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REVIEW ARTICLE

Validation of Purified Water System with Risk Based Approach- A Review

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ABSTRACT

Water is essential for industrial, pharmaceutical and hospital purposes, in the preparation and processing of medicines and other health products and for cleaning and hygiene purposes. Water purification systems must be validated to insure that the specified quality of water is consistently produced for use of all purpose as well as formulation, production, analysis, drinking cleaning and to solve the problems arising in the purification system. Validations of water purification system are performed in three phases by applying various chemical and microbiological tests. Risk assessment is required for every process, equipments, production, etc., in pharmaceutical industry. The aim of the risk assessment process is to remove hazards or reduce the level of its risk by adding Precautions or control measures. Risk assessments are very important as they form on integral part of a good occupational health and safety management plan. They help to create awareness of hazards and risks, Prevent injuries and illnesses when done at the design or planning stage. Qualification plays an important role in validation of purified water system. There are Installation, Operational, and Performance Qualification protocol of purified water storage and distribution system. The FMEA (Failure Mode Effects Analysis) tool complies with the cGMP aspects and meets the regulatory requirements. By this FMEA we can mitigate the risk and controls the probable failure moods of any new facility, equipment or system. So the deliverable capacity can be maintained consistently without any complains and system will work for longer period without any failure moods as per its pre defined specification or regulatory requirements.

KEYWORDS

Purified Water System, Validation, Qualification with Risk Based Approach, Commissioning, Risk Assessments, Failure Mode Effects Analysis Bilayer

INTRODUCTION

Water is the most widely used substance, raw material or starting material in the production, processing and formulation of pharmaceutical products. It has unique chemical properties due to its polarity and hydrogen bonds. This means it is able to dissolve, absorb, adsorb or suspend many different compounds. These include contaminants that may represent hazards in themselves or that may be able to react with intended product substances, resulting in hazards to health.

There is no pure water in nature, as it can contain up to 90 possible unacceptable contaminants. Every industrial or pharmaceutical plant related to health products must rely on appropriate water purification systems, allowing it to meet its particular requirements, especially as to the problems related to storage and internal distribution. Purified water is obtained from drinking water through a typical water purification system of unit operations. Water purification systems must be validated to insure

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that the specified quality of water is consistently produced for use of all purpose as well as formulation, production, analysis, drinking cleaning and to solve the problems arising in the purification system.[1,2]

General Principles for Pharmaceutical Water Systems

- Pharmaceutical water production, storage and distribution systems should be designed, installed, commissioned, qualified and maintained to ensure the reliable production of water of an appropriate quality. It is necessary to validate the water production process to ensure the water generated, stored and distributed is not beyond the designed capacity and meets its specifications.
- The capacity of the system should be designed to meet the average and the peak flow demand of the current operation. If necessary, depending on planned future demands, the system should be designed to permit increases in the capacity or designed to permit modification. All systems, regardless of their size and capacity, should have appropriate recirculation and turnover to assure the system is well controlled chemically and microbiologically.
- The use of the systems following initial validation (installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ)) and after any planned and unplanned maintenance or modification work should be approved by the quality assurance (QA) department using change control documentation.[3]

Water Storage and Distribution Systems

This section applies to Water Purified systems (WPU) for PW, Bulk Highly Purified Water (BHPW) and Bulk Water for Injection (BWFI). The water storage and distribution should work in conjunction with the purification plant to ensure delivery of water of consistent quality to the user points, and to ensure optimum operation of the water purification equipment.[4,5]

General Steps

- The storage and distribution system should be considered as a key part of the whole system and should be designed to be fully integrated with the water purification components of the system.
- Once water has been purified using an appropriate method it can either be used directly or, more frequently, it will be fed into a storage vessel for subsequent distribution to points of use. The following text describes the requirements for storage and distribution systems and point of use (POU).
- The storage and distribution system should be configured to prevent microbial proliferation and recontamination of the water (PW, BHPW, and BWFI) after treatment. It should be subjected to a combination of online and offline monitoring to ensure that the appropriate water specification is maintained.[4,5,6]

Validation

Validation is a process of establishing documentary evidence demonstrating that a procedure, process, or activity carried out in production or testing maintains the desired level of compliance at all stages. In pharma industry it is very important apart from final testing and compliance of product with standard that the process adapted to produce itself must assure that process will consistently produce the expected results. Validation of water purification system was performed in three phases by applying various chemical and microbiological tests.[7,14,26,29]

Validation Requirements

- To reduce the batch variation.
- Assurance of quality
- Reduction of quality cost.
- Reduction in rejections.
- Increased output.

