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Pharmaceutical water system–validation aspects

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ABSTRACT

The aim of conducting validation is to show that the process when operated within certain limits produces the product with high degree of assurance of consistency and specified quality. To obtain water of desired quality, purity and other required specificity validation of water system is must. The validation process not only gives high quality water but it also provides a standard framework to monitor safety, efficacy and process outcome. The purpose of this discussion is an attempt to see the various aspects of validation that includes components of water treatment systems, qualification of equipment, different phases of qualification, documentation, validation, preventive maintenance, change control and post validation monitoring.

Keywords: Validation; Pharmaceutical products; Quality attributes; Water treatment systems

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INTRODUCTION

The purification of water for pharmaceutical applications is an extensive subject. The validation of its process of manufacture is managed by implementing a series of qualification steps that logically lead to its fulfillment. Since, water is one of the most regularly used raw material in pharmaceutical manufacturing, validation of its production system plays a very important role. It is directly as well as indirectly used in the manufacture of all dosage forms and for cleaning the manufacturing equipment's, and is also used as a major components which constitutes the injectable products. Pharmaceutical industry must rely on appropriate water purifying systems, allowing it to meet its pre-specified requirements. Purified water and water for injection is obtained from potable water via a typical water purification system of unit operations. United States Pharmacopoeia (USP) describes several grades of water for pharmaceutical purpose, based on various quality parameters such as microbiological assay values, presence of contaminants, conductivity and total organic carbon (TOC). Water for pharmaceutical purpose need to be constantly tested and should fulfill the well-defined quality attributes. Validation of water treatment systems is mandatory to obtain water with all the desired quality attributes. The purpose of validation is to demonstrate the capability of the water treatment system to continuously supply the required quantity of water with the specified quality attributes, along with the documented evidences. Validation provides the system owner with the means of assessing when a water treatment system is operating outside the established control parameter limits and provides a means for bringing the system back in to the state of control. [1]

Hence, this article in detail discuss the effectiveness, reproducibility and consistency of a water treatment system along with its validation aspects.

I. WATER FOR PHARMACEUTICAL INDUSTRY PURPOSES[2]

Water is one of the most commonly used substances, vehicle, raw materials, or an ingredient in the production, formulation, and processing of pharmaceuticals and also in the cleaning of manufacturing equipment's.

Control of the inorganic, organic impurities and microbiological quality of water is important because propagation of micro-organism is ubiquitous in water and it may occur during the, distribution, refinement and storage of water. Major differences among these grades of water consist of the following quality attributes:

- Microbial counts
- Endotoxin, which is due to the presence of microbes
- Organic and inorganic impurities

The USP identifies several grades of water that are acceptable for use in pharmaceuticals, and also defines the quality attributes for the manufacturing of pharmaceuticals according to its criticality as:

- Potable water
- Purified water
- Water for injection
- Sterile water for injection
- Sterile water for inhalation
- Sterile water for irrigation
- Sterile bacteriostatic water for injection

"Water for injection (WFI) is the most purified water, and careful attention should be paid to the validation of its manufacturing process.

