Goals

When you have completed this manual, you should be able to:

- Perform an audit of a validation system (excluding computer systems)
- Use a range of tools and information, including the contents of this unit to support the audit of a validation system
- Understand and apply appropriate GMP standards/regulations to an audit of a validation system
- Recognize compliance or non-compliance of a validation system to applicable regulations

Definitions

Ancillary system: A system that is not directly part of the equipment undergoing qualification. An example is a compressed air system that may be used in packaging to remove dust and other contaminants.

"As-built" drawings: Drawings of the equipment, indicating utilities etc. placement of equipment components, completed as the equipment was being built or manufactured.

"As is "drawings: Drawings of the equipment as it has been placed/modified within the final location.

Design Qualification: Documented verification that the proposed design of the facilities, equipment, or systems is suitable for the in-tended purpose.

Factory Acceptance Testing (FAT): Pre-delivery equipment testing and inspection performed at the factory.

Installation Qualification (IQ): Documented verification that all key aspects of the design, procurement, and installation of the system adhere to the approved design, and that all manufacturers' recommendations have been complied with.

Operational Qualification (OQ): Documented verification that the equipment or systems and sub-systems, as installed or modified, perform as intended throughout the anticipated operating ranges.

Passivation: The chemical treatment of stainless steel with a mild oxidant, such as a nitric acid solution, for the purpose of enhancing the spontaneous formation of the protective passive film. This process is designed to remove foreign metals, oxides, and corrosion from the surface of stainless steel and corrosion resistant steels, which allows water to move through the pipes and improves corrosion resistance.

Performance Qualification (PQ): Documented verification that the equipment and ancillary systems, as connected together, can perform effectively and reproducibly based

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.

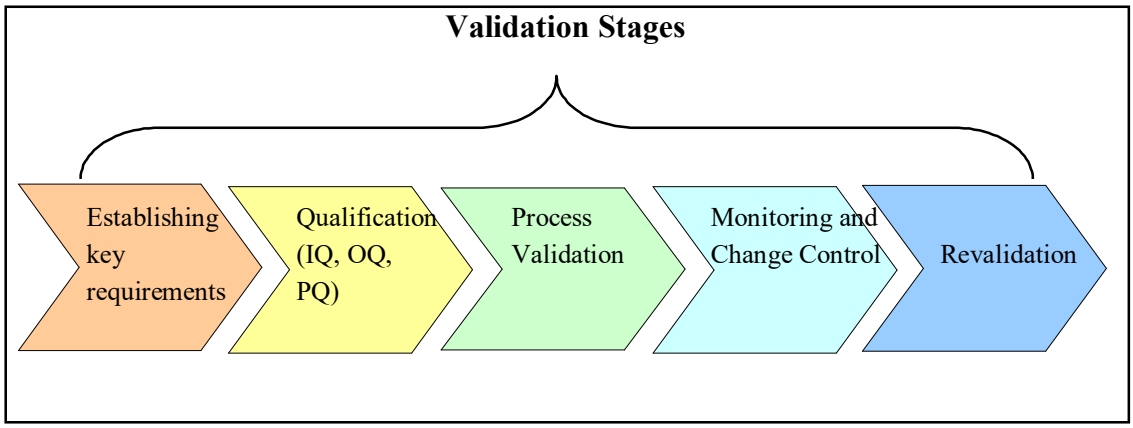
Validation ensures that safe, quality products are consistently manufactured. The validation process gives the manufacturer a further understanding of the process, possibly improved operational efficiency, more robust processes, reduced risk of failure and improved compliance.

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

For relatively simple and off the shelf equipment, the URS and design qualification may be documented by reference to a supplier's specification and included in the purchasing order/specification.

The design qualification documents (actual specification documents) should be reviewed, at a minimum, by both technical personnel for feasibility and suitability and QA for compliance with GMPs. The design qualification takes place before actual construction or installation.

During this qualification, the design for routine cleaning of the equipment should be considered. All design reviews should be documented In addition, for some systems/equipment, extensive Factory Acceptance Testing (FAT) may be performed.

The need to repeat some or all of this testing on site should be considered. Justification for reduced site acceptance testing should be documented.

FAT is an important step in the project and the subsequent validation phases. FAT includes more than just a physical examination of the item to check that all components are present and have been fulfilled. It should ensure that the item meets the agreed specification and requisition and confirm that all vendor documentation is in place. A well-executed FAT can provide a significant, positive contribution to the IQ at the site.

Installation Qualification (IQ) Documentation

Before any work can be started, all installation qualification activities must be recorded and approved in an Installation Qualification protocol. A suggested protocol format includes:

- Signature and Pre-Approval Page
- Publication Record (history of revisions to the document)
- Signature and initial log
- Objectives of Qualification
- System Description
- Installation Qualification Procedure
- Equipment Specifications
- Site Specifications - varies according to qualification
- Safety Specifications
- Set-up, Calibration, Maintenance and Cleaning Procedures and frequency - varies according to site
- Spare/replacement parts listing and location
- Training for Operators and Maintenance Personnel
- A description of tests and a section for recording test results
- Deviation/Exception Summary or List
- Amendments - varies according to site
- Signature and Final Qualification Acceptance/Approval
- Utilities

Such worst case or challenge tests should preferably be performed prior to manufacture of validation batches. Typically they are done during the OQ or PQ stage of validation.

Cleaning validation

The consistent preparation of safe high quality products depends in no small part on the ability to satisfactorily clean and decontaminate premises and equipment to minimize the potential for cross-contamination. Contamination may be chemical as well as microbiological.

The potential consequences for cross-contamination includes regulatory, quality as well as safety aspects. An effective strategy for the development and confirmation of effective cleaning procedures may consist of three phases; assessment of risk, validation of cleaning procedures and development of monitoring procedures to confirm the ongoing effectiveness.

Cleaning validation is performed in order to establish documented evidence that a specified cleaning procedure will provide a high degree of assurance that it can be used to consistently clean a piece of equipment or a facility to a predetermined acceptable level of cleanliness.

A general approach to the validation of cleaning is to use the equipment for the intended process, hold for a predetermined maximum time, clean as per procedure, sample (product residues, cleaning agent) and repeat to show reproducibility. Sampling is generally performed by visual examination (where feasible), swab samples and rinse samples. Sampling sites selected should be representative and include locations difficult to clean.

A range of analytical methods may be required for cleaning validation. Methods may be specific (e.g. bioassay, HPLC or activity assay) or non-specific (e.g. total organic carbon, conductivity or pH). Whichever method used, it should be validated for the application. Limit of detection and recovery are key criteria in such method validations. Recovery studies should be performed prior to sampling and on the material included in the cleaning validation.

Acceptance criteria established for each piece of equipment should be practical, achievable and verifiable. The manufacturer should be able to demonstrate by means of data that the residual level permitted is scientifically sound. Traditionally the pharmaceutical industry has set analytical and clinical/toxicological criteria. In a multi-product facility cleaning validation may be performed based on bracketing of compounds. Worst case or representative compound/-s are then chosen and the data obtained is used to support effective cleaning of all compounds in that bracket.

The established and verified cleaning method should be implemented and conformed to. The cleaning procedures should include the method to be used, maximum allowed intervals between cleanings and between use and cleaning, and for how long time