

Auditing a Validation System

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Auditing a Validation System

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on the approved process method and specifications. This phase qualifies process and procedures and demonstrates that the equipment and ancillary systems do what they claim to do.

Piping and installation drawings (P&ID): Mechanical drawing or blueprints of the required piping system for installation of equipment.

Quality risk management. A systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle.

Worst Case: Conditions within normal parameters most likely to give failure. For processing purposes, "worst case" means those values of normal operating parameters most likely to cause process failure. For sampling locations, "worst case" means those equipment locations most likely to have higher levels of residues after cleaning. For sampling recovery, "worst case" means those procedures, within normal sampling parameters, most likely to give poorer percentage recovery.

Explanation of Topic

Introduction

Validation is the action of proving, in accordance with the principles of GMP, that any procedure, process, equipment, material activity or system consistently leads to the expected results. Documented evidence provides a high degree of assurance that a specific system, equipment or process will consistently produce a product meeting its pre-determined specifications and quality attributes. To put it simply, validation is nothing more than proving that a process actually works.

What should be validated?

We use the terms validation and qualification to cover the documented verification of a spectrum of GMP activities including

- Facilities
- Equipment used in manufacturing
- Equipment used to control the environment(s) where product is manufactured or stored
- Utilities with product contact (e.g., water systems, compressed gases, air)
- HVAC systems
- Alarm systems that monitor utilities and air handling for process and storage areas
- Analytical methods
- Analytical instruments
- Computerized systems (e.g., computerized training system, documentation control system)
- Cleaning processes
- Manufacturing processes

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likelihood of detection of the failure. Appropriate systems are implemented to ensure that the theoretical hazards do not present a hazard to the process. The appropriate limits are set for these systems.

If the risk assessment has been properly carried out and documented, parts of a process that are low risk may be eliminated or paid minimal attention during validation.

Benefits of validation

Validation assures that the entire manufacturing process and support systems work properly before actual production begins.

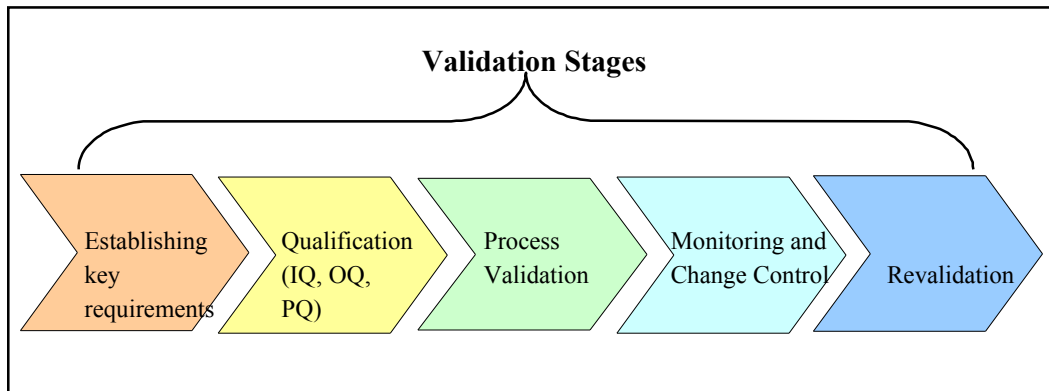
Validation ensures that safe, quality products are consistently manufactured. The validation process gives the manufacturer a further understanding of the process, possibly improved operational efficiency, more robust processes, reduced risk of failure and improved compliance.

General Validation guidelines

The first step to the overall validation process is to define the key requirements of the product/process, e.g. by documenting the appropriate parameters in a User Requirement Specification (URS) and a Functional Specification describing what is needed and how the final result is to be achieved. A design qualification (DQ) is performed to collect documented verification that the proposed design of facilities is suitable for the intended purpose.

The total validation process involves DQ, IQ, OQ, PQ, process validation, maintenance, change control and revalidation.

Rationales used as basis for validation strategies should be documented.



Since validation consists of different stages, critical sections of each stage must be completed before moving to the next stage. Some of these critical sections include complete testing, investigation of critical deviations and/or exceptions, and repair (e.g. wiring connected incorrectly). Deviations must be closed and interim approval of the stage should be obtained prior to beginning the next stage. The protocol for the next

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criteria to be tested against, etc. This directing document is the Validation Plan (VP). The VP is a strategic document which identifies the elements to be validated, the approach to be taken for validation of each element, the organizational responsibilities and the documentation to be produced to ensure full consideration is given to product quality aspects. It shows how the separate validation activities are organized and interlinked. Overall it provides the details and relative time scales for the validation work to be performed.

Specific elements of the VP are qualification/validation methodology, qualification activities, personnel responsibilities, schedule, preventive maintenance, change control, relevant SOPs and documentation requirements.