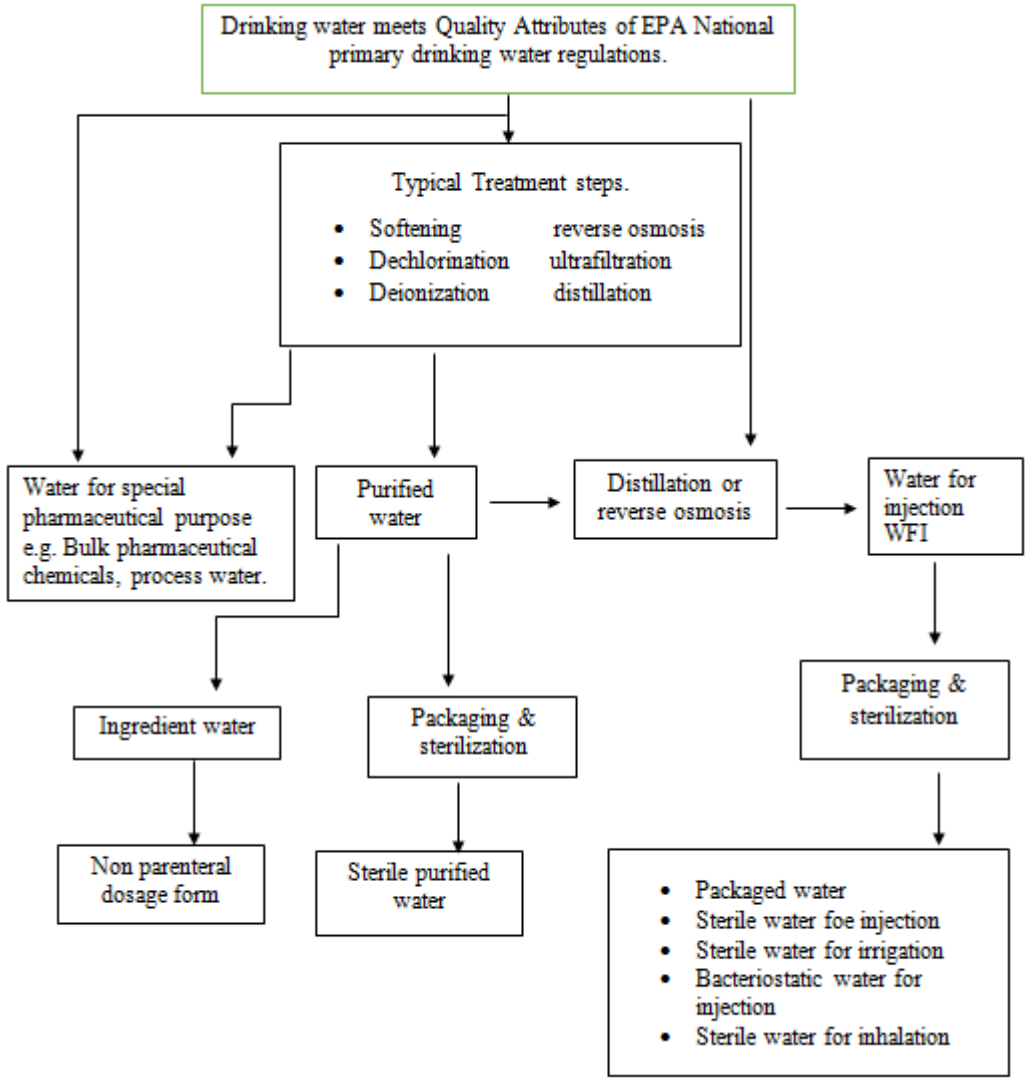

Figure 1: Selection of water for pharmaceutical industry purposes

The quality characteristics of water for a specific application are dictated by the requirement of its usage.

Serial steps that are used for treating water for different pharmaceutical purposes are shown in above figure.

II. VALIDATION AND ITS APPROACHES[3]

An eloquent but very serviceable definition was given in the FDA Guidelines on Sterile Drug Products by Aseptic Processing (1987). It is a documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes".[4]

In essence, validation seeks experimentally obtained answers to: Does the process or device do what it is intended to do? If so, for how long does it do it? For water systems, defines validation as ensuring that the particular system will consistently produce water of predictable quality when operated in the prescribed manner.

In common words validation involves proving

- Engineering design
- Operating procedures and acceptable ranges for control parameters
- Maintenance procedures

To achieve this, the system must be sensibly designed, installed, and tested during and after construction, and therefore for a prolonged period of time under all conditions.

There are two main basic approaches to validation:

i. Depending on evidence obtained through testing: Prospective and Concurrent validation
ii. Depending on the analysis of accumulated (historical) data: Retrospective validation

III. VALIDATION PLAN

This document is not a requirement of the FDA, but it has become almost an industry standard.

