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Validation: A need for water purification system for pharmaceutical products

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Abstract

The key feature of the validation is to illustrate that a validated process, when operated within established range forms consistently a quality product of specified quality with highest degree of assurance. In the last few years, there has been an intensive focus on validation methodologies in the pharmaceutical industry. Its real importance within a productive process is recognized in relation to a product's quality attributes such as purity, safety and effectiveness. This article is intended to discuss the effectiveness, consistency and reproducibility of a water treatment system along with its validation aspects. This article is an attempt to discuss the various aspects of validation along with its approaches

Key-Words: Validation, Water, Purification procedure

Introduction

Water is essential for industrial, pharmaceutical and hospital purposes, in the preparation and preparation of medicines and other health products and also for cleaning and hygiene purposes. Ideally there is no pure water in nature, as it can contain up to 90 possible unacceptable contaminants. Every industrial or pharmaceutical organization which is related to health products must rely on appropriate water purification systems, thus allowing it to meet its particular requirements, especially as to that of problems which are related to storage and internal distribution. Purified water is obtained from drinking water through a typical water purification system of unit operations [1]. It is an essential ingredient of various pharmaceutical preparations and thus is also used to clean various process equipment and hence, plays a viatl role in pharmaceutical processing's [2]. United States Pharmacopoeia (USP) describes several grades of this raw material (i.e., water), based on various quality parameters such as conductivity, total organic carbon (TOC), microbiological values, and presence of contaminants including endotoxins, nitrates and heavy metals. Water testing must be continuous process and it should comply with well defined quality attributes [3].

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Basically Validation means establishing documented evidence that provides a high degree of assurance that a specific process will consistently produce a product which meets its pre-determined specifications and quality attributes. A properly designed water purification system will provide a high degree of assurance that every single step, process, and change has been properly checked before its implementation occurs. Validation of water purification systems is mandatory to obtain water with all the desired quality characteristics [4]. Pharmaceutical water production, storage and conveyance system should be validated because end-product testing alone is not a sufficient evidence to confirm with a high degree of assurance that the system operates as it is required to do so. In order to cater for the ever escalating quality needs of the pharmaceutical industry, water treatment systems, which are highly dynamic in nature, must be validated, closely monitored and controlled. This article is intended to discuss he effectiveness, consistency and reproducibility of a water treatment system along with its validation aspects.

Validation requirements

1. To reduce the batch variation
2. To obtain a good, efficient & pure product of high strength.

Validation

Validation generally involves and is associated with quality assurance associated with a particular product or process intended .These is designed in such a way

that the process ensures total quality of the product at last. To establish this objective there is a need for comprehensive documentation with all necessary information, guidelines and proof. Therefore Validation can be categorized as:

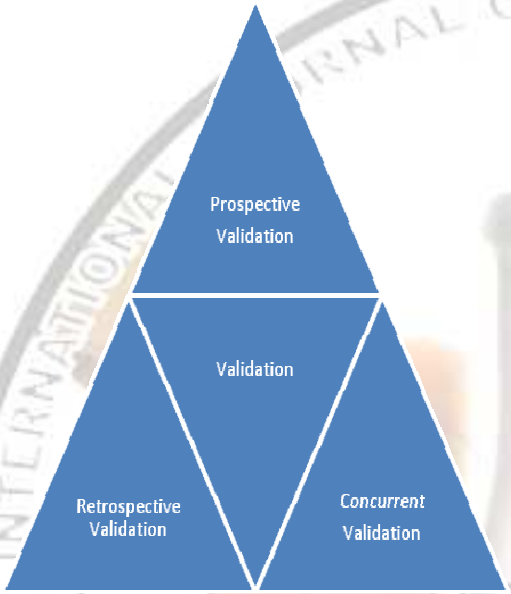

Fig. 1: Types of Validation

Prospective validation

Prospective validation is carried out before a new product is released for distribution or, wherever the revisions may affect the product's characteristics before a product made under a revised manufacturing process is released for distribution.

