Water is a component of every pharmaceutical product, so water system must be validated to ensure the consistent production of high quality water. The pharmaceutical industry places a high priority on the quality of water used in production of finished product, intermediate reagent preparation & analytical processes & especially in case of parenteral products where quality of water must be as per Pharmacopoeia.

In present scenario the quality of pharmaceutical water is maintained by setting a good pharmaceutical water system and this system encompasses system design qualification, attention of the regulatory requirements which are updated time to time. The continuous monitoring of water system is an unequivocal regulatory requirements and a major cost strain on company personnel and resources. Proper water system planning with personnel knowledge in all the physical, chemical, engineering and microbiology issues associated with water is essential. Proper pharmaceutical water system must

1. Achieve & maintain compliance with pharmacopoeia requirements.
2. Have proper sampling system from correct points with appropriate frequency.
3. Troubleshoot common contamination problems.
4. Consistently produce water that meets industry standards for quality.

**INTRODUCTION**

Water is mostly used substances, raw material, or ingredient in the production, processing, and formulation of compendial articles. Control of the microbiological quality of this water is important because proliferation of microorganisms ubiquitous to water may occur during the purification, storage and distribution of this storage substance. If water is used in the final product, these microorganisms or their metabolic products may eventually cause adverse consequences. Water that is used in the early stages of the production of drug substances and that is the source or feed water for the preparation of the various types of purified water must meet the requirements of the National Primary Drinking Water Regulations (NPDWR) (40 CFR 141) issued by the Environmental Protection Agency (EPA). Comparable regulations for drinking water of the European Union or Japan are acceptable. These requirements ensure the absence of coliforms, which if determined to be of fecal origin, may portend or indicate the presence of other microorganisms of fecal origin, including viruses that may be pathogenic for humans. On the other hand, meeting these National Primary Drinking Water Regulations would not rule out the presence of other microorganisms, which, while not considered a major public health concern, could, if present, constitute a hazard or be considered undesirable in a drug substance or formulated product. For this reason, there are many different grades of pharmaceutical water. Filtration, activated carbon beds, chemical additive, organic scavenging devices deionizations, electrodeionization, electrodialysis, reverse osmosis, ultra filtration these are selected unit operations and validation concerns associated with them.[8]

The purpose is to highlight issue that focus on the design, installation. Operation maintenance and monitoring parameters that facilitate water system validation.

**WATER SYSTEM FOR PHARMACEUTICAL PURPOSES.** [1, 2, 15]

The Quality attributes of water for a particular application are dictated by the requirements of its usage. Sequential processing steps followed for treating water for different pharmaceutical purposes are shown in Schematic Fig 1.

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**Keywords:** Validation, Pharmaceutical Water

**Fig 1:** Water system for pharmaceutical purposes
INSTALLATION, MATERIAL OF CONSTRUCTION AND COMPONENT SELECTION

Installation
Techniques are important because they can affect the mechanical, corrosive, and sanitary integrity of the system. Valve installation attitude should promote gravity drainage. Pipe supports should provide appropriate slopes for drainage and should be designed to support the piping adequately under worst-case thermal conditions. Methods of connecting system components including units of operation, tanks and distribution piping require careful attention to preclude potential problems. Stainless Steel welds should provide reliable joints that are internally smooth and corrosion-free. Low carbon SS, compatible wire filter, where necessary, inert gas, automatic welding machines and regular inspection and documentation help to ensure acceptable weld quality. Follow-up cleaning and passivation are important for removing contamination and corrosion products and to reestablish the passive corrosion-resistant surface. Plastic materials can be fused (welded) in some cases and also require smooth, uniform internal surfaces. Adhesives should be avoided due to the potential for voids and chemical reaction. Mechanical methods of joining, such as flange fittings, require care to avoid the creation of offsets, gaps, penetrations, and voids. Control measures include good alignment, properly sized gaskets, appropriate spacing, uniform sealing force, and the avoidance of threaded fittings. [2]

Material of construction should be selected to be compatible with control measures such as sanitizing, cleaning and passivating. Temperature rating is a critical factor in choosing appropriate materials because surfaces may be required to handle elevated operating and sanitization temperature.

