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Review Article

VALIDATION METHODS FOR WATER SYSTEMS OF PHARMACEUTICAL USE

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ABSTRACT

Water is a universal solvent. In pharmaceutical industry, water plays a vital role in the formulation and manufacturing of many products. Different types of waters are used for different types of dosage forms (e.g.: water for injection, sterile water for injection, purified water, etc.). If microbial purification and validation of water handling systems is not proper, this may have effect on quality. To produce best quality products, frequent monitoring, maintenance and validation of water handling systems and all the Total Organic Carbon content, inorganic, organic and microbial limits must be in specified limits as per USP specifications. The present article describes the need for validation and maintenance of water to produce good quality products.

Key Words: Water, water for injection, sterile water for injection, purified water

1.INTRODUCTION

Water is widely used as a raw material, ingredient, and solvent in the processing, formulation, and manufacture of pharmaceutical products, active pharmaceutical ingredients (API's) and intermediates, compendia articles and analytical reagents.[1]

- High-quality water is **essential** for the manufacturing of pharmaceuticals.
- Water is **directly or indirectly** used in the pharmaceutical manufacturing such as a major component in injectable products and in cleaning of manufacturing equipment.
- Water is thus an important raw material in GMP and in validating the manufacturing process.

2.TYPES OF WATER FOR PHARMACEUTICAL INDUSTRY:

Water for pharmaceutical use is classified according to how the pharmaceutical product is administered to the patient.[2] The types of pharmaceutical water are:

(A) Bulk forms:

-Purified Water (PW)

-Highly Purified Water (HPW)

-Water for Injection

-Water for Hemodialysis

(B) Packaged Forms

-Bacteriostatic WFI

-Sterile Water for Inhalation

-Sterile Water for Injection

-Sterile Water for Irrigation,

-Sterile Purified Water.

2.1 Purified Water

Purified water is described in the USP 24 as "water obtained by distillation, ion exchange treatment, reverse osmosis, or other suitable process. It is prepared from water complying with the regulations of the Federal Environmental Protection Agency with respect to drinking water.

-used as excipients in manufacturing of pharmaceuticals.

-used for equipment cleaning especially product contact surfaces of nonsterile chemicals.

-preparation of bulk chemicals.

-contains no added substances.

-not for use in parenteral or sterile dosage.

-prepared using potable water as feed.

Type of purifications

Distillation, Deionization, Ion Exchange, Reverse Osmosis, Filtration.

Purified water Quality Requirements

(1.) Conductivity – 3 stage measurement procedure.

(2.) Total Organic Carbon – 500 ppb limit response.

(3.) Microbial Action Limit – 100cfu/ml maximum – may be lower for specific process and product applications.

(4.) TOC < 500 ppb or oxidizable substance test.

2.2 Water for Injection

Water for injection is described in the USP 24 as "water purified by distillation or reverse osmosis.

-used as excipient in manufacturing of potentials.[3]

-it is a pyrogen –free water.

-preparation of sterile bulk chemicals.

-prepared using purified water as feed.

-Method of preparation is multicolumn distillation.

2.3 Water for injection monograph requirements:

(1.) Meets all requirements for purified water.

(2.) Produced by "distillation or purification process proven to be equal to or superior to distillation."

(3.) TOC < 500 ppb.

(4.) Conductivity < 1.1 μS/cm @ 200^0C.

(5.) Passes Bacterial Endotoxin test –not more than 0.25 EU/ml.

(6.) Microbial Action Limit: 10 cfu/100ml maximum – may be lower for specific process and product applications.

2.4 Water for Hemodialysis

-Water for Hemodialysis is water that complies with the US Environmental Protection Agency National Primary Drinking Water Regulations and that has been subjected to further treatment, using a suitable process, to reduce chemical and microbiological components. It is produced and used onsite under the direction of qualified personnel. It contains no added antimicrobials and is not intended for injection.

2.5 Bacteriostatic Water for Injection

-It is sterile, non-pyrogenic preparation of water for injection containing 0.9% (9mg/ml) of benzyl alcohol added as a bacteriostatic preservative.

-It is supplied in a multiple dose container from which repeated withdrawals may be made to dilute or dissolve drugs for injection.

-The pH is 5.7 (4.5-7.0).

