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VALIDATION OF PURIFIED WATER SYSTEM IN PHARMACEUTICAL INDUSTRY

Validation of Purified Water System

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Validation of Purified Water System

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As we know that water is the most essential part of different pharmaceutical preparations & it is used for the cleaning of machines, equipment's and other accessories during manufacturing hence directly & indirectly it plays a vital role in building of product quality.

Why Water System Validation is Important:

1. The purpose of carrying out water system validation is to assure that the treatment process produces a high quality of water consistently.
2. Water system validation is mandatory in order to study the reproducibility, consistency & effectiveness of water system.
3. Regulatory Guideline requirements
4. In order to achieve desired chemical and microbiological quality as per international guidelines.
5. Validation is complete documented evidence which gives the surety that any specified process consistently gives the end product having predetermined quality parameters and specifications.
6. Establishing the reliability of pharmaceutical water purification, storage, and distribution systems requires demonstrating control of the process through an appropriate period of monitoring and observation.

Water Validation different Steps:

Pharmaceutical water treatment system validation consists of three steps which are:

DQ (Design Qualification):	IQ (Installation Qualification):	OQ (Operational Qualification):
1. It includes all the information about various components of water treatment system. 2. It contains complete schematic diagram of mechanical, electrical and water flow in order to verify the appropriate installation.	1. Installation qualification gives surety and proof that the water system has correctly installed & supplied & meets 2. It involves the development of Installation qualification Protocol, an inspection & test	1. It consists of various inspection and tests in order to verify the reliable operation of equipment, system controls and alert. 2. It is complete documented verification of the system that

3. It defines the purification units, safety of the system, control devices & alarm systems. 4. Specify the sampling plans and sampling point for microbiological and chemical testing, describe sanitization methods, define method of analysis and data plotting.	plan for water system. 3. It is necessary to document and certify all the installation parameters prior to perform operational qualification. 4. For the installation qualification of water system, key elements are: Verification of utilities required including compressed air, steam, electricity & feed water. 5. All these utilities must be checked thoroughly when performing installation of system. 6. All the controlling instruments must be calibrated and certified as per written procedures that they are accurate, precise, selective and specific.	it works throughout the process as per operating ranges consistently. 3. OQ check the operation of water system to provide sufficient quantity of water with specified high-quality water, to maintain parameters like temperature, pressure, flow, TOC, endotoxin, pH, conductivity and microbial level.

PQ (Performance Qualification):

1. When water system has operationally verified, performance qualification step comes.
2. It includes variety of tests designed in order to verify the consistent satisfactory system performance.
3. It is carried out by performing the necessary product test and intermediate test of the process to demonstrate reliable and accurate performance.
4. PQ documents that water quality consistently and continuously meets the predetermined required specifications.

Water Validation Testing Phases:

Complete water system validation requires 1 year long time because of possible operating problems, maintenance errors which might occurs during this period, equipment failure etc. One more reason for such long time is to determine the seasonal change on the microbial quality of feed water and to determine the procedure of system sanitization effectiveness against microorganisms. Water system validation has been categorized into 3 phases: Phase I, Phase II and Phase III.

Phase I Validation:

1. This is preliminary phase and requires a 2 – 4 weeks (14 days minimum) testing period in order to monitor the system deeply.
2. The system is continuously operated in this phase without failure & extensive and frequent sampling is carried out with testing from various locations.
3. Microbiological and chemical testing is performed according to the defined plan.
4. Phase I finalize the sanitizing, cleaning and maintenance procedures along with operating ranges development.
5. Before the end of phase I, system is initiated to operate with some stress or tense conditions like start of system after failure of power or start up after emergency system shut down. System is simulated to operate under normal situation of maintenance like start-up of system after regeneration of resin, filter changing, ozone generator failure etc. & in the last water system (Standard Operating Procedure) SOPs produced.

Phase II Validation:

1. This phase is continuity of previous phase i-e phase I, it carries the sampling plan same as previous phase plan & it also facilitates the monitoring of system for 2 – 4 weeks (30 days) period.
2. In this phase, development of refined SOP's after phase I completion is done.
3. During phase II, manufacturing can be done with that water.
4. This phase describes that the water system is within predetermine ranges and under control.
5. At phase II, testing also assures the continuous persistent and steady production of required quality and quantity when the water system as per (Standard Operating Procedure) SOPs operated.

Phase III Validation:

1. In this phase sampling locations and frequency reduced as compared to previous phases.
2. Phase III represents that the water system shows reliable under control attainment over such a long time period & Phase III typically runs for one year after the satisfactory completion of phase II.
3. Manufacturing can be done during phase III & Feed water seasonal variations also evaluated & monitored in this Phase.
4. Complete microbiological and chemical analysis must be carried out in phase III and results are required to be presented in graphs using computer imitations.
5. Whole validation report should be compiled, written, reviewed and approved as per company's standard procedure.
6. Chemical & microbiological analysis like pH, conductivity, Total organic carbon (TOC) & total bacterial count shall be done throughout the above phases.