The validation plan should contain all the information relevant to the water purification system. Which is a repository for the basic design information, drawings, specifications, procedures and protocols. It will state the reasons for equipment selection, for cleaning and sanitization frequencies, for component replacements and renewals. It will contain the records for equipment modification and of procedural alterations. It will have the equipment and filter logs and any recertification data. In short, it will constitute the major reference file for the entire water production and purification system. As such, it will serve internal investigatory purposes and forms the basis for outside regulatory reviews.

The validation plan is used to set the limits for the validation, to define the scope of the project and the systems included and not included in the qualifications, and what the project is about to prove. For example, if the project includes the use of deionized water to feed a clean-steam generator, the validation plan would define which components would be involved in the preparation of such a water; what general quality attributes each purification unit would be expected to achieve; and the length of time the system will undergo sampling at what frequency. Issues involving choices should be addressed in the validation plan, including the reasons for the choices. It must be made apparent why the selected decisions are appropriate. The validation plan must be consistent with the company QC policies, and should be included in the SOPs.

Such a validation plan will be much appreciated while reviewing the validation at a later date, such as in response to an out-of-tolerance condition, in a quality audit setting, or when performing a revalidation

IV. VALIDATION STEPS[5]

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

- Design Qualification (DQ)
- Installation Qualification (IQ)
- Operational Qualification (OQ)
- Performance Qualification (PQ)

The final validated condition is a sum 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.

Validation sequence

1. Equipment design [6,7]

It is derived from the requirements of the water purification process. With a water system, this generally means that the quality of the water will minimally meet either US pharmacopeia (USP) Purified Water or Water- for injection specification, depending on its usage. It is the design documents that set the standards and goals of the hardware.

The Design Qualification will list the activities necessary to the consistent production of the stipulated grade of water. It will contain a full description of the system specifying its acceptable operating ranges and limits. It will supply full schematics of the electrical, mechanical, and water flows for subsequent verification of their proper installation. It will identify the specific purification units, the various control devices, and the safety and alarm systems, which will specify sampling plans and ports for chemical and microbial testing, stipulate sanitizing methods, and define procedures for the analysis and plotting of data. DQ is prepared according to the URS (Users Requirement Specifications) and pharmacopoeial standards.

The various components of water generation systems that need to be validated include the following:

Table 1: Components of water generation systems

Component	Desired features/functions
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.
Ozone and Heat Sterilants	Strong oxidizing agent, effective at low concentration. Both are used as biocidal.

Table 2: Numerical Interpretation of USP Standards

Component	Purified water	Water-for-injection
Ph	5.0–7.0	5.0–7.0
Chloride (mg/L)	0.2	0.2
Sulfate (mg/L)	1.0	1.0
Ammonia (mg/L)	0.1	0.1
Calcium (mg/L)	1.0	1.0
Carbon dioxide (mg/L)	5.0	5.0
Heavy metals (mg/L)	0.1 as Cu	0.1 as Cu
Oxidizable substances	Pass USP Permanganate test	_
Total solids (mg/L)	10.0	10.0
Pyrogens (EU/mL by limulus amebocyte lysate)	_	0.25

2. Installation Qualification[8]

The IQ protocol will consist of a system description followed by a standard operation procedure section. Before the operational characteristics of the system can be investigated, the proper installation and assembly of the various components of equipment require verification. This follows a careful check that each piece of equipment ordered and received is identical with that stipulated in the system design. The installation qualification confirms the "as-built" drawings, and ensures the suitability of the complete system.

As stated in the FDA guidelines –"This phase of validation includes examination of equipment design; determination of calibrations, maintenance, and adjustment requirements; and identifying critical features that could affect the process and product. Information obtained from these studies should be used to establish written procedures covering equipment calibration, maintenance, monitoring, and control."

For an IQ of water generation system, the following would typical key elements. Utilities requiring verifications includes, compressed air, steam, feed water and electricity. Each elements should be checked at the time of installation of equipment for water generation systems.