- To obtain a good, efficient & pure product of high strength.[8]

Validation Master Plan

All validation activities should be planned. The key elements of a validation programme should be clearly defined and documented in a validation master plan (VMP) or equivalent documents.

- Perform the tests as per the procedure mentioned and record all the relevant data in the format mentioned therein.
- Record all the deviation/discrepancies in the section deviation. Number the deviation serially mentioning format number and page number. Record the corrective action if any to be taken in.
- Qualification team shall decide on approval of performance qualification based in the test results and observation made during the qualification. Upon approval of installation qualification the equipment can be subjected to operational qualification.
- If the equipment does not meet acceptance criteria, action shall be taken to address the discrepancies as mentioned in deviation section. Relevant test or entre performance qualification shall be performed.

Types of Validation

Prospective Validation

Establishing documented evidence prior to process implementation that a system does what it proposed to do based on preplanned protocols. This approach to validation is normally undertaken whenever the process for a new formula (or within a new facility) must be validated before routine pharmaceutical production commences. In fact, validation of a process by this approach often leads to transfer of the manufacturing process from the development function to production.[9,10]

Revalidation

Re-validation provides the evidence that changes in a process and/or the process environment that are introduced do not adversely affect process characteristics and product quality. Documentation requirements will be the same as for the initial validation of the process. Facilities, systems, equipment and processes, including cleaning, should be periodically evaluated to confirm that they remain valid. Where no significant changes have been made to the validated status, a review with evidence that facilities, systems, equipment and processes meet the prescribed requirements fulfils the need for revalidation.[9,10]

Retrospective Validation

It is defined as the established documented evidence that a system does what it purports to do on the review and analysis of historical information. Retrospective validation is used for facilities, processes, and process controls in operation use that have not undergone a formally documented validation process. Validation of these facilities, processes, and process controls is possible using historical data to provide the necessary documentary evidence that the process is doing what it is believed to do. Therefore, this type of validation is only acceptable for well-established processes and will be inappropriate where there have been recent changes in the composition of product, operating processes, or equipment. This approach is rarely been used today because it's very unlikely that any existing product hasn't been subjected to the prospective validation process. It is used only for the audit of a validated process.[9,10]

Concurrent Validation

It is similar to prospective, except the operating firm will sell the product during the qualification runs, to the public at its market price, and also similar to retrospective validation. This validation involves in-process monitoring of critical processing steps and product testing. Concurrent validation is used for establishing documented evidence that a facility and processes do what they purport to do, based on information generated during actual imputation of the process. This approach involves monitoring of critical processing steps and end product testing of current production, to show

that the manufacturing process is in a state of control.[9,10]

Qualification with Risk Based Approach

Risk assessment is required for every process, equipments, production, etc., in pharmaceutical industry. The aim of the risk assessment process is to remove hazards or reduce the level of its risk by adding precautions or control measures, as necessary. Risk assessments are very important as they form on integral part of a good occupational health and safety management plan. They help to:

- Create awareness of hazards and risks.
- Prevent injuries and illnesses when done at the design or planning stage.
- Prioritize hazards and control measures.[12]

The Qualification of Purified Water Storage and Distribution System with Risk Based Approach Is Done For

- To ensure of quality product.
- It is used to address the most significant health, product, equipment, and economy risks.

Potable water after treatment produces purified water. Which is also called as hungry solvent as no minerals microbes are present in the water and water is always ready for microbial contamination and making solution with the endotoxins, nitrates and heavy metals.

So little changes in the operations and maintenance of the system can cause effect on the quality of the purified water, which may leads to change the microbiological values, increase in Total Organic Carbon, increase in conductivity. It is very difficult to know the cause of failure and avoid time consumption, Risk based approach for the qualification of the purified water storage and distribution system is the best method.[12]

Water is one of the key starting materials in almost all pharmaceutical formulation. The commissioning, qualification and validation have been a task for handling this product.