Material should be capable of handling turbulent flow and elevated velocities without wear on the corrosive barrier impact, such as the passivation –related chromium oxide surface of stainless steel.

VALIDATION AND QUALIFICATION OF WATER PURIFICATION, STORAGE, AND DISTRIBUTION SYSTEMS

Establishing the dependability of Pharmaceutical water purification, storage and distribution systems requires an appropriate period of monitoring and observation. Ordinarily, few problems are encountered in maintaining the chemical purity of Purified Water and Water for Injection. However, it is more difficult to meet established microbiological quality criteria consistently. A typical program involves intensive daily sampling and testing of major process points for at least one month after operational criteria have been established for each sampling point.

Validation is the procedure for acquiring and documenting substantiation to a high level of assurance that a specific process will consistently produce a product conforming to an established set of quality attributes. The validation defines the critical process parameters and their operating ranges. A validation program qualifies the design, installation, operation and performance of equipment. It begins when the system is defined and moves through several stages: Qualification of the Design (DQ), Installation (IQ), Operational Qualification (OQ), and Performance Qualification (PQ). A graphical representation of a typical water system validation life cycle is shown in fig 3.

A validation plan for a water system typically includes the following steps [2]:
1. Establishing standards for quality attributes and operating parameters.
2. Defining systems and subsystems suitable to produce the desired quality attributes from the available source water.
3. Selecting equipment, controls, and monitoring technologies.
4. Developing an IQ stage consisting of instrument calibration, inspection to verify that the drawings accurately depict the as built configuration of the water system, and, where necessary, special tests to verify that the installation meets the design requirements.
5. Developing an OQ stage consisting tests and inspection to verify that the equipment, system alerts, and controls are operating reliably and that appropriate alert and action levels are established. This phase of qualification may overlap with aspects of the next step.
6. Developing a prospective PQ stage to confirm the appropriateness of critical parameter operating ranges. A concurrent or retrospective PQ is performed to demonstrate system reproducibility over an appropriate time period. During this phase of validation, Alert and action levels for key quality attributes and operating parameters are verified.
7. Supplementing a validation maintenance program (also called continuous validation life cycle) that includes a mechanism to control changes to the water system and establishes and carries out scheduled preventive maintenance, including recalibration of instruments. In addition, validation maintenance includes a monitoring program for critical process parameters and a corrective action program.
The basic design package should include the following:

- Analysis and plotting of data
- Bacterial testing, stipulated sanitizing methods and defines procedure for alert limits, specifies sampling plans and ports for chemical and microbiological testing, stipulated sanitizing methods and defines procedure for analysis and plotting of data

The basic design package should include the following:

1. Flow schematics for the proposed water system showing all of the instrumentation, controls and valves and component should be numbered for reference.
2. A complete description of features and functions of the system. This is of critical importance to enable production and quality assurance personnel, who may be unfamiliar with engineering terminology, to fully understand the manner in which the system is to be designed, built, operated, monitored and sterilized.
3. Detail specification for the equipment to be used for water treatment and pretreatment.
4. Detail specification for all other system components such as storage tanks, heat exchangers, pumps, valves and piping components.
5. Detailed specifications for sanitary system controls and description of their operation.
6. Specification for construction techniques to be employed where quality is of critical importance.
7. Procedure for cleaning the system, both after construction and on a routine basis.
8. Preliminary standard operating procedures (SOP’s) for operating, sampling and sterilization. These procedures will be cross referenced to the valve and component numbers on the system schematics.
9. Preliminary SOP’s for filter replacement, integrity testing and maintenance.
10. Preliminary sampling procedures to monitor both water quality and operation of the equipment.
11. Preliminary system certification procedures.

