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Validation of Pharmaceutical Water System

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Abstract

The purpose of performing validation is to demonstrate that the process generates the product with a high degree of assurance of consistency and specified quality when operated within specified limits. Validation of the water system is necessary to obtain water of the desired quality, purity, and other requisite specifications. The validation method not only produces high-quality water, but it also offers a uniform framework for assessing process outcome and safety. This discussion aims to examine the numerous validation issues, including water treatment system components, equipment qualification, multiple qualification phases, documentation, validation, change control, and post validation monitoring.

Keywords: Validation, Water system

INTRODUCTION

The most common raw material utilised in the production of finished dosage forms, intermediates, and active pharmaceutical ingredients (API) is water. High purity water is special as a raw material in that it is the only element that must be manufactured by the maker since it cannot be purchased in a ready-to-use state from a vendor.

Every pharmaceutical product, such as parenteral, uses water in some amount during production. In some cases, water is a crucial ingredient. Among all pharmaceutical utilities, it may be the most significant. To get water with all the needed qualities, water treatment methods must be validated. The goal of validation is to show, by recorded proof, that the water treatment system can supply the required amount of water on a consistent basis with the desired quality characteristics. When a water treatment system is running outside of the specified control parameter limitations, validation gives the system owner the ability to detect it and offers a way to get the system back under control. [1]

The water that is used in the early phases of the manufacturing of pharmaceutical substances and which is the source or feed water for the preparation of the various types of purified water must meet the requirements of the national standards on primary drinking water (NPDWR).(40 CFR 141) issued by the Environmental Protection Agency (EPA). Depending on the source, quality, treatment, or use of the water, distinct categories are created. [2]

Based on its source, quality, treatment, or intended use, the water is classified into various types. According to minimal quality standards, including the desired chemical and microbiological purity, various types of water are categorised. [3],[4]

Table 1-Classification of Water system

Level	Type of Water
Level I	Well Water

Level II	Potable Water
Level III	Potable Water used for general batch applications
Level IV	Food and Drug Administration (FDA) water for final rinse, formulation, and WFI

Level I Water: -

Untreated water from a well or surface source is considered Level I and is used for utilities (fire control, lawn irrigation, etc.).

Level II Water: -

Drinking water is classified as Level II (potable), and it must adhere to EPA quality standards. Its source can be a public or private supply with additional chlorine for microbial control and a range of hardness levels.

Level III Water: -

Purified water, which is Level III, is the most challenging to control from a microbiological perspective. It is typically utilised for non-parenteral product formulation and bulk batch applications where there are no viable alternatives. For various operations, it is occasionally employed as the initial cleaning agent.

Level IV Water: -

The most crucial quality level of water is Level IV. It is frequently utilised in parenteral final formulations as well as final rinse water for important product contact surfaces. According to current USP regulations, this water must meet the requirements for water for injection.

Grades of water and Uses[5]

1) Potable water (Drinking water)

- Sources: Public water supply wells, etc.
- Used in early stage of equipment cleaning.
- Initial stage of manufacturing of bulk drugs and API.

2) Purified water

- Produced by purification of potable water.
- Important vehicle in aqueous liquid preparations.
- Topical, cosmetic, oral solutions are prepared using.

3) Water for injection

- Prepared from potable or purified water.
- Used in injectable preparations
- Used for equipment cleaning specially for sterile products

4) Sterile Water for injection

- As a sterile diluent for parenteral products
- Prepared from water for injection by sterilization

5) Sterile water for inhalation .

- Used in preparation of inhalant solutions

6) Sterile water for irrigation

- Sterile Water for Irrigatio0n USP is indicated for use as an irrigating fluid or pharmaceutical aid.