Concurrent validation

Concurrent validation is a substantial part of prospective validation and is carried out with the purpose of ultimately distributing product which is manufactured during the period of validation study. Concurrent validation is feasible when nondestructive testing is sufficient to verify that products meet predetermined specifications and quality attributes. If concurrent validation is being conducted as the initial validation of a new process or a process which has been modified, product should be removed from distribution until all data and results of the validation study have been reviewed properly, and thus it has been confirmed that the process has been sufficiently validated. Concurrent validation may be carried out on a previously validated process to confirm that the process is validated or not. If there have been no changes to the process and no indications that the process is not operating in a state of control, the product could be released for distribution in the market before revalidation of the process is carried out completed.

Retrospective validation

It involves the validation of a process which is based on gathered historical data of production, testing, control, and other information for a product which is already in a state production and distribution. This type of validation uses of collected data and information which may be found in batch records, production log books, lot records, control charts, test and inspection results, customer complaints or lack of complaints, field failure reports, service reports, and audit reports. Historical data must contain enough information to provide an in-depth picture of how the process has been operating and whether the product has consistently met its specifications. Retrospective validation may not be feasible if all the appropriate data was not collected, or appropriate data was not collected in a manner which allows adequate analysis.

Design

A design consideration generally includes general information regarding various parts of water purification systems. The systems should be constructed using modular, off-the-shelf purification components for a cost effective and maximum validation efficiency, which ultimately correlates with pharmacopoeial requirements [4]. These considerations should be designed properly so as to prevent microbial growth and also materials for construction should be selected carefully. The various parts of water purification systems which should be validated should include the following components:

Piping

Generally stainless steel is the choice for the piping system in water purification system. Stainless steel is used due to its noncorrosive characteristic. It can also be deployed over a wide range of temperatures. Plastic piping systems such as polypropylene and polyvinylidene fluoride are frequently used now days, especially in certain biotechnological based applications. Glass or polycarbonate resins are very handy when transparency is required. All pipe joints should either utilize sanitary fittings or it should be butt-welded. Piping systems should comply with frequent sanitization, thermal cycling and must be specified for easy draining of water. They should be designed for reliability, pressure control, and avoidance of extractable contaminants which may affect purity of water [8-10].

Holding tanks

Generally stainless steel is the best choice for the tank required to hold water in water purification system. Storage tanks may vary in size, depending on

requirement; however, 7500 - 15000 liters holding tanks are commonly used. Suitable insulation is required to store the water at high temperature which conserves energy as well. Storage tanks should be provided with a vent to manage the fluctuations in water levels, and thus prevent any possibility of collapse. Vents should be fitted with a hydrophobic air filter to prevent microbial contamination from outside air. Vent filter must be located in a position on the holding tank from where it is readily accessible [11, 12].

Valves

Valves are used to control the flow of water in the water purification system. Various types of valves that are used are as follows:

Gate valves

Gate valves are the most consistently used in industrial piping for purification of water. That's because most valves are required to act as stop valves which either works as fully shut off or fully turn on flow. This is only the reason why gate valves are recommended. Gate valves are employed when a straight-line flow of fluid and minimum restriction is required. The gate is wedge shaped. When the valve is wide open, the gate is fully drawn up into the valve, leaving an opening for flow through the valve the same size as the pipe in which the valve is installed. Therefore, there is little pressure drop or flow restriction through the valve.

Ball valve

A ball valve is a valve with a spherical disc, the part of the valve which controls the flow .The sphere has a hole, or port, through the middle so that when the port is in line with both ends of the valve, flow will occur. When the valve is closed, the hole is perpendicular to the ends of the valve, and thus flow is blocked. The handle or lever is in line with the port position letting to see the valve's position. The ball valve is an integral part of the family of quarter turn valves. Ball valves are very durable and generally perform to achieve perfect shutoff even after years of its disuse. They are therefore an excellent choice for shutoff applications. These valves do not offer the fine control that may be necessary in throttling applications but are sometimes used for this purpose only. Ball valves are used extensively in industrial applications because they are very versatile, supporting pressures up to 1000 bars and temperatures up to 482°F (250°C). Sizes typically range from 0.2 to 11.81 inches (0.5 cm to 30 cm). They are easy to repair and operate. The body of ball valves may be made of metal, plastic or metal with a ceramic center. The ball is often chrome plated to make it more durable