The VP is required to be prepared and approved at an early stage of the project. This plan may or may not include design installation and operational performance qualification protocols as individual documents. Not all projects need to be included in a VP. This document is required when the coordination of many validation activities is necessary.

Examples are:

- Ø Construction of a new manufacturing facility
- Ø Purchase and installation of a new utility, (e.g. a new purified water system)
- Ø Installation of a new packaging line
- Ø Significant refurbishment to existing facilities, utilities and equipment

Equipment Qualification

To ensure that a manufacturing or testing process will work properly, the equipment used in the process must perform reliably and within specifications. To achieve this, the equipment must be qualified.

Design, installation, operation and performance qualification (DQ/IQ/OQ/PQ) are phases of validation that support the startup of new, modified, or retrofitted equipment.

DQ/IQ/OQ/PQ studies establish confidence that the equipment and ancillary systems are capable of consistently operating within the established design and operating limits and tolerances.

Design Qualification (DQ)

Design qualification (DQ) may be established as a separate process with its own protocol or may be combined in the Validation Plan. The purpose of this qualification is to assure that a proposed new or modified facility, system or equipment meets GMP requirements, is suitable for its intended purpose and defines how the Users Requirement Specification (URS) are to be met.

The URS establishes agreed and properly defined facilities/utilities/equipment functionality requirements. Variables should be specified in terms of expected reliability, consistency and capability.

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The protocol should include the roles and responsibilities for IQ development, execution, assurance of completion and maintenance. It should identify functional groups required to review and approve the protocol. Functional groups should include those who can provide a technical evaluation (e.g., Engineering, Maintenance) and QA. QA should always be an approver to ensure that all GMP and regulatory requirements have been considered, met, and documented as appropriate. If all critical items in the protocol have been addressed and approved, but there are some remaining items, the next phase of qualification may be executed provided that there is written documentation to justify it. The IQ protocol should include piping and instrumentation diagrams (P & ID), HVAC drawings and equipment drawings.

Installation Qualification Execution

Installation qualification (IQ) occurs during the equipment installation phase. Equipment is compared to the original design and installation plans, found either in the Purchase Order or design specification. This phase ensures that the manufacturer's and the company's engineering specifications agree. Equipment type and "as - built" conditions are verified against the design specifications. During this phase, materials of construction, manufacturer's identification (serial number) are verified against the purchase specifications and the manufacturer's specifications.

During the installation qualification, utilities completion and calibration take place. The utilities, (electrical, water, steam, vacuum, compressed gases and HVAC) are checked to determine if they are connected properly. Wiring installation of electrical lines (loop checks) is conducted. Software that is used in a computer is checked for the correct version and that it is installed correctly.

Instruments are also calibrated to verify that indicators for temperature, pressure, flow, weight, volume, etc. are accurate. Piping systems are reviewed to verify that they have been correctly installed and that the composition of materials is in agreement with the design specifications. Piping systems are also reviewed to ensure that the lines have been degreased, and passivated, if the water systems use stainless steel piping. Piping should also be identified and tagged.

The installation qualification should include a review of pertinent maintenance procedures; repair parts lists, and calibration methods for each piece of equipment. The objective is to assure that all repairs can be performed in such a way that will not affect the characteristics of material processed after the repair. In addition, special post-repair cleaning and calibration requirements should be developed to prevent inadvertent manufacture a of non-conforming product

Information from the installation qualification should be used to:

- Ø develop written procedures on calibration
- Ø establish a preventative maintenance program
- Ø determine which calibration, maintenance and adjustment requirements could affect the process and product.

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Performance Qualification Execution

Performance qualification is a bridge between Operational Qualification and Process Validation. In Performance Qualification, production materials, qualified substitutes, or simulated product may be used to test the upper and lower operation limits or “worst case” conditions. Performance Qualification is a test of the overall system, with equipment and ancillary systems tested together.

Process Validation

Process Validation includes establishing documented evidence, which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics.

A predetermined number of validation batches should be manufactured to demonstrate that, under normal conditions and defined ranges of operating parameters, the commercial scale process appears to make an acceptable product. It should normally cover the manufacture of at least three consecutive batches of material.

Validation should be performed under conditions to be used for routine manufacture. The batch size should be the same as or representative of the intended commercial scale batches. Sampling and testing should be carried out to ensure compliance with the most stringent requirements.