Pharmaceutical Water Specifications

Parameters	Purified Water	Water for Injection
Conductivity	< 1.3 µS/cm (25°C)	< 1.3 µS/cm (25°C)
Total Organic Carbon	< 0.5 ppm	< 0.5 ppm
Bacteria	100 CFU/mL	10 CFU/mL
Endotoxin	Non specified	< 0.25 EU/mL

Water purification Techniques

1. **Filtration**

- For the primary filtration of water, it is a simple and widely used procedure. The purification of various types of water using this method may use cloth filters, carbon filters, or filters with specified pore sizes.
- Multimedia filters containing gravel, manganese greensand and anthracite are used.
- Manganese greens and removes iron and other particles. Anthracite provides a light layer that is easily backwashed, reducing much of load from greensand.
- Manganese greensand and anthracite together are effective at removing suspended solids of sizes as small as 5-10 µ
- Sand beds are sanitized with chlorine with contact time of 1.5-20 min to prevent growth of microorganisms.

2. **Softening**

- The water softener is used to remove hardness (calcium and magnesium) from the water, replacing these with sodium ions. Ion exchange resins are used.
- Removing hardness protects the RO system by keeping hardness scale from forming on the membrane surface.
- Cation exchange resins have sulfonic acid and anions exchange resins have quaternary Ammonium.
- Carbon dioxide is liberated by the process. To counter this base is added to increase pH of feed water. So that CO2 is converted to bicarbonate and carbonate which is rejected by RO membrane (bicarbonate —carbonic acid —CO2).
- Degassifiers can also be used to liberate CO2. Degassifiers are placed just before RO filters.

3. **Dechlorination**

- By passing through activated carbon beds or sodium bisulfite is used which act as a reducing agent.

Deammonification

- Ammonia is present in water because municipalities use chloramine for water treatment.
- Deammonification is achieved by partial nitration of ammonia and subsequent anaerobic oxidation of residual ammonia by nitrite to nitrogen gas which is removed using degassifier.

4. **Reverse osmosis**

- Double layer RO filters are used.
- There are three types of membranes which are used: - Cellulose Acetate, polyamide membranes, polysulfonated polysufones.
- Earlier cellulose acetate membranes were used which were best operated at pH 4.5(because hydrolysis

of this membrane is minimum) due to acidic pH bicarbonate forms CO2 and it increases the conductivity of water.

- Polysulfonated polysufone membranes are not affected by chlorine.
- Polyamide membranes are used. The membranes are operated at pH 8.5 therefore rejects bicarbonate.
- Reduces ionic impurities.
- Reduces microbiological substances.
- Membrane rejects molecular weight greater than 150dalton. It rejects 99.9% of organics present.
- Major disadvantage of polyamide membranes is that it is affected by chlorine therefore poly sulfonated polysulfone can be used.

5. Ultrafiltration:

- Polysulphone membranes or chromic ultra-filters are used because of their hygienic design and the thermal tolerance of the membrane, which al-lows hot water sanitization.
- Used to decrease the endotoxin level in the water
- Weight cutoff at 10000-20000 daltons (specified by US FDA)

6. Distillation:

- Stills made of neutral glass, quartz are used to prevent entrapment of droplets
- Stills vaporize water, leaving nonvolatile impurities in the still.
- Then water is condensed and separated from volatile impurities.
- High temperature is required therefore it is costly and not used for purified water.
- But used to produce water for injection.

7. Deionisation:

- Effective method of improving the chemical quality attributes of water by removing cations and anions
- Charged resins are used that require periodic regeneration by acid and base
- Cationic resins are regenerated with HCL or sulfuric acid which replace captured H+ ions. Anionic resins are generated with NAOH and KOH which replace captured negative ions with OH- ions[6]

Validation of Purified Pharmaceutical Water

- Validation is defined as "a documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting pre-determined acceptance criteria"
- The purpose of validation is to demonstrate the capability of the water treatment and air handling system to continuously supply the required quantity of water and air with the specified quality attributes. "Documented" means to provide documented "evidence."
- In the pharmaceutical industry, it is very important that in addition to final tests and product compliance, it is guaranteed that the process constantly produces the expected results. The desired results are established in terms of specifications for the outcome of the process. The qualification of systems and equipment is therefore part of the validation process. In common words, validation involves testing of-[7]