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Post Validation Monitoring of Water:

1. It comprises of routine check and balance of the water system, normal sampling and routine analysis & maintenance of equipment.
2. All the phases should be monitored in order to assure that the required desired conditions are satisfactorily set as specification.
3. All these checks should be clearly documented in the respective log book as well as in the reference validation protocol & Report
4. Any deviation or change from this procedure should be documented and investigated.
5. There must be a written procedure or program for maintenance of equipment part should be defined in the protocol.
6. The procedure should have all the details of items required to check calibration and maintenance frequency.

Re-validation of Purified water System:

Re-validation is important which can occur due to various condition Periodic Re-validation & Re-validation after any changes

Periodic Re-validation:

1. Over certain period of time water system need to be change & Periodic Re-validation is done to evaluate the impact of the change.
2. During periodic Re-validation some areas of water system should undergo changes like Standard Operating Procedure, Specification & calibration etc.

Re-validation after any changes:

1. It should be done to evaluate the quality & system of water after any changes.
2. Addition or deletion of any parts or utilities to the existing water system
3. Addition or deletion of any user point or expansion of distribution system
4. Any major change in the process equipment or any maintenance work performed after any major breakdown

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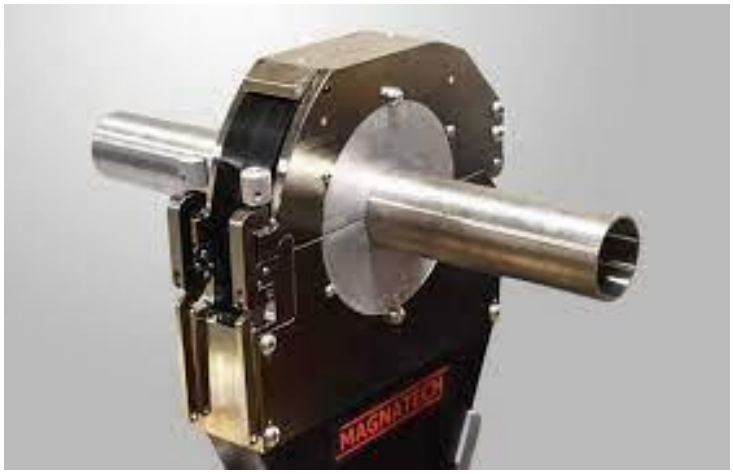
What is Orbital Welding?

When high quality results are required, orbital welding is the first choice for connecting pipes. The welding torch - in most cases, TIG welding (Tungsten Inert Gas) is used - travels around the pipes to be connected, guided by a mechanical system.

The name orbital welding comes of the circular motion of welding tool around the work piece.



PASSIVATION REPORT

NEW LOOP PURIFIED WATER SYSTEM

Passivation

Passivation is mandatory for the New Loop System in Pharmaceutical Industries. 5% volume/volume Nitric Acid Solution in Purified Water shall be used and shall be circulated for at Least 2 hours at Ambient Temperature. On line Passivation shall be carried out as per written pre-approved procedure and the same shall be documented.

Rinsing

The system shall be filled with PW and circulated for 15 minutes and shall be flush at each user point outlet and equipment connection thoroughly then again, the system will be rinsed with PW until the pH is balanced with inlet pH and conductivity within the range of supply conductivity.

A. INITIAL FLUSHING

1. Quantity of water taken: 250 Liter
2. Initial flushing started at: 11:15 (Date: .....)
3. Initial flushing ended at: 11:45 (Date: .....)

B. PASSIVATION SODIUM HYDROOXIDE ---------- FIRST STEPS

1. Quantity of water taken: 250 Liter
2. Quantity of sodium hydroxide added: 7.5 Kg
3. Concentration of solution: 3%
4. Recirculation started at: 13:30 (Date: .....)
5. Recirculation ended at: 14:30 (Date: .....)
6. Temperature during recirculation: 61^{o}C
7. Duration of recirculation: 1 Hour

C. FLUSHING

1. Quantity of water taken: 375 Liter

2. 1st flushing started at: 15:00 (Date: .....)
3. 1st flushing ended at: 15:15 (Date: .....)
4. 2nd Flushing Start: 15:45 (Date: .....)
5. 2nd Flushing End: 16:00 (Date: .....)
6. 3rd Flushing Start: 16:20 (Date: .....)
7. 3rd Flushing End: 16:35 (Date: .....)
8. Each Flushing Duration: 15 Min. 9. pH of rinse water: pH Result