Calibration of all process controlling instruments according to written procedures and certification that they meet the specified tolerance limits for accuracy, precision, and also in terms of selectivity or specificity should be performed and documented. Documentation on system design specifications including materials data and calibration certificates.

3. Operational qualification [9]

When installation of the equipment assemblage has been verified as being correct, it becomes possible to undertake the OQ documentation of the system. The purpose of OQ is to establish, a documented evidence through system testing, that all critical components are capable of operating within established limits and tolerances. It is the functional testing of system components mainly the critical components. The purpose of OQ is also to verify and document that the water generation system provides acceptable operational control under "at-rest" conditions.

Operation Qualification checks the ability of water purification system to provide water of sufficient quantity along with high degree of quality to ensure the achievement of specifications, to maintain general parameters like pressure, temperature, flow at set points, to maintain any critical parameters (pH, TOC, endotoxin, microbial level, conductivity etc.) ,includes the tests that have been developed from knowledge of processes, equipment system, and tests include a condition or a set of conditions with lower operating limits, sometimes referred to as `worst case' conditions.

4. Performance qualification [10]

The purpose of the PQ protocol is to provide a rigorous testing to demonstrate the reproducibility and effectiveness of the total integrated system. The system's set points, control sequences, and operating parameters are probed. The process is challenged repeatedly to prove its consistent performance. All the acceptance criteria are to be met under "worst-case" process conditions. When failures occur they should be identified and corrected. Tests should be re-run to vouch for the elimination of the causes of failure. Consistency of acceptable product water quality is sought.

The purpose of PQ is to verify, prove and document that water generation system provides acceptable control under `Full Operational' conditions. PQ should follow successful completion of IQ and OQ.

According to the FDA's advice: "The observed variability of the equipment between and within runs can be used as a basis for determining the total number of trials selected for the subsequent PQ studies of the process." PQ is used to demonstrate consistent achievement of critical parameters over time (such as pH, TOC, conductivity).PQ and OQ tests are sometimes performed in conjunction with one another.

Qualification phases [11]: Three phase approach recommended according to WHO Technical Report Series 929 to prove heftiness and reliability.

i. **Phase I:** This requires a testing period of 2 - 4 weeks for monitoring enactment deviation. Periodic sampling along with testing at predetermined assay tests are performed on the samples as per the defined plan. This phase also involves the development of appropriate operating ranges along with the completion of cleaning, sanitizing and maintenance procedures. At the end of this phase, systems are simulated to perform under stress conditions such as start-up after power failure or emergency halts. The system is also tested under standard maintenance restorations, filter changes, etc.

ii. **Phase II:** This phase involves the same sampling scheme as in phase I. It should include further monitoring of the system for a test period of 2 - 4 weeks. After the completion of the phase I, all the refined SOPs are deployed. During this phase water is utilized for manufacturing purpose. This step establishes that the system is under control, within predetermined specifications. Testing at this phase also ensures consistent production and delivery of water of required quantity with high degree of quality when the system is operated in accordance with SOPs.

iii. **Phase III:** This is a confirmatory step in which frequency and number of sampling locations are less than the previous phases and proves that the system exhibits prolonged reliable performance and is under control over an extended period of time. It requires a duration of around one year after the satisfactory end of phase II. During this phase, water can be used for manufacturing purpose. Periodic deviations of the feed water are also examined in this phase. This final phase should be commenced only after satisfying the requirements mentioned in the protocols for phase I and II test. In this phase, a complete microbiological and chemical analysis must be done and results should be presented graphically using various computer applications. A written, reviewed and approved complete validation report should be prepared according to the firm procedures. Validation project is considered only after the approval of final reports by appropriate authorities.