1. Engineering design
2. Operational procedures and acceptable ranges for control parameters.
3. Maintenance procedures

1. Validation Plan:

This document is not an FDA requirement but has become almost an industry standard. The validation plan must contain all the information concerning the water purification system. Which are positive for basic information about design, plans, specifications, procedures, and protocols. Indicate the reasons for the choice of equipment, for the cleaning and disinfection frequencies, for the replacement and renewal of the components. It will contain the records of equipment changes and procedural alterations It will have records of equipment and filters and recertification data. In short, it will be the main reference file for the entire water production and purification system. As such, it will be used for internal research purposes and will form the basis for external regulatory reviews [8]

2. Validation Steps:

A sequence of steps is involved in the validation of the pharmaceutical water system. Traditionally these steps are identified as

1. Design Qualification (DQ)
2. Installation Qualification (IQ)
3. Operational Qualification (OQ)
4. Performance Qualification (PQ)

The final validated condition is a total of the proceeding qualification. It is necessary that the efficacy and proof of the tests trials and experiments be performed successfully at least three consecutive times to constitute positive conformation satisfactory to the FDA validation requirement.[9]

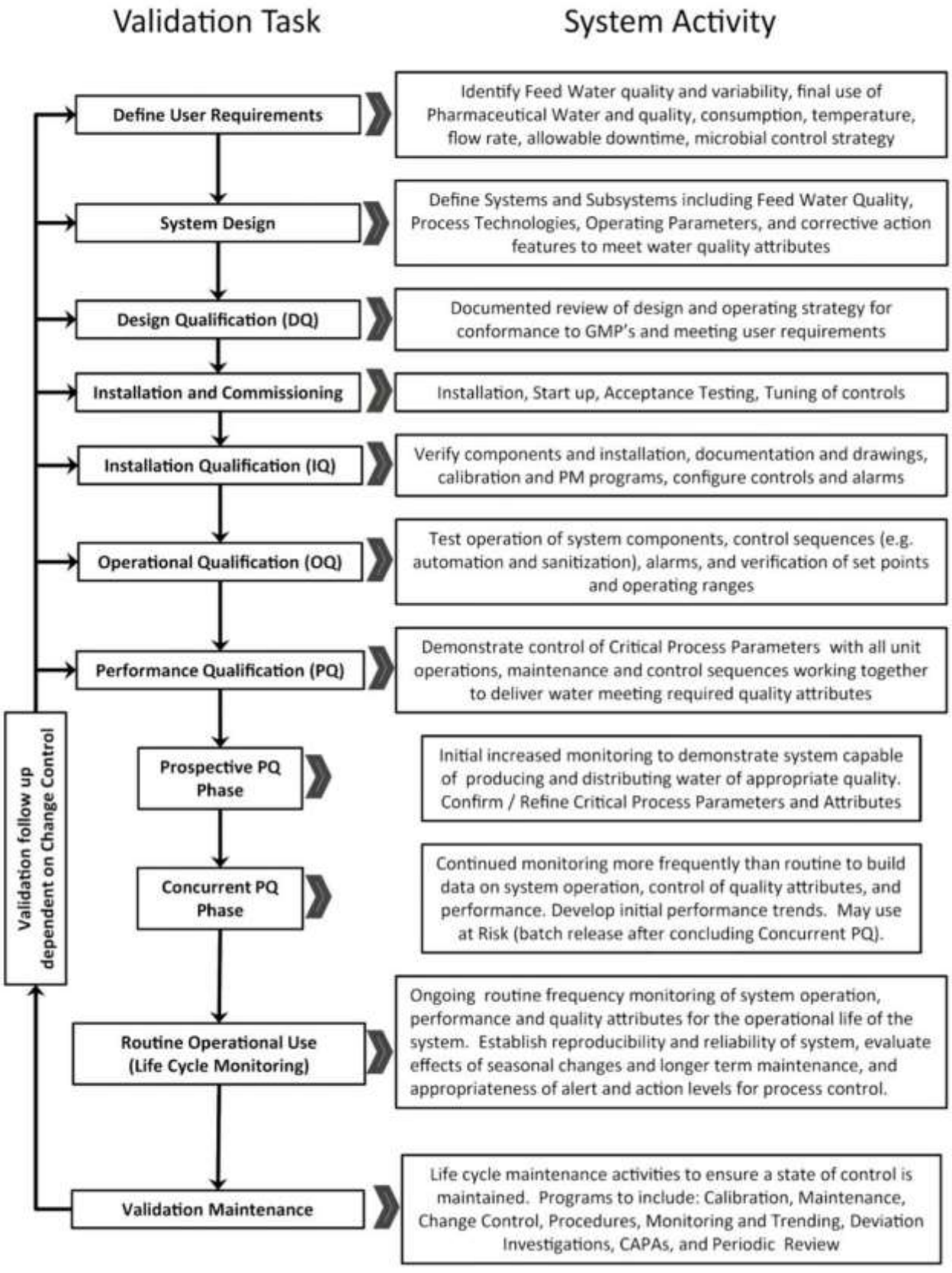

Fig.1-Water system validation lifecycle [16]

User requirement specification

The user requirements for the water system should identify the design, operation, maintenance, and quality elements needed to produce the desired water type from the available source water, including its anticipated attribute variability. The essential elements of quality need to be built in at this stage and any GMP risks mitigated to an acceptable level.

Design Qualification

Based on the URS, supplier designs the equipment. This is 1st step in the qualification of new water supply systems. Define process schematically by use of PFD and P&IDs.

It is documented the design of the system & will include:

- Functional Specification. (Storage, purification, etc)