Butter fly valve

A butterfly valve is a valve which can be used for isolating or regulating flow. The closing mechanism takes the form of a disk. Operation is similar to that of a ball valve, which allows for quick shut off. Butterfly valves are generally favored because these are cheaper in cost to other valve designs as well as being lighter in weight, meaning less support is required. The disc is positioned in the center of the pipe, passing through the disc is a rod connected to an actuator on the outside of the valve. Rotating the actuator turns the disc either parallel or perpendicular to the flow. Unlike a ball valve, the disc is always present within the flow; therefore a pressure drop is always induced in the flow, regardless of valve position. A butterfly valve is from a family of valves called quarter-turn valves. The butterfly valve is a metal disc mounted on a rod. When the valve is closed, the disc is turned so that it completely blocks off the passageway. When the valve is fully open, the disc is rotated a quarter turn so that it allows an almost unrestricted passage of the fluid. The valve may also be opened incrementally to throttle flow

Diaphagram valve

Diaphragm valves are used on shut-off and throttling service for liquids, slurries and gas. The seal is achieved by a flexible membrane which is usually a elastomer, and possibly attached with a metal part. The membrane is fitted by the effect of a stem or compressor with lineal movement until contact is made against the seal of the body. The operating parts of the diaphragm valve are protected from the flow. This property makes this valve suitable for various viscous liquid and also hazardous, abrasive and corrosive flows as it's due to inherent property of its sealing system which avoids any cross contamination. Diaphragm valves are available in a wide variety of metals, solid plastics, plastic, rubber and glass linings. They are well equipped to the handling of multiple chemical applications both clear fluids as well as the slurries. The diaphragm valve has an extended use for applications at low pressures and slurry fluid where most other kinds of valves corrode or become obstructed. It is a quick opening valve. There are two types of diaphragm valves:

• **Weir**: The Weir Diaphragm valve can be used for either off/on or throttling services

• **Straightway**: named also straight-Thru is only used for on/off services

Filters

Filters are used at employed at various sites of water purification systems for the purpose of removing of undissolved solids and bacterial contaminants.

Granular or cartridge filters are used preferably for pre-filtration. Filters which are used commonly used downstream from carbon beds should have 11 - 50 µ pore size while membrane filters which are used to remove bacteria should have a pore size of 0.2 µ. Various control measures for the filter includes pressure and low flow monitoring, back washing and replacing filter media. For consistently maintaining the efficiency of water treatment systems and avoiding any sort of endotoxins contamination or bacterial growth filters must be maintained regularly. [9].

Deionizers

Deionization is a method often used by various laboratories to produce purified water on-demand and is able to purify water to a maximum resistivity of 18.2 megohm/cm at 25 ºc. A deionization assembly usually consists of one to four cylindrical cartridges hooked up for plumbing and hanging on a wall near a sink. While it doesn't produce absolutely pure water, it is convenient and quick, and may be sufficient for many applications. It is an excellent system for removing dissolved solids and gases, although it shows very ofently poor rating for other impurities. It mechanism works by exchanging hydrogen ions for cationic and hydroxyl ions for anionic contaminants in the feed water. The deionization resins are tiny spherical plastic beads through which the feed water is passed. After a while the when all the impurities replaces all of the hydrogen and hydroxyl groups in the resin, and thus it has to be replaced or regenerated.

Reverse osmosis (RO Units)

Reverse osmosis system includes an additional integrated pretreatment cartridge pack with activated carbon, a 0.5µ prefilter, and a calcium hardness sequestering compound. Sequestering agent is a solid, long chain polyphosphate that weakly binds calcium ions and minimizes calcium carbonate precipitation. Combination of pretreatment protects the RO membrane from damage due to fouling from particulates, chlorine oxidation and formation of mineral scale on membrane surface. Periodic chemical sanitization treatments should be carried out on RO units so as to keep a control on bacterial growth [7, 11].