5. Preventive maintenance [11]

This element is frequently considered to be the responsibility of the Site Maintenance and Operations department and often is given a low priority within an engineering design team. There is a clear requirement to keep a facility in a state of qualification. A preventative maintenance program is an essential component of a schedule of work to achieve this objective. The Validation Master Plan must identify the need for this program and, hence to flag its importance to the designers. The role of vendors and suppliers is very important in this area. Operation and maintenance manuals should be considered as a key part of the specification program. This activity should be conducted during the design phase, and the documentation required should be included in the requisition. The execution of a preventive maintenance program can take on greater relevance within the pre commissioning and commissioning phases demonstrating that, once qualified, a unit has been maintained both in a proper manner and in accordance with the supplier's instructions.

6. Change control [11]

A smoothly operating water system may undergo departures for reasons other than alterations in its water supply. These are to be explained, defined, and documented appropriately. Given water purification units such as ion-exchange beds may become exhausted, RO membranes will require cleaning, tanks and pipes may need re-sanitization, and so on. In general, the devices and accoutrements constituting the system will periodically require such maintenance-related activities as replenishment, refurbishing, cleaning, sanitization, replacement, and renewal of different kinds. Furthermore, the various items will require attention on different time schedules. The necessary system documentation will, therefore, also include a body of information relating to the proper maintenance of each piece of equipment. Much of this will be initially forthcoming from the equipment suppliers and may, indeed, constitute stipulations connected with their guarantees of equipment performance. The relevant documentation composes the standard maintenance procedures necessary to the system’s correct handling.

V. REVALIDATION [12]

Revalidation and evaluation should be executed depending upon the impact of the change on the water generation system. Routine monitoring and examination will continue under the same condition as those that existed during the original validation. Routine maintenance or replacement of parts should provide a specific written procedure, which must be validated at the time of initial validation.

CONCLUSION

It can be concluded that the water purification system is efficient in removing organic, inorganic and microbial contamination, and since water is a universal solvent used in the pharmaceutical manufacturing industries for the production, processing and cleaning of all equipment’s a very keen attention should be given for its purification. Qualification and validation of the system should be performed over a period of time so as to prove its reliability and robustness of the system for producing water of specified quality with a high degree of assurance. And each and every reports should be documented for better work.

REFERENCES

[1] Hultqvist A. Practical guidelines for qualifying purified water systems. *Pharm Technol Europe* **2007**; 19(12). Available form: http://www.ptemag.com/pharm techeurope/Validation/Article Standard/Article/de tail/480191. Accessed on **24May2009**.

[2] P M A Deionized Water Committee *Pharm Technol.* **1985**; 9(11): 50-56.

[3] Johnson W M, Berry I R, Nash R A. Validation of water systems for sterile and non-sterile products. Pharmaceutical Process Validation. Marcel Dekker Inc, NewYork.**1993**; 2:299-317.

[4] Food and Drug Administration, Guideline on general principles of process validation. FDA, Rockville, MD 1984.

[5] Swarbrick J, Boylan J C, Nash R A. Validation of pharmaceutical processes. Marcel Dekker, New York. **2002**; 2:2917-2931

[6] Tunner J, Katsoulis G, Denoncourt J, Murphy S. *Pharm Engg*, **2006**; 26(4):1-8.

[7] Gupta R M, Vishweshwar S, Bhingare C L, Trivedi N. Design qualifications for water purification system. Express Pharma Pulse2002. http://www.expresspharmaonlin e.com/**20020704**/technology1.shtml. Accessed on 29th May **2009**.

[8] Guide to inspections of high purity water systems (US FDA, **1993**). Available from: http://www.bcg-usa.com/regulatory/docs/1993/FDA199307E.pdf. Accessed: **2nd June2009**.

[9] Dvorak B I, Skipton S O. Drinking water treatment: Distillation. **2008**. Available from: http://www.ianrpubs.unl.edu/epublic/live/g1493/build/g1493.pdf. Accessed on 25th May **2009**.

[10] Nebel C, Nebel T. *Pharm Manuf* **1984**; 4(2):16-23.

[11] Agalloco J, Carleton FJ. Validation of pharmaceutical processes. Informa health care, New York. **2007**; 3:703-

709.
[12] Raghunandanan R. *Pharma Times* **2009**; 41 (4):15-18.