D. PASSIVATION Nitric Acid-------- SECOND STEPS

1. Quantity of water taken: 250 Liter
2. Quantity of nitric acid added: 10 Liter
3. Concentration of solution: 4%
4. Recirculation started at: 17:15 (Date: .....)
5. Recirculation ended at: 20:15 (Date: .....)
6. Temperature during recirculation: 38 ^{o}C
7. Duration of recirculation: 3 Hour

E. FINAL FLUSHING

1. 1st Final flushing started at: 20:45 (Date: .....)
2. 1st Final flushing ended at: 21:00 (Date: .....)
3. 2nd Final flushing started at: 21:15 (Date: .....)
4. 2nd Final flushing ended at: 21:30 (Date: .....)
5. 3rd Final flushing started at: 21:45 (Date: .....)
6. 3rd Final flushing ended at: 22:00 (Date: .....)
7. Duration in each flushing: 15 Min.
8. pH at supply line: pH-07
9. pH at return line: pH-07

Checklist for Auditing Pharmaceutical Water System

Pharmaceutical water system is a key and a critical aspect of pharmaceutical product manufacturing. It plays a major role, irrespective of the type of product produced (sterile or non-sterile). The water system is a direct impact, and therefore needs proper attention. To ensure that the said system operates and produces the intended water quality, the system needs to be audited regularly. Following are the checkpoints that give a true idea about the condition of the water system:

1.0 System Design Information:

1.1 Flow-rate in Distribution system > 1.5 m/sec?

1.2 Is the system designed to meet maximum production department?

1.3 Is the distribution slope greater 1:100?

2.0 Equipment:

2.1 Is the P&ID drawing available?

2.2 Is Component specifications provided by the supplier including all kinds of drawings, certificates etc.?

2.3 Whether the materials used in tanks and pipelines meet the requirements (purified water):

2.3.1 Is the MOC of equipment in contact 316L? Check the supporting certificates.

2.4 Whether the valves used in system are sanitary type (316L Diaphragm valves). Check the supporting certificates?

2.5 Is the distribution pump sanitary type and uses water as a lubricant?

2.6 Is the pipe connection Tri-clover type (TC) instead of threaded and made through orbital welding? Check for the supporting certificates.

2.7 Is the gasket food grade i.e. Silicon or poly tetra fluoro ethylene? Check for the supporting certificates.

2.8 Is the PW storage tank breathing filter hydrophobic in nature?

2.9 Is the PW storage tank breathing filter sterilizable? Check supporting certificates.

2.10 Are system operation, maintenance, cleaning and disinfection procedures are in place?

2.11 Are operation and maintenance personnel are trained in the operation? Check the personnel training record.

2.12 Is there a water sampling procedure/schedule? Whether the sampling schedule include the P&ID representing sampling point with identification, sampling frequency, sampling methods and quality specifications?

2.13 Is the operator trained on sampling procedure? Check the training records.

2.14 Is the specification of PW & WFI in line with the Pharmacopeial requirements?

2.15 Is there a preventive maintenance plan for the waters system? Check the status of the planned and executed maintenance in the PM schedule.

2.16 Whether the water quality trending/review is done periodically(monthly, quarterly, biannually and annually)? Check the previous water trends.

2.17 Does the water quality review report have failed data? If so, whether there is a corresponding investigation report depicting root cause identified and identification of CAPA?

2.18 Check the water system breakdown maintenance records? Check the coverage of the breakdown maintenance or preventive maintenance in the system operation logbook.

2.19 Is there any change(s) made to the system? Have adequate studies carried out post changes to ensure continued compliance to the quality standards? Check the supporting documents.

2.20 Is the water system re-validated on regular basis? Check the revalidation study protocol and reports.

2.21 Does the validation include:

2.21.1 Detailed description of water system

2.21.2 Water and distribution system P&ID, marked with sampling points and points of use.

2.21.3 Whether IQ/OQ/PQ have been performed?

2.21.4 Periodic Revalidation and revalidation after a change impacting the quality of the product.

2.22 Verify PQ is done in compliance with USP requirements under phase 1, 2 & 3 requirements.

2.23 Are there any deviations in the validation report? Are there any unqualified items? If yes, check the relevant records and reports.

3.0 Purified Water:

3.1 Source of Water:

3.1.1 Is the source drinking water?

3.1.2 Is the source water tested for compliance to drinking water standards on an annual basis?

3.2 Water System:

3.2.1 Is the P&ID in compliance with the as built system?

3.2.2 Are the instruments of the system calibrated periodically? Check the calibration certificates.

3.2.3 Is Activated carbon storage tank is regularly cleaned and disinfected? Check the method of cleaning whether it is with hot water at 80 degrees or using pure steam or others.