-The semi-rigid vial is fabricated from a specially formulated polyolefin. It is a copolymer of ethylene and propylene.

2.6 Sterile Water for Inhalation

-for inhalation solutions.

-water for injection that is sterilized and contains no antimicrobial agents, except when used in devices in which it is liable to contamination over a period of time or other added substances.

-It is for inhalation therapy only, not for parenteral administration.

2.7 Sterile Water for Irrigation

-sterile water for irrigation is a sterile, distilled, non-pyrogenic water for injection intended only for sterile irrigation, washing, rinsing and dilution purposes.pH5.5 (5.0-7.0).

-sterile contains no bacteriostatic, antimicrobial agent or added buffer and is intended for use

Only as a single-dose or short procedure irrigation. When smaller volumes are required the

Unused portion should be discarded.

2.8 Sterile Water for Injection

It is packaged and rendered sterile used for reconstitution of dry powders injections.

-sterile water for injection is a clear, colourless, odourless liquid.

-It is sterile, hypotonic, non-pyrogenic and contains no bacteriostatic or antimicrobial agents.

-sterile water for injection USP is a diluent or solvents suitable for IV injection after first having

been made approximately isotonic by the addition of suitable solute.

-pH 5.5(5.0-7.0).

-The EXCEL container is Latex-free; PVC-free; DEHP-free.

2.9 Sterile Purified Water

It is sterile purified water sterilized and suitably packaged. It contains no antimicrobial agent.

-Do not use sterile purified water in preparations intended for parenteral administration. For such purposes use water for injection, bacteriostatic water for injection, or sterile water for injection.

Water systems should be included in the check list of self-inspection also as these are likely to be subject of regulatory inspection.

3.PHARMACEUTICAL WATER SPECIFICATIONS

According to USP[22]

Table.No.1: USP Specifications

Parameters	Purified water(PW)	Water for injection(WFI)
Conductivity	<1.3µs/cm@25°C	<1.3µs/cm@25°C
pH	5.0-7.0	5.0-7.0
Total organic carbon(TOC)	<500ppb	<500ppb
Total bioburden	<10,000CFU/100ML	<10CFU/100ML
Endotoxin	N/A	<0.25 Endotoxin units/ML
Coliform level	0/100ML	0/100ML
Sterility	< 100 cfu/ml	< 10 cfu/100ml
Pathogens	Absent	Absent

National primary drinking water regulations (NPDWR's)

Table.No.2: Specifications as per NPDWR's

Crypto ,Giardia, Virus	99%, 99.9%, 99.99% removal.
Heterotropic plate count	<500 CFU/ML
Turbidity	<5NTU(<1NTU)
Disinfectant byproducts (chlorine, bromite, haloacetic acid, tri halomethanes)	0.01, 1.0, 0.06, 0.10mg/L
Disinfectants (chloramines, chlorine, chlorine dioxide)	4.0, 4.0, 0.80mg/L

Inoraganic Metals: Limits apply

Arsenic- 0.01mg/L, Cadmium-0.005mg/L, Chromium-0.10mg/L, Copper-1.3mg/L, Lead-0.015mg/L, Mercury-0.002mg/L, Nitrate-1mg/L, Sodium-o.05mg/L, Thalium-0.002mg/L.

Organic Compounds: Limits apply

Benzene – 0.005mg/L, Benzo(a) pyrene (PAH's) – 0.0002mg/L, CCl_4 – 0.005mg/L , Chlorobenzene 0.1mg/L , DBCP – 0.0002mg/L , O-Chlorobenzene 0.6mg/L, Dichloromethane 0.005mg/L, Toulene 1mg/L.

4.WATER PURIFICATION TECHNIQUES

a. Reverse Osmosis

Reversed Osmosis, or RO, is the finest available membrane separation technique. RO separates very fine particles or other suspended matters, with a particle size up to 0.001 microns, from a liquid. It is capable of removing metal ions and fully removing aqueous salts.[2]

In a reverse osmosis system, the water is put under pressure and forced through a membrane that filters out the minerals and nitrate. These systems are compact and easy to operate and require minimal labor, which make them suitable for small systems and for systems where there is a high degree of seasonal fluctuation in water demand.