- Technical/Performance specification for equipment. (Requirements of water flow, pipe size)
- Various components of Water system need to validate.[10],[11]

Table 5- Components of Water generation system

Components	Desired Function
Piping	Selected material: stainless steel; should be designed for reliability, pressure control, nullifying presence of extractable contaminants.
Holding Tanks	Optimal size/capacity: 2000-4000 gallons, Hydrophobic air filters- restrict entrance of microbes in tanks.
Valves	Generally used types: Gate, Ball, Butterfly and Diaphragm
Filters	Removes undissolved solids and bacterial contaminants Control measures: Pressure and flow monitoring, backwashing, sanitizing and replacing the filter media etc.
Deionizers and Reverse Osmosis	Removes dissolved solids, resins must be periodically regenerated.
Carbon Beds	Removes organic chlorine compounds and low molecular weight carbon compounds, required design features: selection of proper particle size, avoidance of hydraulic channeling etc.
UV lights	Biocidal wavelength: 254 nm; UV dose variables: lamp intensity, residence time distribution and water transmittance should be properly measured.
Distillation still	Deactivates bacterial endotoxins and removes dissolved solids not otherwise removed by RO units and deionizers.

Installation Qualification

In this a careful check is made to ensure that each piece of equipment ordered has been received and is

according to system design.

IQ involves the following activities: -

1) Review of P & ID
2) Verification of material of construction
3) Welding inspection: - All welds join in the system should be checked for following parameters.

- Pin holes must absent
- Thermal cracking must be absent
- Welded tubing section must be aligned properly

4) Inspection for dead legs
5) Verification of steel passivation: - A layer of nonreactive material is applied over stainless steel for preventing its oxidation.
6) Pressure test: - Hydrostatic test are performed to check leaks. [12]

Operational Qualification

After successful installation qualification, a report is prepared. The second step is operational qualification, which is carried out to ensure that the system meets the requirements as specified in system designing.