Steps in Qualification

Equipment Qualification or Equipment Validation

This type of validation includes following things, they are installation qualification and operation qualification phases of equipment validation include:

- Examining equipment design and supplied documentation;
- Determining installation requirements;
- Establishing any needed environmental control and procedures;
- Installing the equipment;
- Verify correct installation;
- Establishing manufacturing procedure for the monitoring, operation, and control of the equipment including the minimum number of operators.[12]

Types of Qualification

Installation Qualification (IQ)

I.Q is a method of establishing with confidence that all major processing, packaging equipment and ancillary systems are in conformance with installation specifications, equipment manuals, schematics and engineering drawings. This stage of validation includes examination of equipment design, determination of calibration, maintenance and adjustment requirements. Installation qualification (IQ) should be performed on new or modified facilities, systems and equipment. [11]

Operational Qualification (OQ)

The critical operating parameters for the equipment and systems should be identified at the O.Q stage. The plans for the O.Q should identify the studies to be undertaken on the critical variables, the sequence of those studies and the measuring equipment to be used and the acceptance criteria to be met. The completion of satisfactory I.Q and O.Q exercises should permit a formal "release" of the equipment for the next stage in the process validation exercise as long as calibration, cleaning, preventive maintenance and operator training requirements have been

finalized and documented. Operation qualification (OQ) should follow Installation qualification.[11]

Performance Qualification (PQ)

Performance qualification (PQ) should follow successful completion of Installation qualification and Operational qualification. PQ should include, but not be limited to the following:

- Tests, using production materials, qualified substitutes or simulated products that have been developed from knowledge of the process and the facilities, systems or equipment.
- Tests to include a condition or set of conditions encompassing upper and lower operating limits.[11]

Design Qualification (DQ)

- The first element of the validation of new facility, systems or equipments could be design qualification.
- The compliance of the design with good manufacturing practice (GMP) should be demonstrated and documented.[11]

Commissioning

"A well planned, documented to the start-up and turnover of facilities, systems and equipment to the end user that results in a safe and functional environment that meets established design requirements and stockholders expectations."[15,26]

Commissioning Master Plan

The Commissioning Master Plan (CMP) is a high level document, which gives a guideline which system should be commissioned in a project. The water system in a pharmaceutical plant should invariably be in the scope. The basic headlines for CMP should include, based on the above we can chart out the CMP for pharmaceutical water systems. The usual steps from where the commissioning phases start will be from the design review to operational testing and inspections.

Steps in Commissioning of Water System

Design Review

Commissioning phase is starting from design of the equipment. Most from the industry also reference this document as design qualification (DQ).[16,17]

FAT Factory Acceptance Tests

This is very important as far as quality of the equipment is considered. It has to be understood that there are some corrections, which are best done at the vendors premises. Hence this test gains more popularity and acceptance. This article suggests very strongly, to include, this in CMP. This is not a regularity requirement but in turn may save time and money for the project.[16,17]

Delivery Inspection

This is more like a business to check decision, to check the correct delivery of the equipment at site.

SAT Site Acceptance Test

We recommend doing all these tests as per the qualification guidelines. These will include most of the tests carried out in IQ phases of qualification. If the tests are done here correctly as per the guidelines are not be repeated during the IQ phase. Just cross-referencing them would be sufficient. All the physical inspection tests are done during these periods.[16,17]

Qualification of Water System

The documented verification that all aspects of facility, utility or equipment can affect product quality.

- IQ Adheres to approved specifications.
- OQ operate as intended throughout all anticipated ranges.
- PQ performed as intended meeting acceptance criteria.

IQ & OQ

These are done only for the direct impact systems highlighted during the risk analysis of the manufacturing process.

PQ (Performance Qualification) and PV (Process Validation)

PV here a very thin line exists between PQ and PV. Most of the organizations term this line as taking trails with actual product and with product. But in case of water system this is quite tricky as water is the product all together. We would rather term the difference as taking the water for production or for testing. As clarified in the USP the three stage process for water system validation. The first phase can be part of performance qualification. From phase 2 onward the process validation can start. The details of phase 1, 2 and 3 for process validation of water are detailed in USP. In brief the 3 stage of process validation are as below:

Stage 1 (Investigational Phase)

We will last for usually 2-4 weeks. We will require taking frequent samples and analyzing the same for details and deterioration of water quality. During this phase the system is on and all functions functioning as per production like conditions, but the water is visually not taken for production. In this phase we basically understand our own systems are unique and no system can be or similar to the other even if they are built with the same design conditions.

