

A Review on Pharmaceutical Validation

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ABSTRACT

Quality is the primordial intention of any industry and its products manufactured. Multiple views on obtaining such quality are the current interest in the pharmaceutical industry, and it has been maintained by validation. Validation is documented evidence that provides a high degree of assurance. Validation has become one of the pharmaceutical industries' most recognized subjects. This article provides detailed information about pharmaceutical validation and its importance. Quality is always an imperative prerequisite when we consider the product. In this article, we discuss the types of validation, process validation, equipment validation, cleaning, and analytical method validation. Validation is the process that is used to confirm that the analytical procedure employed for a specific test is suitable for the intended use.

Keywords: Analytical method validation, Cleaning validation, Equipment validation, Process validation, Validation, etc.

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INTRODUCTION

Validation is the process of establishing documentary evidence demonstrating that a procedure, process, or activity carried out in testing, and then production, maintains the desired level of compliance at all stages. In the pharmaceutical industry, it is very important that in addition to final testing and compliance of products, it is also assured that the process will consistently produce the expected results (Figure 1).¹

The prime objective of any pharmaceutical plant is to manufacture products of requisite attribute and quality consistently, at the lowest possible cost. Although validation studies have been conducted in the pharmaceutical industry for a long time, there is an ever-increasing interest in validation owing to their industry's greater emphasis in recent years on quality assurance program and is fundamental to an efficient production operation. The concept of validation has expanded through the years to embrace a wide range of activities, from analytical methods used for the quality control of drug substances and drug products, to computerized systems for clinical trials, labeling, or process control, validation is founded on, but not prescribed by regulatory requirements, and is best viewed as an important and integral part of current good manufacturing practices (cGMP). The word validation

simply means an assessment of validity or action of proving effectiveness. Validation is a team effort where it involves people from various disciplines of the plant.^{2,3}

NEED OF VALIDATION

- The pharmaceutical industry uses expensive material, sophisticated facilities, equipment, and highly qualified personnel.
- Detailed study and control of the manufacturing process batch validation are necessary if failure cost is to be reduced and productivity is improved.
- It would not be feasible to use equipment not knowing if it will produce the product we want, not to employ the people with no assurance that they can do or fail to implement process checks or examination to assure that product meet specifications.
- The efficient use of these resources is necessary for the continued success of the industry. The cost of product failures, rejects, reworks, recalls, complaints are a sufficient part of the total production cost.
- Assurance of quality and cost reduction.⁴

TYPES OF VALIDATION

Generally, validation has four major types. These are as follows:

- Process validation
- Equipment validation
- Analytical method validation
- Cleaning validation (Figure 2)

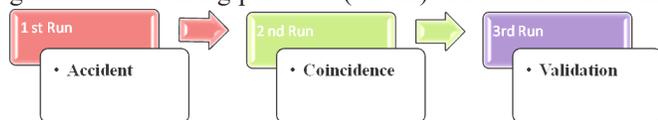


Figure 1: Validation process

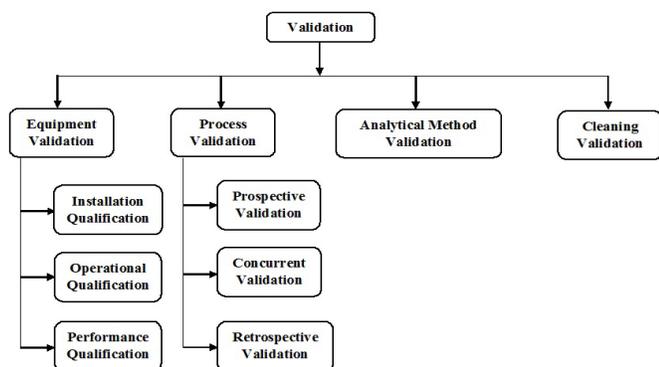


Figure 2: Types of validations

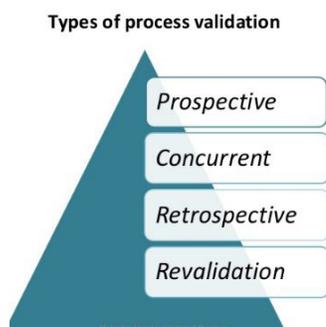


Figure 3: Types of process validation

Process Validation

The process validation is a component of the coherent prerequisites of a quality management system. Process validation is the most essential and perceived parameters of current good manufacturing practices. The objective of a quality system is to produce items that are matched with their proposed use uniformly. Process approval is a key component in guaranteeing that these standards and objectives are met.^{5,6}

- Retrospective validation
- Prospective validation
- Concurrent validation
- Revalidation

Retrospective Validation

Establishing documented evidence prior to process implementation that a system does what it proposed to do based on pre-planned protocols. This approach to validation is normally undertaken whenever the process for a new formula must be validated before routine pharmaceutical production commences. Validation of a process by this approach often leads to the transfer of the manufacturing process from the development function to production. The retrospective validation is used for facilities, processes, and process controls in operation use that have not undergone a formally documented validation process.

Prospective Validation

It is used for facilities, processes, and process controls in operation use that have not undergone a formally documented validation process. Validation was conducted prior to the distribution of either a new product or a product made under

a revised manufacturing process. Validation is completed, and the results are approved prior to any product release establishing documented evidence prior to process implementation that a system does what it proposed to do based on pre-planned protocols. Each prospective validation step will be described in the qualification/validation documents.

Concurrent Validation

It is a combination of retrospective and prospective validation. Performed against an approved protocol, but the product is released on a lot-by-lot basis, usually used on an existing product not previously validated or insufficiently validated. 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.

