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PHARMACEUTICAL VALIDATION: A REVIEW

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Abstract:

The action to dispose of non-conforming products initiated by quality assurance. Achieving and maintaining the quality of the final product validation is an important step. For maintaining the quality, validation is an important tool. The main goal of any industry and its products manufactured is Quality. If each process step is validated, then we can assure that the final product is of the best quality. The demonstrated documented proof that gives the high intensity of affirmation that a specific process constantly produces a product meeting its proposed specifications and quality characteristic is process validation.

Keywords: *Validation, Analytical method validation, Cleaning validation, Process validation, Equipment validation, Performance qualification.*

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INTRODUCTION:

Validation is the documentary evidence demonstrating that a procedure, process, or activity, carried out in testing, and then production which maintains, the desired level of compliance at all stages. Quality, safety, and efficacy are designed into the product.[1] Quality cannot be adequately assured just by in-process; and finished-product inspection or testing. Validation studies have been conducted in the pharmaceutical industry for a long time that increases interest in validation owing to their industry's greater emphasis in recent years on quality assurance program and is fundamental to a systematic production operation. The term validation has expanded through the years to accept 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 process control. Validation is an important and integral part of current good manufacturing practices (cGMP). Validation is a team effort where it involves people from different disciplines of the plant.[3,4]

VALIDATION:

The validation process is the documented evidence that provides a high degree of assurance to the desired result with predetermined compliance. Validation is a tool of quality assurance. To check and improve the quality since a wide variety of procedures, methods, or activities are validated. In the mid-1970s, first proposed the concept of validation by the Food and Drug Administration (FDA) to improve the quality of pharmaceutical products. Validation supports the respective company's promise of quality assurance in different pharmaceutical organizations or industries. The confirmation of the quality in equipment systems, manufacturing process, software, and testing methods are provided by validation. [32,33]

NEED OF PHARMACEUTICAL VALIDATION:

An inherent part of quality assurance is validation. It involves the systematic study of systems, facilities, and processes aimed at determining whether they perform their intended functions satisfactorily and consistently as specified. Validation improves the process and confirms that the process has been properly developed and is under control. A validated process is one that signifies a high degree of assurance that uniform batches will be produced that meet the required specifications.[5]

The pharmaceutical industries are concerned about validation because of the following reasons.

i. Assurance of quality.
ii. Cost reduction.
iii. Government regulation [6]

STRATEGY FOR VALIDATION:

The Validity of a particular strategy must be exhibited in lab experiment tests utilizing tests or gauges that are like the unknown examples broke down in the schedule. The arrangement and execution must take after an approval convention ideally written in a well-ordered format as below:

1. Improve a validation protocol or working system for the validation
2. Describe the application reason and range of the technique
3. Describe the execution parameters and acceptance criteria
4. Describe validation tests
5. Confirm pertinent execution qualities of the hardware
6. Select quality materials, e.g., standards and reagents
7. Execute pre-validation tests[29,30,31]

TYPES OF VALIDATION:

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

I. Analytical method validation
II. Cleaning validation
III. Process validation
IV. Equipment validation

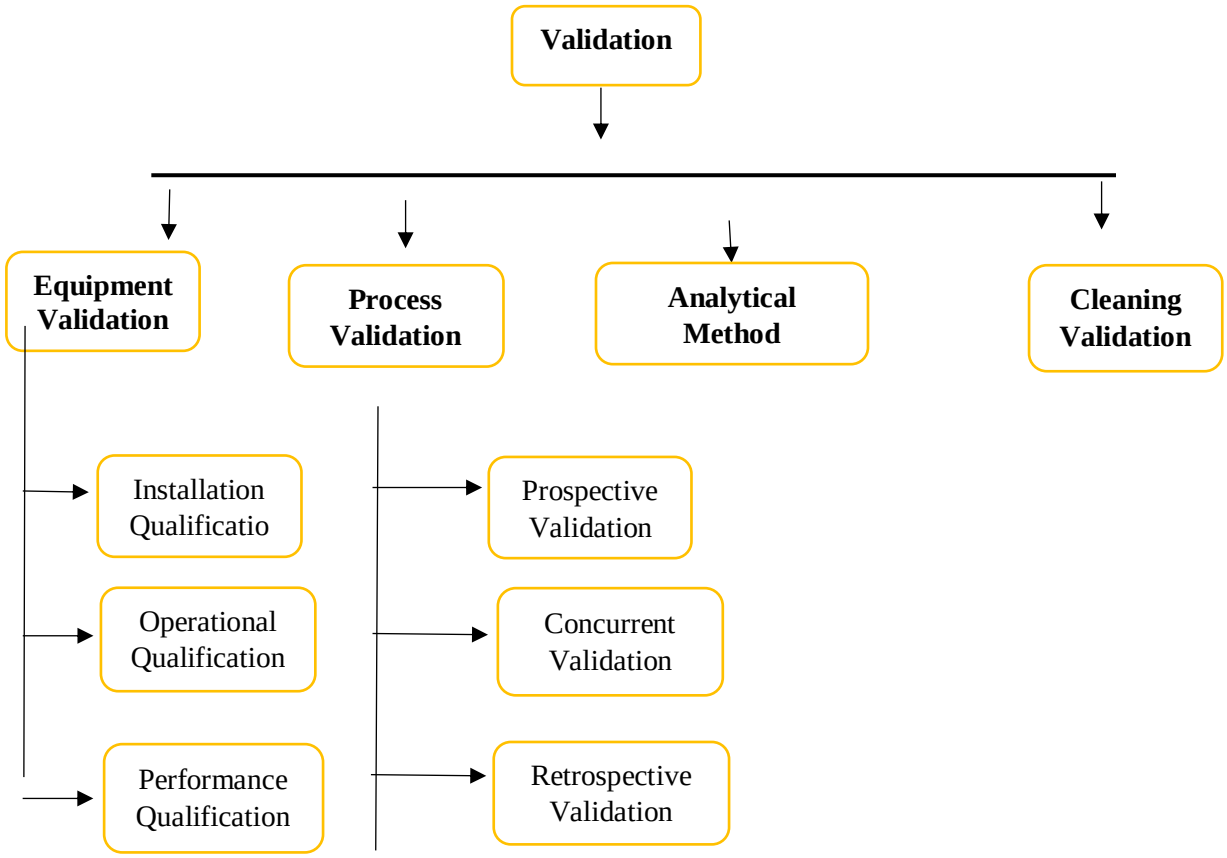

Fig: Types of Validation

I. Analytical method validation: To make proof that the method will do what it is supposed to do, accurate, reliable, and consistent results is the goal of method validation. As per the International Conference on Harmonization (ICH) guidelines, the validation parameters are described below.[7]

1) Accuracy: Accuracy has stated the closeness of agreement between the values found and values that are already available. It also is defined as the closeness between the true value and the observed value. It is sometimes called trueness, and it could be determined by using at least nine determinations over a minimum of three concentrations over the specified range.[8]

2) Precision: The closeness of agreement between a series of measurements multiple samplings of the same homogeneous sample under prescribed conditions. The precision of the test method is usually expressed as the standard deviation or relative standard deviation of a series of measurements.[31] Precision are of three levels:

a. **Repeatability:** It states that the exactness below a similar operating condition over a brief interval of time and is also called intra-assay precision. A minimum of six replicates test preparation of a similar or consistent sample ready at the 100% check.[10]

b. **Intermediate precision:** It expresses the exactness inside research laboratories, in distinct days, through distinct analysts, and on distinct instruments or equipment. Two different analysts, each preparing six sample solutions, as per the specified method.

c. **Reproducibility:** According to the analytical technique, reproducibility refers to the precision between different analytical labs; every research facility set up an aggregate of six sample solutions.[11]

3) Specificity: The analytical technique should reveal specificity at every stage of development. The technique should have the power to unequivocally assess the analyte of interest, whereas, within the presence of all expected parts,

which can encompass degradants, excipients/sample matrix, and sample blank peaks. [12]