b. Membrane Ultrafiltration

Ultrafiltration is a membrane separation technique in which very fine particles or other suspended matters, with a particle size in the range of 0.005 to 0.1 microns, are separated from a liquid. It is capable of removing salts, proteins and other impurities within its range. Ultrafiltration membranes have a nominal pore size of 0.0025 to 0.1 microns.[3]

c. De-chlorination

Chlorine has a downside: it can react to chloramines and chlorinated hydrocarbons, which are dangerous carcinogens. To prevent this problem chlorine dioxide can be applied. Chlorine dioxide is an effective biocide at concentrations as low as 0.1 ppm and over a wide pH range. ClO_2 penetrates the bacteria cell wall and reacts with vital amino acids in the cytoplasm of the cell to kill the organism. The by-product of this reaction is chlorite. Toxicological studies have shown that the chlorine dioxide disinfection by-product, chlorite, poses no significant adverse risk to human health.[4]

d. Softening

One of the most commonly used ion exchangers is a water softener. This device removes calcium and magnesium ions from hard water, by replacing them with other positively charged ions, such as sodium.

e. **Demineralization**

Demineralization is the removal of minerals and nitrate from the water. By this method, the hardness of the water can be removed.

f. **Filtration**

It is a simple and highly employed process generally for the primary purification of water. This technique may employ cloth filters or carbon filters or any defined pore size filters for the purification of several types of water.

g. **UV Treatment**

UV-radiation is also used for disinfection nowadays. When exposed to sunlight, germs are killed and bacteria and fungi are prevented from spreading. This natural disinfection process can be utilized most effectively by applying UV radiation in a controlled way.

h. Deionization

Deionization is commonly processed through ion exchange. Ion exchange systems consist of a tank with small beds of synthetic resin, which is treated to selectively absorb certain cations or anions and replace them by counter-ions. The process of ion exchange lasts, until all available spaces are filled up with ions. The ion-exchanging device than has to be regenerated by suitable chemicals.

i. Ozonization

Ozone has been used for disinfection of drinking water in the municipal water industry in Europe for over a hundred years and is used by a large number of water companies, where ozone generator capacities up to the range of a hundred kilograms per hour are common. When ozone faces odours, bacteria or viruses, the extra atom of oxygen destroys them completely by oxidation. During this process the extra atom of oxygen is destroyed and there are no odours, bacteria or extra atoms left. Ozone is not only an effective disinfectant, it is also particularly safe to use.[5]

5 .VALIDATION OF WATER SYSTEMS:

Validation is the process whereby substantiation to a high level of assurance that a specific process will consistently produce a product conforming to an established set of quality attributes is acquired and documented.

A validation program qualified and documents the design, installation, operation and

Performance of equipment. A validation plan for a water system typically includes the following steps:

1.Establishing standards for quality attributes of the finished water and the source water.

2.Defining suitable unit operations and their operating parameters for achieving desired finished water quality attributes from the available source water.

3.Selecting piping, equipment, controls and monitoring technologies.

4.Developing an IQ stage consisting of instrument calibrations, inspections to verify that the drawings accurately depict the final configuration of water system and where necessary special tests to verify that the installation meets the design requirements.

5.Developing an OQ stage consisting of tests and inspections to verify that the equipment, system alerts and controls are operating reliably and that appropriate alert and action levels are established.

6.Developing a prospective PQ stage to confirm the appropriateness of critical process parameter operating ranges.

7.Assuring the adequacy of ongoing control procedures.

e.g.: Sanitization frequency.

8.Supplementing the validation maintenance program that includes a mechanism to control changes to the water system and establishes and carries out scheduled preventive maintenance including recalibration of instruments.

9.Instituting a schedule for periodic review of the system performance and requalification.

10.Completing protocols and documenting step 1 to 9.

6. 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.[9]

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.[10]

• 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.[11]

• ***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.

7. 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[12].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

The 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[13]. Following verification of the system, the analyst should test for the following:

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

• Determine whether critical parameters, such Bob Elms and Cindy Green 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.)

8. PERFORMANCE QUALIFICATION

During the PQ phase, one 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[14]. 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[15].

9. TEST REPORTS

At the completion of each qualification phase (IQ, OQ, and PQ), one 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. (One should compile a comprehensive report at the end of the study.) Data obtained during validation must support the 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.[16]

10. RE-VALIDATION

The period or conditions for re-validating the *sys*tem should be defined and documented early in Special Edition: Utilities Qualification Bob Elms and Cindy Green the validation cycle. Circumstances requiring revalidation include:

• A change in system design which potentially could affect flow rates, temperature, storage, delivery, sampling, or water quality.

