VALIDATION

In pharmaceutical manufacturing industry, validation is very important part of quality assurance and in Good Manufacturing Practice activities or guidelines.

The concept of validation was first proposed by Food and Drug Administration (FDA) officials, Ted Byers and Bud Loftus, in the mid 1970's in order to improve the quality of pharmaceuticals.

Food and drug administration (FDA): Establishing documented evidence that establishes a high degree of certainty that a particular process will consistently produce a product meeting its pre-determined specifications and quality attributes.

World health organization (WHO): Action of providing that any procedure, process, equipment, material, activity, or system actually leads to the expected results.

ISO: Validation is the confirmation by examination and the provision of objective evidence that the particular requirements for a specific intended use are fulfilled.

European committee (EC): Action of providing in accordance with the principles of good manufacturing practice that any procedure, processes, equipment material, activity or system actually leads to the expected results. In brief validation is a process for effective Quality Assurance.

NEED FOR VALIDATION:

- Validation should thus be considered in the following situations:
- Totally new process
- New equipment
- Before introduction of a new method into routine use
- Process and equipment which have been altered to suit changing priorities;
- Process where the end-product test is poor and an unreliable indicator of product quality

SCOPE:

- Validation requires an appropriate and sufficient infrastructure organization, documentation, personnel and finances.
- Analytical Test Methods

- Instrument Calibrations
- Process Utility Services
- Raw Material
- Equipment
- Facilities
- Product Design
- Cleaning
- Operators

CLASSIFICATION OF VALIDATION:

- Process Validation
- Method Validation
- Equipment validation
- Cleaning Validation
- Computerized system validation

PROCESS VALIDATION:

As per FDA Nov 2008, 'The collection of data from the process design stage throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality products.

Process validation life cycle:

Stage 1 - Process Design:

The commercial process is defined during this stage based on knowledge gained through development and scale-up activities

Stage 2 - Process Qualification:

During this stage, the process design is confirmed as being capable of reproducible commercial qualification of the facility, utilities and equipment.

Stage 3 - Continued Process Verification:

Maintenance, continuous verification and process improvement. Ongoing assurance is gained during routine production that the process remains in a state of control.

Assessed by collecting and monitoring information during commercialization.

Types of Process validation:

- Prospective validation
- Retrospective validation
- Concurrent validation
- Revalidation

Prospective validation:

Establishing documented evidence prior to process implementation. Product development stage. (premarket)

This is performed for all new equipment, products and processes. It is a proactive approach of documenting the design, specifications and performance before the system is operational. This is the most defendable type of validation.

It is normally undertaken for a new drug product or new facilities are introduced into a routine pharmaceutical production.

Retrospective validation:

This is establishing documented evidence that the process is performed satisfactorily and consistently over time, based on review and analysis of historical data.

The source of such data is production and QA/QC records. The issues to be addressed here are changes to equipment, process, specifications and other relevant changes in the past.

Concurrent validation:

Involves monitoring of critical processing steps and end product testing of current production.

Establishing documented evidences, a process does what it is supposed to do based on data generated during actual implementation of the process.

Revalidation:

Revalidation provides the evidence that changes in a process and / or the process environment, introduced either intentionally or unintentionally, do not adversely affect process characteristics and product quality.

This approach is essential to maintain the validated status of the plant, equipment, manufacturing processes and computer systems.

Categories:

Re-validation in cases of known change (including transfer of processes from one company to another or from one site to another)

Periodic Re-validation is carried out at scheduled intervals.

Re-validation is done when there is:

- Change of raw materials (Physical properties: density, viscosity, etc.)
- Change in starting material
- Changes in packing material
- Changes in process (mixing time, drying temperature)
- Change in equipment (addition of automatic detection systems)
- Production area and support system changes
- Transfer of processes to another site.

METHOD VALIDATION:

Method validation is the process to confirm that the analytical procedure employed for a specific test is suitable for its intended use. The method needs to be validated or revalidated.

• Before their introduction into routine use

• Whenever the conditions change for which, the method has been validated, e.g., an instrument with different characteristics

• Whenever the method is changed, and the change is outside the original scope of the method.

EQUIPMENT VALIDATION

As per FDA, May 1987, ‘Action of proving of providing that any equipment works correctly and leads to the expected results is equipment qualification. It is not single step activity but instead result from many activities.

Regulatory guidelines dictate that the equipment and instruments used to manufacture regulated products, such as APIs and finished pharmaceutical drugs, must be qualified to ensure the products are made in a safe environment.

CLEANING VALIDATION

A process of attaining and document in sufficient evidence to give reasonable assurance, given the current state of science and technology, that the cleaning process under consideration does, and/or will do, what it purpose to do."
Objective:
• To minimize cross contamination.
• To determine efficiency of cleaning process
• To do troubleshooting in case problem identified in the cleaning process and give suggestions to improve the process

COMPUTER SYSTEM VALIDATION:

In the context of drug manufacturing, CSV involves validating the computer systems (software and hardware) used in critical processes to ensure data integrity, security, and reliability.

CSV can be costly and time-consuming, particularly if you're validating on paper and haven't adopted a risk-based approach to determine the appropriate level of testing and documentation required to meet regulatory expectations.

DOCUMENTATION OF VALIDATION

Validation master plan: Plan on process involved

Validation protocol: Procedure and acceptance criteria, Execution of validation

Validation report: Documented results

VALIDATION MASTER PLAN

Validation in general requires a meticulous preparation and careful planning of the various steps in the process.

It should provide an overview of the entire validation operation its organizational structure, its content and planning.