Stage 2 (Short Term Control)

We will last for 4-6 weeks. We will have to take frequent samples and analyze in the same way as in phase 1. The only difference exists that during this phase water can be taken that no production batches should leave the factory till the phase is completed.

Stage 3 (Long Term Control)

This is final but long term validation of water system. This will last for 1 tear usually encompassing all the seasonal variations in the water system and how they react to the same. During this process sampling, procedures and the frequent sampling, this was done during the phase 1 and, will be reduced. Here the water is taken for production and material also shipped. But care is taken for batches where abnormality of water quality is observed.[16]

Risk Assessment

Risk assessment is the most important tool to determine the required amount of validation. During the validation process risk assessment may be applied. The following steps are as follows

- Risk assessment Create awareness of hazards and risks.
- It prevents injuries or illness when done at the design or planning stage.
- Prioritize hazards and control measures.

Principles of Quality Risk Management

- The evaluation of the risk and the quality should be based on scientific knowledge and ultimately link to the protection of the patient.
- The level of effort, formality and documentation of the quality risk management process should be proportionate and equal with the level of risk.

General Quality Risk Management Process

Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of product lifecycle. A model for risk management is outlined in the diagram

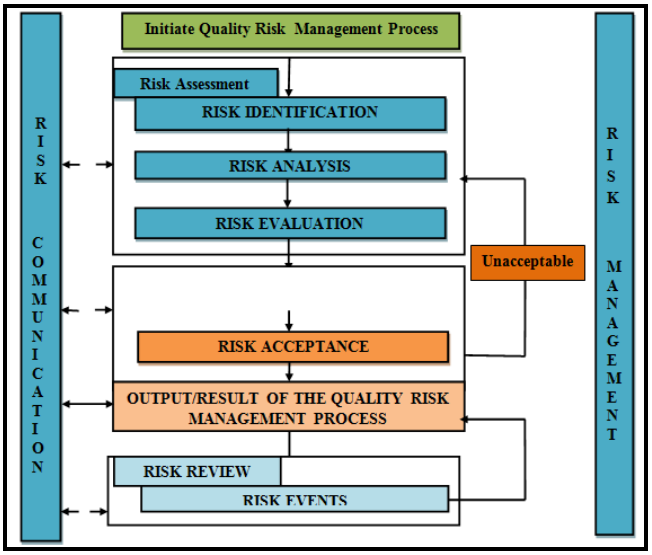

Figure 1: Overview of a Typical Quality Risk Management Process

Initiating a Quality Risk Management Process

Quality risk management should include systemic processes designed to coordinate, facilitate and improve science based decision making with respect to risk. Possible steps used to initiate and plan a quality risk management process might include the following

- Define the problem and/or risk question, including pertinent assumptions identifying the potential for risk.
- Assemble background information and/or data on the potential hazard, harm or human health impact relevant to the risk assessment.
- Identify a leader and critical resources.
- Specify a timeline, deliverables, and appropriate level of decision making for the risk management process.[17]

Risk Assessment

Risk assessment consists of the identifications of hazards and the analysis and evaluation of risks associated with the exposure to those hazards. Quality risk assessments begin with a well defined problem description or risk question. When the risk in question is well defined, an appropriate risk management tool and the types of information that will address the risk question will be more readily identifiable. As an aid to clearly defining the risk for risk assessment purposes, three fundamental questions are often helpful

- What might go wrong?
- What is the likelihood (probability) it will go wrong?
- What are the consequences?

Risk Identification

It is a systematic use of information to identify hazards referring to the risk question or problem description. Information can include historical data, theoretical analysis, informed options, and the concern of stakeholders. Risk identification addresses the "what might go wrong?" question, including identifying the possible consequences.

Risk Analysis

Risk analysis is the estimation of the risk associated with the identified hazards. It is the qualitative process of liking the likelihood of occurrence and severity of harms.

Risk Evaluations

It compares the identified and analyzed risk against given risk criteria. Risk evaluations consider the strength of evidence for all the three fundamental questions.