• The consistent surpassing of alert and action levels.[17]

• 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[18].

11. SAMPLING CONSIDERATIONS

Water systems should be monitored at a frequency that a sufficient to ensure that the system is in control and continuous to produce water of acceptable quality. Samples should be taken from represented locations within the processing and distribution system. Established sampling frequencies should be based on system validation data and should cover critical areas including unit operating sites. The sampling plan should take into consideration the desired attributes of the water being sampled. For example: Systems for water for injection because of their more critical microbiological requirements, may require a more rigorous sampling frequency[22].

Analysis of water samples often serve two purposes:

1.In-process control assessments and

2.Final quality control assessments.

In-process – control analysis are usually focused on the attributes of the water within the system. Quality control is primarily concerned with the attributes of the water delivered by the system to its various uses.

12. FREQUENCY OF WATER SYSTEM VALIDATION

Water system should be monitored at a frequency which will ensure that the system is in control and continues to produce water of pre-determined quality. Samples should be taken from representative locations within processing and distribution system. The analyst who collects samples should have training in aseptic handling practices. Samples should be tested within few hours, these should be chilled to less than 8^{o}C, but these should not be frozen. Sampling points should be well designed and hygienic. Sample points for sub-systems, deionizers and RO should be as close to the downstream side as possible. “Target”,”alert” and “action” limits at different sampling locations should be included in specifications and an action plan should be available[22]. Sample sizes should be at least 100-500ml. The sample container should be inert and securely closable, preferably single use and sterile. The container of sample should be properly labelled, i.e.

- Date and time of sampling,
- Sampling location,
- Sampler’s name,
- Sampler’s signature.

Frequency of monitoring should be such as would give water of acceptable quality.

(1.) Potable water - once a year

- (i) For Indian Standards

- (ii) For pesticides, if it is ground water and the source is located near agricultural land.

(2.) Water from storage tank - once a month -

(i) for turbidity

(ii) dissolved solids

(iii) pH value

(iv) chlorine content

(v) TOC and pathogens.

(3.) Purified water and water for Injection – once a week-for I.P specifications.

(4.) Purified water and water for injection – twice a week - for microbial purity.

13. MAINTANENCE OF WATER SYSTEMS AND SYSTEM OVERVIEW

There should be controlled maintenance program undertaken should be documented the records should be reviewed for problems and faults.[23]

Water systems should be reviewed at appropriate regular intervals. The team for reviews should include at least the following:

-representative from engineering;

-representative from QA;

-representative from operation and maintenance.

The system review team may look into the below aspects;

-system performance and reliability;

-quality trends;

-failure events;

-out of specification results;

-investigation of concerns;

-changes to installation, if any;

-updated installation documentation;

-sop's, log-books;

-changes made since the last review.

14. QUALIFICATION, COMMISSIONING AND VALIDATION

1.Validation Master Plan and Site Master Plan.

2.User requirement specification and process and instrumentation diagram.

3.Direct impact system designation for critical utility system: purified water system.

4.GMP review and component criticality review=design qualification (DQ).

5.System construction completion, pre-commissioning, commissioning dossier.

6.Installation Qualification(IQ)=After pre-commissioning, vendor validation documentation review, Installation confirmation with P and ID yellow- line markup and system walk down.

7.Operation Qualification (OQ) =After IQ and commissioning with PW water yeasting, critical operation and functional testing with PW water testing (optional for 28-days).

8.Performance Qualification(PQ)=After OQ, PW water testing for 28-days from all key testing points and user points for all USP PW/WFI tests.[22]

15. PROTOCOL

Purpose: To provide the guideline to validate the water system for the pharmaceutical industry.

Procedure: The following types of water systems are preferable for use in the pharmaceutical industry.

The validation process is divided into following stages:

-Prevalidation of the full system.

-Construction Validation

-Start –up Validation

-Functional operation

-Procedures Verification

-Quality limits

-System Qualification

-Approval of the system for use.