**B. Installation qualification (IQ)** [3, 4, 11]

This is first qualification document; it will consist of the system description following by the procedures section. Proper installation, assembly of the various items of equipments shall be verified. After careful checking of each piece of equipment ordered and reviewed shall be done and recorded for similarity. It ascertains that all the unit components are installed as per the specifications and according to the design drawing. IQ provides construction verification in that established specifications have been complied. This also involves instrument connections, review the instrumentation drawings, review and verify the MOC, examination and documentation of welds, inspection for dead legs and pipe slopes, verification of stainless steel passivation and any other information. IQ conforms the “As-Built” drawing and ensures the suitability of the completed system. Absence of leaks shall also be checked. IQ should cover why and how is the water purification system with complete description of system and purification system. Feed water shall be identified in this stage. List out the major components of the system like pump, filters, UV lights, controls, valves, drains, control system etc. and verify adequate to the design specification. Make the list of instruments and controls, calibration of these instruments shall be traceable to the national and international standards. Calibrations of instruments can be performed at the end of IQ process and recorded as a part of IQ or at the beginning of the operational qualification. Once the IQ is complete, system is recommended for operational qualification (OQ).

**C. Operational qualification (OQ)** [3, 4, 11]

After successful completion of IQ the OQ of the system is possible. The system should be carefully clean and all construction derbies removed to minimize any chance of contamination and corrosion. After completion of cleaning, equipment should be started up and carefully checked for the proper operation. OQ verifies the capabilities of processing units to perform satisfactorily within operational limits. Consideration of feed water quality of system capacity, temperature control, flow rates are involved in OQ. Focus the critical items and parameters during OQ. Alarm controlling of utilities, like steam pressure (high/low), pressure differential limits shall be checked. Calibration needs are determined for each limit. System should be challenges with minimum and maximum operations inputs and output results. Results shall be checked and shall be within acceptance limit. Operation, cleaning and preventive maintenance SOP shall be finalized with actual operation and with operation and maintenance manuals. Training of SOP technical staff shall be covered in OQ, after finalization of SOP. Any change can be addressed through change control system and approvals. Any deviation shall be approved and recorded. Verify all the functional and operational parameters are as per acceptance criteria, complete the OQ documents. Review and approve OQ protocol and report.

The system is ready for Performance Qualification (PQ) or Validation.

**D. Performance qualification (PQ)** [3, 4, 15, 16]

The purpose of PQ is to provide rigorous testing of demonstrate the effectiveness and reproducibility of the total integrated process. Three phases approaches shall be used to satisfy the objective of the providing the reliability and robustness of the system in service over an extended period. The three phase validation is regulatory expectation.

1) **PHASE 1**

Test period shall be 2-4 weeks (14 days minimum) for monitoring the system intensively. During this period the system should operate
continuously without failure or performance deviation. The following should be included in the testing approach.

- Under take chemical and microbial testing in accordance with a defined plan.
- Sample the incoming feed water daily to verify its quality.
- Sample after each step in the purification step daily.
- Develop appropriate operating ranges.
- Develop and finalize operating, cleaning, sanitizing and maintenance procedures.
- Demonstrate production and delivery of product water of the required quality and quantity.
- Verify provisional alerts and action levels.
- Use and refine the SOP for operation, maintenance, sanitizing and trouble shooting.
- Develop and refine test – failure procedure.

2) PHASE 2

A further test period of 2-4 weeks (30 days) should be spent carrying out further intensive monitoring, while developing all the refined SOP’s after the satisfactory completion of phase 1. The sampling scheme should be generally the same as in phase 1. Water can be used for manufacturing purpose during this phase. The approach should also

- Demonstrate consistent operation within establish ranges; and
- Demonstrate consistent production and delivery of water of the required quantity and quality when the system is operated in accordance with the SOP.

3) PHASE 3

Phase 3 typically runs for one year after the satisfactory completion of phase 2. Water can be used for manufacturing purpose during this phase which has the following objectives and features:

- Demonstrate extended reliable performance.
- Ensure that seasonal variations are evaluated.
- The sample locations, sampling frequencies and test should be reduced to the normal routine pattern based on established procedures proven during phase 1 and 2.
- After completion of phase 3 of the qualification program of water system, a routine plan should be established based on results of phase 3.