Revalidation

It means repeating the original validation effort or any part of it, and includes an investigative review of existing performance data. This approach is essential to maintain the validated status of the plant, equipment, and manufacturing. Possible reasons for starting the revalidation process include:

- The scope of revalidation procedures depends on the extent of the changes and the effect upon the product.
- Significant increase or decrease in batch size.
- The necessity of periodic checking of the validation results.
- The transfer of a product from one plant to another (Figure 3).⁷

Equipment Validation

Design Qualification (DQ)

The documented verification that the proposed design of the facilities, systems, and equipment is suitable for the intended purpose (Figure 4).

In this qualification, compliance of design with GMP should be demonstrated. The principles of design should be such as to achieve the objectives of GMP with regard to equipment. Mechanical drawings and design features provided by the manufacturer of the equipment should be examined.

Installation Qualification (IQ)

Establishing confidence that process equipment and ancillary systems are capable of consistently operating within established limits and tolerances food and drug administration (FDA). The documented verification that the facilities, systems, and equipment as installed or modified complies with the approved design and the manufacturer's recommendations. Installation qualification should be carried out on new or modified facilities, systems, and equipment. The following main points should be included in the installation qualification:

- Checking of installation of equipment, piping, services, and instrumentation.
- Collection of supplier's operating working instructions and maintenance requirements and their calibration requirements.
- Verification of materials of construction.
- Sources of spares and maintenance.

peak quantitative noise relation that we have to calculate from blank chromatograms. Then, calculate the concentration at the signal to quantitative noise relation is concerning 3:1.

LoD can be expressed as,

$$\text{LoD} = 3.3 \times \text{SD}/S$$

Where, SD = Standard deviation of response, S = Slope of calibration curve.²¹

Limit of quantitation (LoQ): It is characterized by the least quantity of an analyte that can be quantified with exactness and precision.

LOQ can be communicated as,

$$\text{LoQ} = 10 \times \text{SD}/S$$

Where SD = Standard deviation of response, S = Slope of calibration curve.²²

Linearity: Linearity may be characterized as the capacity of an analytical technique to produce outcomes that are directly related to the concentration of an analyte in the standard solution.²³

Range: It can be characterized as the interval amongst upper and lower quantities of analyte in the sample. The minimum of the specified range to be 80 to 120% of the test sample for the assay test.²⁴

Ruggedness: Ruggedness is the degree or measure of reproducibility under different situations, such as, in different laboratories, different analysts, different machines, environmental conditions, operators, etc.²⁵

Robustness: It is characterized by the level of ability of an analytical technique to stay similar by minute purposely change in the technique parameter. The different technique parameters, which can be modified in high-performance liquid chromatography are pH, drift rate, the temperature of the column, and mobile phase composition.²⁶

Cleaning Validation

Cleaning validation is the process of assuring that cleaning procedures effectively remove the residue from manufacturing equipment/facilities below a predetermined level. Cleaning validation primarily applicable to the cleaning of process manufacturing equipment in the pharmaceutical industry. The term cleaning validation is to be used to describe the analytical investigation of cleaning procedures or cycle. It should also explain the development of acceptance criteria, including chemical and microbial specifications, limits of detection, and the selection of sampling methods.

Objectives

The reasons for validating the cleaning procedure:

- It is a customer requirement.
- It ensures the safety and purity of the product.
- It is a regularity requirement in active pharmaceutical ingredient (API) product manufacture.
- Pharmaceutical products and API can be contaminated by other pharmaceutical products, cleaning agents, and microbial contamination. The objective of the cleaning validation is to verify the effectiveness of cleaning

procedures for removal of product residues, degradation products, preservatives, excipients and/or cleaning agents, as well as, the control potential microbial contamination.

Elements of Cleaning Validation

The cleaning validation should demonstrate that the procedure consistently removes residues of the substance previously manufactured down to levels that are acceptable and that the cleaning procedure itself does not contribute unacceptable levels of residual materials to the equipment. The limits set should be practical, achievable, and justifiable. In API manufacture, there may be partial reactants and unwanted byproducts that may not have been chemically identified.

Sampling Techniques

The selection of either of these techniques must be consistent with sound scientific judgment and must support the objective of the study, which is to demonstrate that the amount of residual material in the equipment has been reduced to acceptable levels. There are three known sampling methods:

Direct Surface Sampling

It involves the determination of the type of sampling methods used and its impact on the test data to check the interference of the sampling material with the test. Therefore, early in the validation program, it is crucial to assure the sampling medium and solvent if they are satisfactory and be readily used. The advantages of direct sampling are that areas hardest to clean and which are reasonable, acceptable, can be evaluated, leading to establishing a level of contamination or residue per given surface area.

Swab Sampling

Swabbing (or direct surface sampling) method or swab sampling does not cover the entire equipment surface area, therefore, sites must be chosen with care. It is important that, as a minimum, the swab sites represent worst-case locations on the equipment and that the result is then extrapolated to account for the total product contact surface area. The solvent used for swabbing should provide good solubility for the compound and should not encourage degradation.

Rinse Sampling

Sampling and testing of rinse samples for the residual active ingredient is a commonly adopted method to evaluated cleanliness. This is a fairly convenient method in many cases and requires control over the solvent used for rinsing, the contact time, and the mixing involved. The solvent should be selected based on the solubility of the active ingredient and should either simulate a subsequent batch of product or at least provide adequate solubility.²⁷⁻²⁹

CONCLUSION

This article gives an idea that what is validation, its types, why it is necessary. Validation has been proven assurance for the process efficiency and sturdiness, and it is the full-fledged quality attributing tool for the pharmaceutical industries. The method validation process and minimum requirements to be

included in a regulatory method, cleaning procedures, and steps involved in each validation type are also discussed. Validation is a necessary process in the pharmaceutical industry, and it is used to assure that the quality is worked into the procedures supporting the development of drug and production.

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