•*Microbial investigations*

-viable count

-pseudomonas and coliform

-pyrogens

•*Chemical investigation*

-Investigation according to the pharmacopoeia (USP 24).

-Quick limit –test for an indicator ion.

•*Physical investigation*

-conductivity

-pH

-temperature

-pressure testing.

After finishing the above stages, a monitoring program should be established.

(1.) Pre-validation of total system design

-Flow schematics for the designed (layouts) water system showing all of the instrumentation valves, controls and monitors, numbered serially.[21]

-Complete description of the features and function of the system.

-Specifications for the equipment (storage tanks, heat exchangers, pumps, values and piping components) to be used for water treatment and pre-treatment.

-Detailed specifications for sanitary system controls.

-Procedures for cleaning the system, both after construction and ongoing.

-Sampling procedures to monitor water quality and the operation of the equipment.

(2.) Construction Validation

Construction Validation shall be conducted to avoid irreparable damage due to the use of unsuitable techniques.

-System components and construction materials.

Major equipment, such as distillation unit and WFI storage tanks, should be inspected before it is shipped from the supplier to verify operational function and compliance with specifications.

Equipment should be examined immediately upon arrival.

-verification of construction procedures

List of Procedures should be established and reviewed.

-Construction Completion.

-As-built drawing completed and approved.

-Checking for proper slope for draining.

- Pressure testing of the system

During construction it is impossible to avoid contamination of the piping with airborne ferrous particles from installation of structural steel and carbon steel piping components. If the stainless steel piping is allowed to become wet, e.g., from a hydrostatic pressure test, the system should be tested with dry, oil-free air. If water is used, then provision must be made thoroughly clean the system immediately after the hydrostatic pressure test.

-Post-construction cleaning

Flush the system to remove dust and major debris. Recirculate detergent or alkali cleaner at elevated temperatures to remove grease or oil. Flush and recirculate an acid at elevated temperatures to dissolve any ferrous particles in the system. Flush with water of the same quantity as will be used in service. The cleaning procedure shall be validated by making chemical analysis of surface residues.[21]

-System functional check out

The instrumentation and controls should be adjusted and calibrated to ensure proper monitoring and control of functions.

(3.) Start-up Validation

-Functional operation

-Verify consistency of operation of equipment and controls by repeated cycles of start-up and

Shutdown of all equipment and controls. Simulate manual, automatic and emerging conditions.

-Verify suitability of design under all conditions.[22]

-Establish preliminary monitoring program to ensure validation conditions, specificity and Calibration maintenance.

-Equipment logs, filter logs and monitoring records must be properly documented.

(4.) Quality limits

- Verify that water produced by system meets all predefined chemical, microbiological and Pyrogenecity specifications.

- Verify sanitization temperature and pressure by steam.

- Establish target and alert limits for chemical and microbial quality.

(5.) System Qualification

- Once the validation report is completed and approved, a qualification run should be made with the system to verify that validations will be duplicated in normal operation.

(6.) Approval of Use:-

If all requirements have been satisfied and all validation documents have been approved, the quality assurance managers may release the water system for production use.[22]

(7.) Microbial Investigations: Water for Injection

(7.1) Viable count

Procedure

Take 100ml sample from each tap point, one before the start of the production, and the second at the middle of the working day. An equivalent sample taken from the last sample point of the generating device and from the first sample point of the returning water should be used as a reference.

Requirements: Viable Count ≤ 10 cfu/100ml for each sample.

Frequency: Preproduction and concurrent validation: three working days a week (e.g., Monday, Wednesday, and Friday).

Ongoing Validation: - each tap point once a week.

Reference sample each working day.

(7.2) Pseudomonas and Coliform

Procedure:

Take 300ml sample from the last sample point of the generating device and from the first sample point of the returning water.[22]

Requirements:

Pseudomonas/Coliform: 0 cfu/ml for each sample.

Frequency: Each last day in the work week.

(7.3) Pyrogens:

Procedure:

Take 10ml sample from each tap point. An equivalent sample taken from the last sample point of the generating device and from the first sample point of the returning water should be used as a reference.

Requirements: - ≤ 0.25 EU/ml for each sample.

Frequency: Preproduction and concurrent validation: each tap point, once a week.

Ongoing Validation: - Each tap point, once a month.