Documented procedure is developed for the maintenance adjustment and control of the equipment involve. Limits should be specified with in which the plant will operate e.g., conductivity limit, water velocity

Regular tests are carried out such as: -

Water Velocity Test: - This test is conducted to check the quantity of water at the point with all other outlets in usage at rated flow. The flow velocity should not be less than 1.5 m/sec.

Reynolds Number Determination: - The Reynolds number measures the turbulence of water flowing in the distribution pipelines. If the Reynolds number is above 2000, the water has turbulent flow. If the Reynolds number is below 2000, the water may have laminar flow, which may lead to biofilm development.

Pre validation requirements

Before validation of system begins few things must be available by IQ and OQ.

1) IQ documentation must include description of system along with a drawing.
2) The print should show all equipment in the system from feed water to point of use.
3) It must show all sampling points.
4) The print should be compared annually to the actual system to ensure its accuracy and to detect on reported changes. [13]

Performance Qualification

In the Who Technical Report series 937, three phase approach has been recommended

Phase 1- During this phase a test period of 2 to 4 weeks should be spent monitoring the system.

Activities done during this phase

1. Sampling of incoming feed water daily to verify its quality.
2. Sampling after each step in the purification process should be done daily.
3. Sampling at each point of use.
4. During this phase operation parameters, cleaning and sanitizing procedures are developed.

5. Testing of water for chemical and microorganism is done.
6. At the end of 2 to 4 weeks, the firms should have developed the SOPs for operation of water system

Phase 2

After completion of phase 1 the further period of 2 to 4 weeks should be spent on monitoring on water system. The second phase of the system validation is to demonstrate that the system will consistently produce the desired water quality when operated in accordance with the SOPs. The sampling is performed as in the initial phase and for the same time. At the end of this phase, the data should demonstrate that the system will consistently produce the desired quality of water.

Water can be used for manufacturing purpose during this phase.

Phase 3

It usually runs for one year after successful completion of phase 2

Water can be used for manufacturing purposes during this phase. This phase has following objectives

1. To demonstrate the reliable performances in long run.
2. To evaluate seasonal variation in feed water
3. To reduce sample location sample frequencies and bring them down to normal routine pattern.

Regular Monitoring should be carried out. Monitoring should include both online instrument monitoring such as flow, pressure, temp, conductivity and offline sample testing for chemical, physical and microbiological specifications. [14]

Validation Document

The last part of validation is the compilation of the data with any conclusion into the final report. The final report must be signed by the appropriate person and the QA of the water system.

Revalidation

Revalidation should only be carried out when the system or the operational parameters have undergone a significant change. The same conditions that prevailed during the initial validation will apply to routine monitoring and inspection. A specific written method that must be validated at the time of the initial validation should be used for routine maintenance or the replacement of parts.[15]

Change Control

Controlling change is necessary for the mechanical setup and state of operation. The effects of proposed changes on the overall system should be assessed. After changes are made, it should be decided whether the system needs to be requalified. Drawings, manuals, and procedures that will be impacted by a water system modification should be updated.[16]

Pharmaceutical Water Testing

To determine the suitability of water for whatever pharmaceutical application it is intended, it must be tested for the presence of contaminants including but not limited to organic carbon, electrolytic materials, and microbiological organisms.

Total Organic Carbon: Total Organic Carbon (TOC) test is a method used to measure the level of organic contaminants present in water. In the context of water system validation, TOC testing is used to ensure that the water produced by the system meets the required quality standards for its intended use.

Total organic carbon test procedure.

- **Sample Collection:** A water sample is collected from the system being tested and placed in a TOC vial. The sample should be representative of the water being used in the system and should be collected at a location that is downstream of any point-of-use treatment.
- **Sample Preparation:** The water sample is then acidified and sparged with carbon dioxide to remove inorganic carbon and to convert any remaining organic carbon to carbon dioxide.
- **TOC Analysis:** The TOC analyzer measures the total amount of carbon present in the water sample. This is typically done by using a combination of physical and chemical methods such as Ultraviolet (UV) oxidation, or high-temperature catalytic oxidation.
- **Data Analysis and Reporting**: The TOC analyzer generates a report that includes the total carbon content of the water sample. The results are compared against the established specifications for the water in question.