If the validation batches are intended for commercial use, the conditions under which they are prepared and manufactured must comply with the GMP requirements. Prospective process validation should normally be applied to API and to medicinal products. The general principle is to validate a manufacturing process and the “same” process can typically be used for several related products. Rather than to develop a plan for each product manufactured by a process, it can be possible to develop a plan for that process instead. There are two general principles that could be applied. “Matrix approach” generally means a plan to conduct process validation on different strengths of the same product. “Family approach” describes a plan to conduct process validation on different, but similar products. Either approach must demonstrate that the process is consistent for all the strengths or products involved. The plan should be designed to evaluate all likely sources of variation in the products manufactured by the process. Process validation must be completed, evaluated, documented and approved before commercial distribution.

Worst Case and Challenge Tests

The process should be challenged by making deliberate changes to demonstrate its robustness and to define its limits of tolerance. In challenging a process to assess its adequacy, the conditions should simulate those that could be encountered during actual production. These tests should be repeated enough times to assure that the results are meaningful and consistent.

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equipment is considered clean prior to use. For modern, highly automated, equipment the logical sequencing of cleaning activities should be critically reviewed for adherence to validated procedures. Maximum permitted time for campaign manufacturing should be included in cleaning validation studies.

Normally an ongoing monitoring program is set up to confirm satisfactory operation of the established cleaning process. Key process parameters may be reviewed for automated systems, in other cases monitoring based on swabs/rinse samples or visual examination may be conducted.

Validation of Analytical (Chemical, Physical and Microbiological) Test

Methods

Validation of methods is performed to confirm that the performance characteristics of a method meet the requirements for the intended application. An assessment of validation studies demonstrating that the method is suitable for its intended purpose shall be documented appropriately.

Test methods described in any submission for manufacturing authorization, including development pharmaceuticals, in-process control during manufacture, control tests on intermediate products, control tests on finished products and stability testing should be appropriately validated for the phase of development before use. Methods used in testing of commercial finished products, raw material or packaging component must be validated before use.

Appropriate level of revalidation of methods may be required by regulatory authorities when methods are transferred from one site to another, methods are transferred from one laboratory to another, if significant changes are made in the manufacturing of major starting materials or if the composition of the finished product is changed.

Methods and equipment described in pharmacopoeias may be considered validated. Suitability for use of pharmacopoeial methods should be established by testing/technical review and documented. When claiming compliance with pharmacopoeias, unless the exact method is being used, a cross validation should be performed.

A number of parameters should be considered in validation of quantitative methods. These parameters include tolerance limits, specificity, accuracy, precision, detection limit, quantification limit, linearity and range.

Maintenance of Validated Status/Change Control

The suitability of a facility, utility, process or equipment must be maintained through its operating life. Systems and documentation need to be in place to support this. Such monitoring systems should include SOPs, performance monitoring, calibration, maintenance and cleaning, change control, and periodic review by internal audits. Where no significant changes have been made to the system or process, and a quality review confirms that the system or process is consistently producing material meeting its specifications, there is normally no need for revalidation.

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- Verify that a Validation Protocol exists for each validation project, which identifies qualification activities for DQ/IQ/OQ/PQ and their locations.
- If DQ is performed as a separate qualification,
 - Ø Verify that there is a system to manage the setup of a preventive maintenance and change control program for new equipment. This management system may be part of the IQ/OQ process or part of the site's change control system.
- Ensure that the site has performed the following checks during the IQ phase.
 - Ø For electrical and instrumentation completion,
 - Verify that there is documentation of loop checks.
 - Verify that the software version installed is documented.
 - Ø For installation and instrumentation,
 - Verify that the delivered equipment and instrumentation meet the defined specifications of equipment order.
 - Ø For utilities completion,
 - Verify that there is documentation (e.g., a utilities checklist) of the connection of utilities to equipment.
 - Ø For piping systems completion,
 - Verify that the system "walk down" was completed.
 - Verify that any red line changes to the P&ID's have been submitted.
 - Ø Verify that the following documentation is correct:
 - As built engineering and installation drawings
 - calibration documentation
 - weld documentation
 - material of construction certifications
- Ensure that the Operational Qualification is complete.
 - Ø Verify that the valve sequencing (e.g. API tanks) is correct by comparing it against the piping and installation drawing.
 - Ø Verify that ranges for process and safety alarms have been set according to process parameters.
 - Ø Verify that critical alarms are present by comparing the alarms against a list of critical parameters.
 - Ø Verify that the range tested in the protocol encompasses the current alarm condition.
 - Ø Verify that "worst case" conditions have been tested for the equipment and ancillary systems.
- Ensure that the documentation system is operating in full compliance.
 - Ø Verify that when any protocol has been approved, any changes to the protocol followed the site's change control process.
- Ensure that the Performance Qualification is complete.
 - Ø Verify that the testing performed is within established acceptance criteria.
- Ensure that appropriate SOPs and batch documentation are developed for the equipment and systems being qualified. Ensure that any restrictions to use are implemented.
- Ensure process validation has been performed and that manufacturing is performed within validated criteria