REVALIDATION

Revalidation should be performed only when there has been a significant change to the system or to the operational parameters. Routine monitoring and inspection will continue under the same condition as those that existed during the original validation. Routine maintenance or replacement of parts should have a specific written procedure, which must be validated at the time of original validation. [5]

SANITIZATION

Microbial control in water systems is achieved primarily through sanitization practices. System can be sanitized using either thermal or chemical means. In-line UV light at a wavelength of 254 nm can also be used to sanitize water in the system continuously. Chemical methods, where compatible can be used on a wider variety of construction materials. These methods typically employ oxidizing agents such as halogenated compounds, hydrogen peroxide, ozone, or peracetic acid. Halogenated compounds are effective sanitizers but are difficult to flush from the system and tend to leave biofilms intact. Compounds such as hydrogen peroxide, ozone, and peracetic acid oxidize bacteria and biofilms by forming reactive peroxides and free radicals (notably hydroxyl radicals). The short half life of these compounds, particularly ozone may require that it be added continuously during the sanitization process. Hydrogen peroxide and ozone rapidly degrade to water and oxygen; peracetic acid degrades to acetic acid in the presence of UV light. [1, 2, 3, 5]

ALERT AND ACTION LEVELS

The individual monograph for Purified Water and Water for Injection do not include specific microbial limits. These were purposefully omitted since most current microbiological techniques available require at least 48 hours to obtain definitive results. By that time, the water from which the sample was taken has already been employed in the production process. Failure to meet a compendial specification would require rejecting the product lot involved. And this not the intent of an alert or action guideline. The establishment of quantitative microbiological guideline for water for pharmaceutical purposes is in order because such guideline will establish procedures that are to be implemented in the event that significant excursions beyond these limits occur. [1, 5]

Alert level are levels or ranges that, when exceeded, indicate that a process may have drifted from its normal operating condition. Alert levels constitute a warning and do not necessarily require a corrective action.

Action level are levels or ranges that, when exceeded; indicate that a process has drifted from its normal operating range. Exceeding an Action level indicates that corrective action should be taken to bring the process back into its normal operating range.

OPERATION, MAINTENANCE AND CONTROL [1, 2, 3, 5, 15]

A preventive maintenance program should be established to ensure that the water system remains in a state of control.

Operating procedure – Procedures for operating the water system and performing routine maintenance and corrective action should be written, and they should also define the point when action is required. The procedure should be well documented, detail the function of each job, assign who is responsible for performing the work, and describe how the job is to be conducted.

Monitoring program – Critical quality attributes and operating parameters should be documented and monitored. The program may include a combination of in-line sensors or recorders (e.g. a conductivity meter and recorder), manual documentation of operational parameters (such as carbon filter pressure drop) and laboratory tests.

Sanitization- Depending on system design and the selected units of operation, routine periodic sanitization may be necessary to maintain the system in a state of microbial control. Technologies for sanitization are described above.

Preventive maintenance – A preventive maintenance program should be in effect. The program should establish what preventive maintenance is to be performed, the frequency of maintenance work, and how the work should be documented.

Change control – The mechanical configuration and operating condition must be controlled. Proposed changes should be evaluated for their impact on the whole system. The need to requalify the system after changes are made should be determined. Following a decision to modify a water system, the affected drawings, manuals and procedures should be revised. [1, 2, 3, 5]
DISCUSSION
There are many types of purified water systems used in pharmaceutical facilities. Although most of them share common features, each system is custom designed for a specific application. Developing a proper design requires a good understanding of system operation and careful attention to details. Simply following common rules of thumb does not necessarily guarantee a reliable system – no matter how much money is spent. On the other hand, with a good understanding, it is often possible to design, install and validate a functional and reliable Purified Water System with less capital investment and lower operating costs.

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