceutical-Grade Water by Distillation," *Pharm. Technol.*, **4**, 103 (1980).
4. Disessa, P., "Production of High Quality Steam Utilized in the LVP Sterilization Process," *J. Parenter. Sci. Technol.*, **35** (2), 51 (1981).
5. *Geneva Reports*, "Qualification of a System for Distillation, Storage and Distribution of Water for Injection," 1980, pp. 80–92.
6. Giorgio, R. J., "Considerations in the Design of Hot Circulating Water-For-Injection Systems," *Pharm. Technol.* (1978).
7. Hoiss, J., "A New System for Generating Extremely Pure Water," *Pharm. Technol.*, **4**, 62 (1980).
8. Klink, A. E., and Artiss, D. H., "Good Manufacturing Practices for Water: Classes, Methods of Manufacture, Testing Requirements and Intended Uses," *J. Parenter. Drug Assoc.*, **32**, 5 (1978).
9. Klink, A. E., "Validation of Water Systems," PMA Meeting, March 1978.
10. Klink, A. E., "Water Systems Training Program for Field Investigators and Engineers—FDA," September 17, 1980.
11. Kuhlman, H. C., "Technical Processes in the Production of Water for Injection," *J. Parenter. Sci. Technol.*, **35** (2), 54 (1981).
12. Lastra, R., and Stadnisky, W., "Evaluating the USPXX Standards for Water and Monitoring Water Purification Equipment," *Pharm. Eng.* **2** (1), 44 (1981).
13. Otten, G., "Thermocompression Water Stills," *Bull. Parenter. Drug Assoc.*, **30**, 21 (1976).
14. Rechen, H. C., "Water for Injection in Device Manufacture," MD & DI, **3** (5), 66 (1981).
15. Saari R., et al., "Production of Pyrogen-Free Distilled Water for Pharmaceutical Purposes," *Bull. Parenter. Drug Assoc.*, **31**, 248 (1977).
16. Scruton, S. H., "Upgrading Water Purity for Manufacturing Non-Sterile Pharmaceutical Products," *Pharm. Technol.*, July 1980.
17. "Survey Results Process Water for Parenteral Operations," *Pharm. Eng.*, **1** (2), (1981).
18. Title 40 CFR Environmental Protection Agency, Part 141, National Interim Primary Drinking Water Regulations, August 27, 1980, *Fed. Regist.*, **45** (168), 57332.
19. Title 42 CFR Public Health, Chapter I, Subpart J, Drinking Water Standards.
20. "Water Seminar," PMA, Atlanta, GA, 1982.