4) **Limit of detection (LoD):** The lowest quantity of an analyte is detected by the chromatographic separation; although, it is not necessary that this quantity will quantify as a precise value. A blank resolution is injected, and peak to peak quantitative noise relation that we have to determine from blank chromatograms. The formula for calculating LoD is,
   LoD = 3.3 δ/S
   Where δ = standard deviation of intercepts of calibration curves.
   S = the slope of the linearity plot. The slope shall be estimated from the calibration curve of the analyte.[13,31]
5) **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,
   LoQ = 10 × SD/S,
   Where SD = Standard deviation of response, S = Slope of the calibration curve.[14]
6) **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.
7) **Range:** It can be characterized as the interval between upper and lower quantities of analyte in the sample. The minimum of the specified range is to be 80 to 120% of the test sample for the assay test.[15]
8) **Ruggedness:** Under the different conditions such as in different labs, different analysts, different machines, environmental conditions, operators, etc. ruggedness is the degree of reproducibility. [16]
9) **Robustness:** The ability of an analytical technique to stay similar by minute purposely change in the technique parameter. The different technical parameters are pH, drift rate, the temperature of the column, and mobile phase composition, which can be modified in high-performance liquid chromatography.[17]

II. **Cleaning Validation:** Cleaning validation provides documented setup with a high degree of surety that particular system/equipment or part of the equipment is consistently clean-up to predetermined quality and acceptable limits. Pharmaceutical products are contaminated by various substances such as lubricants, airborne materials, prepared product residues, and microbes. Hence, an adequate cleaning procedure plays an essential role to prevent contamination and cross-contamination. [18,19]

III. **Process Validation:** The manufactured product will meet their predetermined criteria and quality attributes with reproducible and constant results because the process validation is assuring and documenting the process within specified and designed criteria.[20]
   Types of Process Validation:
   1. Prospective validation
   2. Concurrent validation
   3. Retrospective validation
   4. Revalidation

1. **Prospective Validation:** It is documented evidence in which the system does what it purports to do based on a pre-planned protocol. Before distribution, either a new product or a product made under a revised manufacturing process is performed on at least three successive consecutive batches is usually carried out by this type of validation.
2. **Concurrent validation:** It is akin to the prospective validation, but the difference only the operating firm will sell the product during the qualification runs to the public at its market price.
3. **Retrospective Process Validation:** The formation of documented evidence that a system does what it purports to do on review and analysis of historical information is known as retrospective process validation. The origin of such data is production, QA, and QC records.
4. **Revalidation:** It is the repetitive action of a validation process. Batch size, formulation, equipment plans, or site location and in the case of sequential batches that do not meet product and process specifications and is also carried out at specific time intervals in case of no changes.[21,22,23,24]

IV. **Equipment Validation:** Equipment validation is known as qualification. Equipment validation is classified into the Design Qualification (DQ), Installation Qualification (IQ), Operational Qualification (OQ), and Performance Qualification (PQ). An IQ documents specific static attributes of a facility or item to prove that the installation of the unit has been accurately performed and that the installation specifications of the manufacturer have been met. [19,25,32]

Types of Qualifications:

1. **Design Qualification (DQ):** For the intended purpose, the documented verification that the proposed design of the facilities, systems, and equipment is suitable. The objectives of GMP with respect to equipment the principles of design should be such as to achieve.
2. **Installation Qualification (IQ):** On the new or modified facilities, systems, and equipment, installation qualifications should be carried out. The following main points should be considered in the installation qualification:
   - **i.** Examine the installation of equipment, piping, services, and instrumentation.
   - **ii.** Assembly of supplier's operating working instructions and maintenance requirements and their calibration requirements.
   - **iii.** Verification of materials of construction. Sources of spares and maintenance.
3. **Operational Qualification (OQ):** The facilities, systems, and equipment are the documented verification as installed or modified, perform as intended throughout the anticipated operating ranges. OQ should include the following:
   - **i.** Tests developed from the knowledge of the processes, systems, and equipment.
   - **ii.** Defining lower and upper operating limits.
   - **iii.** Sometimes, these are called "worst-case" conditions.
4. **Performance Qualification (PQ):** It is defined as the process to verify that the system is repeatable and consistently producing a quality product, or in other words, the process to demonstrate that the instrument can fulfill requirements outlined in the design qualification. The process is effective and reproducible, establishing the confidence by performance qualification that a process is in accordance with the design qualifications. [26,27,28,33]

CONCLUSION:

This article gives ideas about what is validation, validation types, how validation tools play a crucial role in assuring the quality attributes and their parameters. Validation is the important and acknowledged parameter of cGMP. Overall we will conclude that the aim of the validation is to indicate that processes involved within the development and manufacture of medicine, like production, cleaning, and analytical testing.

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