Water Conductivity: The procedure for conducting a water conductivity test for water system validation typically involves the following steps:

- Obtain a conductivity meter, which is a device that measures the electrical conductivity of a liquid.
- Fill a clean container with the water sample to be tested.
- Turn on the conductivity meter and ensure that it is calibrated to the correct range for the water sample.
- Immerse the conductivity meter's probes into the water sample and record the conductivity reading.
- Repeat the test multiple times to ensure accuracy and consistency of the results.
- Compare the conductivity results to the acceptable range for the specific water system to determine if the system is properly validated.
- It is important to note that the conductivity test should be performed by trained personnel and the equipment should be calibrated and maintained according to the manufacturer's instructions.

Biofilms: Biofilms test for water system validation procedure

- The procedure for conducting a biofilm test for water system validation typically involves the following steps:
- Obtain a biofilm test kit, which includes materials and instructions for growing and analyzing biofilm samples.
- Collect a water sample from the water system to be tested.
- Prepare the sample for analysis by filtering it, if necessary, and making sure it is at the correct temperature and pH.
- Follow the manufacturer's instructions to grow a biofilm from the water sample in a controlled environment.
- Analyze the biofilm for the presence and concentration of specific microorganisms or biomarkers that are indicative of a healthy or unhealthy biofilm.
- Compare the results to the acceptable range for the specific water system to determine if the system is properly validated.

It is important to note that the biofilm test should be performed by trained personnel and the equipment should be calibrated and maintained according to the manufacturer's instructions. Also, it is essential to use the proper techniques and protocols for sampling, growing, and analyzing biofilms to ensure the accuracy of the results.

Chemical analysis as per USP

1. Description: - A clear, colourless, and tasteless liquid
2. pH: - Take about 100 ml sample and add 0.5 ml of saturated KCL and read pH at 25°c on suitable calibrated pH meter.
3. Conductivity: - Take 100ml of sample in closed bottle and read the conductivity at 20°c on suitable calibrated conductivity meter.
4. Acidity or Alkalinity: - To 10ml of freshly boiled and cooled sample in a borosilicate glass flask add 0.05ml of methyl red solution. The resulting solution is not red. To 10ml of bromothymol blue solution the resulting solution is not blue
5. Ammonium: - To 20ml of sample add 1ml of alkaline potassium mercuric Iodide solution and allow to stand for 5 min. When viewed vertically the solution is less intensely colored than a solution prepared at the same time by adding 1ml of alkaline mercuric iodide solution to a solution containing 4ml of ammonia standard solution and 16 ml of ammonia free water.
6. Calcium and Magnesium: - To 10ml of sample add 2 ml of ammonia buffer pH 10 and 50 ml of mordant black mixture and 0.5 ml of 0.01M EDTA, a pure blue color is produced.
7. Chloride test: - to 10 ml of sample add 1ml of 2M Nitric acid and 0.2ml of 0.1M silver nitrate, the appearance of solution does not change for at least 15 min.
8. Sulfate: - To 10 ml of sample add 0.1 ml of 2M HCL and 0.1ml of Barium chloride. The appearance of solution does not change at least one hour.
9. Residue on evaporation: - Evaporate 100ml of sample to dryness on water bath. The residue weight not more than 1mg (0.001%).

Conclusion

It can be concluded that the water purification system is effective for eliminating organic, inorganic, and microbial contamination and since water is a universal solvent used in the pharmaceutical industries for the production, processing, and cleaning of all equipment, it must be pay special attention for its purification. The system qualification and validation must be performed over a period to demonstrate its reliability and robustness of the system to produce water of specific quality with a high degree of safety. And each of the reports must be documented for a better job.

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