Risk Control

Risk control includes making to reduce and/or accepts risks. The purpose of risk control is to reduce the risk to an acceptable level. The amount of efforts used for risk control should be proportional to the significance of the risk.

Risk Reduction

Risk reduction might include actions taken to mitigate the severity and probability of harm.

Risk Acceptance

Risk acceptance can be formal decision to accept the residual risk and it can be a passive decisions in which residual risk are not specified.

Risk Communication

It is the sharing of information about risk and risk management between the decision makers and others. The included information might relate to the existence, nature, form, probability, severity, acceptability, control, treatment, detectability, or other aspects of risks to quality. Communication need not be carried out for each and every risk acceptance.

Risk Review

Risk management should be ongoing part of the quality management process. A mechanism to review or monitors events should be implemented. The output/results of the risk management process should be review to take into account new knowledge and experience. Once a quality risk management has been initiated, that process continues to be utilized for events that might impact the original quality risk management decision, whether these events are

planned or unplanned. The frequency of any review should be based upon the level of risk. Risk review might include reconsideration of risk acceptance decisions.[17,18]

Risk Management Methods

Quality risk management supports a scientific and practical approach to decision making. It provides documented, transparent, and reproducible methods to accomplish steps of the quality risk management process based on current knowledge about assessing the probability, severity and sometimes, delectability of the risk. The various methods are[17,18]

- Basic risk management facilitation methods (Flow charts check sheets etc.)
- Failure Mode Effects Analysis (FMEA)
- Failure Mode Effects and Critically Analysis (FMECA)
- Fault Tree Analysis (FTA)
- Hazards Analysis and Critical Control Points (HACCP)
- Hazards Operating Analysis (HAZOP)
- Preliminary Hazards Analysis (PHA)
- Risk Ranking and Filtering
- Supporting Statistical tools

Basic Risk Management Facilitation Methods

Some of the simple techniques that are commonly used to structure risk management by organizing and facilitating decision making are[17,19]

- Flowcharts
- Check sheets
- Process mapping
- Cause

Failure Mode Effects Analysis (FMEA)

It provides for an evaluation for potential failure modes for process and their likely effect outcomes and/or product performance. Once failure modes are established, risk reduction can be used to eliminate, reduce, or control the potential failure. FMEA relies on product and process understanding. FMEA methodically breaks down the analysis of complex process into manageable steps. It is a powerful tool for summarizing the important modes of failure, factors causing these failures, and the likely effects of these failures.[17,21,22,23]

Potential area of use set (s)

FMEA can be used to appropriate risk and monitor the effectiveness of risk control activities. FMEA can be applied to equipment and facilities and might be used to analyze a manufacturing operation and its effect on product or process.[17,21,22,23]

Failure Mode Effects and Critically Analysis (FMECA)

FMEA might be extended to incorporate an investigation of the degree of severity of the consequences, their respective probabilities of occurrence, and their delectability, thereby becoming a failure mode, effects and criticality analysis. FMECA can identify where additional preventive actions might be appropriate to minimize risks.

Potential area of use(s)

FMECA application in the pharmaceutical industry should mostly be utilized for failures and risk associated with manufacturing processes.[17,23]

Hazards Analysis and Critical Control Points (HACCP)

HACCP is a systematic, proactive and preventive tool for assuring product quality, reliability, safety.

It is a structured approach that applies technical and scientific principles to analyze, evaluate, prevent and control the risk or adverse consequences of hazards due to design, development, production and use of products.

Potential area of use(s)

HACCP might be used to identify and manage risks with physical, chemical, and biological hazards.[17,24]

Fault Tree Analysis (FTA)

The FTA tool is an approach that assumes failure of the functionality of a product or process. This tool evaluates system failures one at a time but can combine multiple causes of failure by identifying casual chains. The results are represented pictorially in the form of a tree of fault modes.

Potential area of use(s)

FTA can be used to establish the pathway to the root cause of the failure. FTA can be used to investigate complaints or deviations in order to fully understand their root cause and to ensure that intended improvements will fully resolve the issue and not lead to other issues.[17]

Hazards Operating Analysis (HAZOP)

HAZOP is based on a theory that assumes that risks events are caused by deviations from the design or operating intentions. It is brainstorming technique for identifying hazards using so called guidewords. Guide words are applied to relevant parameters to help identify potential deviations from normal use or design intentions. HAZOP often uses a team of people with expertise covering the design of the process or product and its application.