Ultra Violet light

Ultraviolet water purification lamps produce UV-C or "germicidal UV," a radiation of much greater intensity than normal sunlight. All of UV lamp's output is concentrated in the 254 nanometers (nm) region in order to take full advantage of the germicidal properties of this wavelength. Most ultraviolet purification systems are combined with various forms of filtration, as UV light is capable of killing microorganisms such as bacteria, viruses, molds, algae, yeast, and oocysts like cryptosporidium and giardia. UV light generally has no impact on chlorine, heavy metals, and other chemical contaminants. UV water treatment offers many advantages over other forms of water treatment for microbiological contaminants. Most importantly, it does not introduce any chemicals to the water, it produces no bi-products, and it does not alter the taste, pH, or other properties of the water. Accordingly, in addition to producing safe drinking water, it is not harmful to your plumbing and septic system. Further, it is easy and cost-effective to install and maintain without any special training

Ozone

Ozone is a very strong oxidizing agent with powerful disinfecting properties and can be easily removed from water by exposure to UV light. It is an effective bactericidal, veridical, fungicidal as well as sporicidal agent in water treatment systems. It directly attacks the outer surfaces of microorganism and destroys their cell walls and membranes. In contrast to other oxidants and disinfectants, the use of ozone results in far fewer toxic disinfection byproducts. Its production rate can be controlled by process parameters in order to avoid incorrect dosing and to ensure optimized efficiency. More commonly, heat is also used to control microbial growth in water treatment systems. While circulating through distribution loops, treated water is heated to 80 ºC in the storage tanks.

Equipment validation

Validation of water treatment systems follows the same protocol as does the validation of other pharmaceutical manufacturing equipment. It is necessary that the system should be checked regularly and certified as properly installed, equipped and properly functioning as per its design [11, 17]. Equipment validation has the following steps: The typical three-stage qualification protocol is followed, starting with the Installation Qualification (IQ), Operational Qualification (OQ), Performance Qualification (PQ).

Installation qualification

The IQ step consists of calibrating the instrument, inspections to confirm that the drawings accurately confirms the as-built configuration of the water system, and where necessary, special tests are performed to verify that the installation meets the design requirements [4] . The vendor-provides IQ protocol package for each of the individual primary components which were used to provide verification of the hydraulic and various electrical connections as well as the system drawings. An internal generated IQ protocol collected the details of all reference documentation, instrument and utilities verifications, spare parts verification, and drawing verification for the entire

system. For an effective IQ of water treatment system, the following key elements should be taken into consideration: [11]

- Utilities requiring verifications includes electricity, compressed air, steam and feed water. Each should be checked properly at the time of installation of equipment for water purification 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.
- Verify documentation on system design specifications including materials data and calibration certificates.

Operational qualification (OQ)

OQ protocol was used to test the primary components to prove that they were operating according to the design specifications. "A validation master plan for a water system typically includes an OQ stage consisting of tests and inspections to verify that the equipment, system alerts, and controls are operating reliably4 .This included testing of the equipment's controls and operation with both liquid path hydraulic and electronic tests. Specific testing of the system operating alerts was performed by challenges the system by exceeding the system limits using a calibrated instrument from the manufacturer. The internally generated OQ protocol covered the overall system OQ, which verified system operation including the distribution loop (point of use pressures, temperatures, and flow rates), water system generation, storage system operation, and alarms. [11]:

Performance qualification (PQ)

The Performance Qualification (PQ) was to demonstrate that the system produced and maintained re-circulating water that meets the compendial requirements of USP purified water over a suitable time period. The qualification period was chosen to strike a balance between time and testing burden, the need to demonstrate a robust system (reliability), as well as the knowledge that the system was intended and would continue to be monitored after completion of the qualification testing. After considering these requirements, a ten-week qualification period was approved.

Conclusion

Water treatment systems must be operated within regulatory guidelines as with pharmaceutical production facilities. To validate these systems, there must be documented evidence that the system is operating consistently and according to the desired specifications. Validation is a tool for total quality management and it is necessary for process optimization, safety, efficacy and assurance of quality. Such validation protocols also fulfill regulatory requirements and provide good business sense. Successful accomplishment of validation is ensured by various testing phases. Usually, a three-phase testing approach is recommended over an extended period to prove reliability and robustness of the system for producing water of specified quality with a high degree of assurance.

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