(8.) Chemical Investigation

(8.1) Investigation according to the pharmacopoeia (USP 24)

Procedure:

From the last sample point of the generating system and from the first sample point of the returning water a sample of 1litre from each must be taken at the same time, at the beginning of the working week and at the moment when water is first pumped through the distribution network circuit.

Requirements: - Fulfilling of the pharmacopoeia requirements (USP 24).

Frequency: Pre-validation and Concurrent validation: once a week.

Ongoing validation: once a month.

(8.2) Quick limit-test for an indicator ion: Chemical investigations are rather time consuming. Therefore an indicative test, in which the indicator ion is the chloride ion (Cl^-), to get information about the status of the water system quickly.[22]

Procedure: After 3min of pre-rinsing, a sample of 50ml is taken from the last sample point of the generating device and from the first sample point of the returning water.

Limit test: To 10 ml of the water sample, 1ml of dilute HNO_3 and 0.2ml of $AgNO_3$ solution are added.

Used Reagents: Dilute HNO_3

Contains about 12.5% M/V of HNO_3

$AgNO_3$ solution

A 1.7% M/V solution.

Requirements:- The test solution should show no change in appearance for atleast 15min.

Frequency: Concurrent validation: Daily

Ongoing validation: At the first working day of the week.

(8.3) Total Organic Carbon (TOC) Test

To measure any microbial growth in the PW/WFI water system – biofilm and to measure any resulting carcinogenic compounds (e.g.: phenols) that would be toxic for human ingestion or IM/IV injection and to detect any potential endotoxin build-up.[22]

-potential solutions: pooling of test samples depending on the LOD and LOQ of the test, alternate-day or weekly testing during 28-day testing.

-potential solutions: more frequent ozone treatment to eliminate TOC with validated reduce testing schedule and plan pH, total bioburden, and endotoxin levels.

(9.) Physical Investigation

(9.1) Conductivity:

For monitoring system performance, a conductivity meter should be present or built in the water system for continuous measurement of the conductivity. If this device is not available samples must be taken manually and measured respectively.[22]

Procedure:

After pre-rinsing for 3min, samples of about 50ml should be taken.

Requirements: Normally, for pharmaceuticals, the requirement is ≤ 1µS/cm, but this depends on the local terms of reference.

Frequency:

Concurrent validation: at the start and in the middle of each working day.

Ongoing validation: at the start of each working day.

(9.2) pH:

In purified water, it is hardly possible to measure the pH.

Procedure:

After pre-rinsing for 5min, samples of about 50ml should be taken from the sample point of the returning water, after which a few drops of a saturated potassium chloride solution should be added. Then pH can be measured.

Requirements: The pH for each sample should be between 5 and 7.

Frequency: Concurrent validation: at the start and in the middle of each working day.

Ongoing validation: at the start of each working day.

(9.3) Temperature:

The temperature within the system plays an important role from a microbiological point of view.

Requirements: For water prepared by distillation and to be used as water for injection, the requirement is > 80^{o}C, systems with built-in reverse osmosis modules and ultrafiltration devices must comply with the supplier specification.

(9.4) Pressure testing:-

The pressure within the system is an essential factor for functioning of the water generating and distribution system. Therefore, pressure prior to and after subunits of the system should be registered continuously.[22]

Requirements: Should meet supplier specification.

(10.) Microbial Limits

(10.1)Total Bioburden: To measure microbial growth in the PW/WFI water system that will lead to increase TOC and exdotoxin levels.[23]

(10.2.) Endotoxin level testing with LAL: To measure toxins resulting from cellular breakdown during and after microbial growth in the PW/WFI water system that will lead to toxic shock if injected.

16. CONCLUSION

A water purification system should be designed so that the performance based alert and action levels are well below water specifications. With poorly designed or maintained water systems, the system owner may find that initial new system microbial levels were acceptable for the water uses and specifications. This is a serious situation, which if not correctable with more frequent system maintenance and sanitization, may require expensive water system renovation or even replacement. Therefore , if cannot be overemphasized that water systems should be designed for ease of microbial control, so that when monitored against alert and action levels and maintained accordingly the water continuously meets all applicable specifications.

Thus, there is a need of validation of water systems to ensure the quality of every grade of water samples that are employed for their use in pharmaceutical industry. The importance of validation of water systems has thus been depicted by satisfying all its attributes.

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