Potential area of use(s)

HAZOP can be applied to manufacturing process, including outsourced production and formulation as well as upstream suppliers, equipment and facilities for drug substances and drug products. It has also been primarily in the pharmaceutical industry for evaluating process safety hazards.[17,25]

Preliminary Hazards Analysis (PHA)

PHA is a tool of analysis based on applying prior experience or knowledge of a hazard or failure to identify future hazards, hazardous situations and event that might cause harm, as well as to estimate their probability of occurrence for a given activity, facility, product, or system. A relative ranking of the hazard using a combination of severity and likelihood of occurrence.

Potential area of use(s)

PHA might be useful when analyzing existing systems or prioritizing hazards where circumstances prevent a more expensive technique for being used. It can be used for product, process and facility design as well as to evaluate the type of hazards for the general product.[17]

Risk Ranking and Filtering

Risk ranking and filtering is a tool for comparing and ranking risks. Risk ranking of complex systems typically involves evaluation of multiple diverse quantitative and qualitative factors for each risk. The tool involves breaking down a basic risk question into as many components as needed factors involved in the risk. These factors are combined into a single relative risk score that can be used for ranking risks. "Filters" in the form of weighing factors or cut-off for risk scores, can be used to scale or fit the risk ranking to management or policy objectives.

Potential area of use(s)

Risk ranking and filtering can be used to prioritize manufacturing sites for inspection/audit by regulators of industry. (17)

Supporting Statistical Tools

Statistical tools can support and facilitate quality risk management. They can enable effective data assessment, and in determining the significance of the data set(s), and facilitate more reliable decision making.[17]

Failure Mode and Effects Analysis (FMEA)

Failure mode and effects analysis (FMEA) is methodology for analyzing potential reliability problems early in the development cycle where it is easier to take actions to overcome these issues, thereby enhancing reliability through design. FMEA is used to identify potential failure modes.[17,21,22,23]

Types of FMEA

- *Design* - analysis of products prior to production.

- *Process FMEA* - analysis of manufacturing and assembly processes.
- *Concept* - analysis of systems or subsystems in the early design concept stages to analyse the failure mechanisms.
- *Equipment* - analysis of machinery and equipment design before purchase.
- *Service* - analysis of service industry processes before they released to impact the customer.
- *System* - analysis of the global system functions.
- *Software* - analysis of the software functions.

Timing

The FMEA should be updated whenever

- A new cycle begins (new product/process)
- Changes are made to the operating conditions
- A change is made in the design
- New regulations are instituted
- Customer feedback indicates a problem

Uses

- Development of system requirements that minimize the likelihood of failures.
- Development of designs and test systems to ensure that the failures have been eliminated or the risk is reduced to acceptable level.
- Development and evaluation of diagnostic systems
- To help with design choices (trade-off analysis

Limitations

- If used as a top-down tool, FMEA may only identify major failure modes in a system.
- Fault tree analysis (FTA) is better suited for "top-down" analysis. When used as a "bottom-up" tool FMEA can augment or complement FTA and identify many more causes and failure modes resulting in top-level symptoms.

Advantages

- Improve the quality, reliability and safety of a product/process
- Improve company image and competitiveness
- Increase user satisfaction
- Reduce system development time and cost
- Collect information to reduce future failures, capture engineering knowledge
- Reduce the potential for warranty concerns
- Early identification and elimination of potential failure modes
- Emphasize problem prevention
- Minimize late changes and associated cost
- Catalyst for teamwork and idea exchange between functions
- Reduce the possibility of same kind of failure in future
- Reduce impact on company profit margin improve production yield

CONCLUSION

The FMEA (Failure Mode Effects Analysis) tool complies with the cGMP aspects and meets the regulatory requirements. By using this FMEA tools we can mitigate the risk and controls the probable failure moods of any new facility, equipment or system. By using this technique we can keep our purified water system in validated condition for longer period of time. The purified water storage & distribution has been tested and verified for installation qualification, operational qualification, and performance qualification as per the protocol.

So the deliverable capacity can be maintained consistently without any complains and system will work for longer period without any failure moods as per its pre defined specification or regulatory requirements.

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