3.2.4 Check whether the filters are replaced periodically or based on some acceptance criteria pertaining to the performance? Check the supporting documents and records.

3.2.5 Is the dosing of chemicals viz. Sodium hypochlorite, descaling agent, pH correction, sodium metabisulphite controlled? Check the procedures and records.

3.2.6 Is the system incorporate with UV germicidal lamp?

3.2.7 Are there any criteria for replacement of UV lamps? If so check the supporting documents and records.

3.3 Storage tank:

3.3.1 Is the tank cleaned manually or it incorporates a spray ball?

3.3.2 Is the tank easy to clean?

3.3.3 Is the level sensor sanitary type?

3.3.4 Is there a frequency for the replacement of vent filter? If so, check the procedure and records of replacement.

3.3.5 Are the drains provided with the non-return valves to avoid back flow?

3.4 Piping and Distribution System:

3.4.1 Is the distribution system a closed loop?

3.4.2 Is the connection between the pipelines in line with the requirements?

3.4.3 Are U bends supplemented with sanitary type diaphragm valves provided with 0 dead leg at the user point?

3.4.4 Is the pipeline marked with the distinct color code with an arrow showing the direction of the flow?

3.5 Circulation Pump:

3.5.1 Is the pump placed at the lowest point?

3.6 Environment:

3.6.1 Is the room in which water system is installed maintained in the clean state?

3.6.2 Are the equipment surfaces clean or are there any stains, marks on the surfaces?

3.6.3 Are there any leakages observed in the equipment/systems?

3.7 Cleaning and Disinfection:

3.7.1 Is there a cleaning and disinfection method in place? Is the method of cleaning in line with the cleaning instructions in the SOP? Are the records of cleaning and disinfection maintained?

3.7.2 Check the cleaning and disinfection method w.r.t. Usage of ozone, hot water or pure steam, chemicals. If chemical is used record check reagent name.

3.7.3 Check whether residues of chemical used is checked in the rinse sample?

3.8 Sampling/Daily Monitoring:

3.8.1 Is all sampling as well as points of use are covered for the routine monitoring?

3.8.2 Are generation points as well as supply and return sample points (Storage and Distribution System) are covered in monitoring plan on daily basis.

3.8.3 Is the sampling for daily monitoring carried out in line with the sampling schedules?

3.8.4 Check for the deviations if any form the sampling schedule and look for the CAPA closure for the same.

4.0 Water for Injection:

4.1 Water Source:

4.1.1 Is PW used a feed water to WFI generation system?

4.2 Water System:

4.2.1 Is the P&ID in compliance with the as built system?

4.2.2 Are the instruments of the system calibrated periodically? Check the calibration certificates.

4.2.3 Check whether the filters are replaced periodically or based on some acceptance criteria pertaining to the performance? Check the supporting documents and records.

4.3 Storage Tank:

4.3.1 Is the tank cleaned manually or it incorporates a spray-ball?

4.3.2 Is the level sensor sanitary type?

4.3.3 Is there a frequency for the replacement of vent filter? If so, check the procedure and records of replacement.

4.3.4 Are the drains provided with the non-return valves to avoid back-flow?

4.3.5 Is there a temperature monitoring facility inside the storage tank and as well as in return line? Does the temperature meet the requirements?

4.3.6 WFI is maintained at which temperature? >80ºC or <4 ºC

4.3.7 Is the system sterilized at 121 deg. Centigrade for 1hr along with the loop? Check the records and SOP.

4.3.8 Is the system cleaned and disinfected on a periodic basis? Check the procedure and the cleaning and disinfection records.

4.4 Distribution System

4.4.1 Is the distribution system a closed loop?

4.4.2 Is the connection between the pipelines in line with the requirements?

4.4.3 Are U bends supplemented with sanitary type diaphragm valves provided with 0 dead leg at the user point?

4.4.4 Is the pipeline marked with the distinct color code with an arrow showing the direction of the flow?

4.4.5 Is there a system and instruments in place to ascertain leakages in the heat exchanger, if used for to maintain the temperature of distribution loop?

4.4.6 Is the material of heat exchanger in contact with WFI SS316L?

4.4.7 Are the heat exchanges cleaned regularly? Check the Sop and supporting records.

4.4.8 Is the heat exchanger surface clean or rusty?

4.5 Circulation Pump:

4.5.1 Is the pump placed at the lowest point?

4.6 Environment:

4.6.1 Is the room in which water system is installed maintained in the clean state?

4.6.2 Are the equipment surfaces clean or are there any stains, marks on the surfaces?

4.6.3 Are there any leakages observed in the equipment/systems?

4.7 Sampling/Daily Monitoring:

4.7.1 Is all sampling as well as points of use are covered for the routine monitoring?

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