It should be a summary document and should therefore be brief, concise and clear.

It is a document that summaries the firm's overall philosophy intentions and approach to be used for establishing performance adequacy.

Objectives:

- It serves as resource for development of equipment qualification and system validation project plans
- It answers to the inspector's question on the company's approach for validation
- It demonstrates corporate commitment and support for equipment qualification and computer system validation.
- It helps personnel at all management levels understanding how qualification and validation is approached and implemented in the organization.

The Validation Master Plan may contain elements (and policy) such as:

- Approval page and table of contents
- Introduction and objectives
- Facility and process description
- Personnel, planning and scheduling
- Responsibilities of validation team members
- Process control aspects
- Equipment, apparatus, processes and systems qualified, validated – and to be qualified or validated
- Acceptance criteria
- Documentation, e.g. validation protocols and reports
- SOPs
- Training requirements and other elements

Format and content:

- Introduction: Validation policy scope location and schedule
- Organization structure: Personnel responsibilities

- Plant/process/product description: rational for inclusions or exclusions and extent of validation
- Specific process consideration that are critical and those requiring extra attention
- Key acceptance criteria
- Documentation format
- Reference to the required SOPs
- Time plans of each validation project and sub-project
- List of products/processes/systems to be validated, summarized in a matrix format, validation approach
- Revalidation activities, actual status and future planning

Validation protocol:

A written plan stating how validation will be conducted including test parameters, product characteristics, production and packing equipment and decision points on what constitutes acceptable test results.

A qualification or validation protocol may contain:

- Objectives of the validation and qualification study
- Site of the study
- Responsible personnel
- Description of the equipment
- SOPs
- Standards
- Criteria for the relevant products and processes

Validation report:

A qualification or validation report should reflect the elements of the protocol, and may contain elements such as:

- Title
- Objective of the study
- Reference to the protocol
- Details of materials, equipment, instruments, personnel
- Programmes and cycles used
- Details of procedure and test methods

ANALYTICAL METHOD VALIDATION

Method validation is the process to confirm that the analytical procedure employed for a specific test is suitable for its intended use. The method needs to be validated or revalidated.

• Before their introduction into routine use

• Whenever the conditions change for which, the method has been validated, e.g., an instrument with different characteristics

• Whenever the method is changed, and the change is outside the original scope of the method.

Purpose of validation:

• Enable the scientists to communicate scientifically and effectively on a technical matter.

• Setting the standards of evaluation procedures for checking compliance and taking remedial action.

Validation Parameters:

• Accuracy

• Precision

• Specificity

• Limits of Detection

• Limit of Quantitation

• Linearity

• Range

• Ruggedness

• Robustness

• System suitability test

Accuracy:

It is defined as the closeness of agreement between the actual (true) value and means an analytical value obtained by applying a test method number of times.

Spike and recovery studies are performed to measure accuracy; a known sample is added to the excipients and the actual drug value is compared to the value found by the assay.

Accuracy is expressed as the bias or the % error between the observed value and the true value (assay value/actual value x 100 %.)

The accuracy is acceptable if the difference between the true value and mean measured value does not exceed the RSD values obtained for the repeatability of the method.

Precision:

The precision of an analytical method is the degree of agreement among individual test results when the method is applied repeatedly to multiple sampling of a homogenous sample.

Precision is the measure of the degree of repeatability of an analytical method under normal operation and is normally expressed as the per cent relative standard deviation (%RSD) or the coefficient of variation (% CV) for a statistically significant number of samples.

According to the ICH, precision should be performed at three different levels:

- repeatability,
- intermediate precision, and
- reproducibility.

Repeatability:

Repeatability is the result of the method operating over a short time interval under the same conditions (or) is the % RSD of multiple determinations of a single sample in a single test run (intra-assay precision). It should be determined from a minimum of nine determinations covering the specified range of the procedure (for example, three levels three repetitions each) or from a minimum of six determinations at 100% of the test or target concentration.

Intermediate precision:

Intermediate precision expresses within-laboratories variations: different days, different analysts, different equipment, etc.

Reproducibility:

Reproducibility expresses the precision between laboratories (collaborative studies, usually applied to standardization of methodology).

Specificity:

An analytical method can assess unequivocally the analyte of interest in the presence of components that may be expected to be present, such as impurities, degradation products and matrix components.

It is not possible to demonstrate that an analytical procedure is specific for a particular analyte.

In such a case, a combination of two or more analytical procedures is recommended to achieve the necessary level of discrimination.

Limits of Detection:

The limit of detection (LOD) is defined as the lowest concentration of an analyte in a sample that can be detected, not quantitated.

It is a limit test that specifies whether or not an analyte is above or below a certain value. It is expressed as a concentration at a specified signal-to-noise ratio, usually two or three-to-one.

$$\mathbf{LOD = 3.3\sigma / S}$$

Here σ is the standard deviation of the response and S is the slope of the calibration curve.

Limit of Quantitation:

The limit of quantitation (LOQ) is defined as the lowest concentration of an analyte in a sample that can be determined with acceptable precision and accuracy under the stated operating conditions of the method.

That is, as the LOQ concentration level decreases, the precision increases. If better precision is required, a higher concentration must be reported for LOQ.

$$\mathbf{LOQ = 10\sigma / S}$$

Here σ is the standard deviation of the response and S is the slope of the calibration curve.

Linearity:

An assay can obtain test results, which are directly proportional to the concentration of an analyte in the sample. The determination of linearity will identify the range of the analytical assay. It can be measured as the slope of the regression line and its variance or as the coefficient of determination (r) and correlation coefficient (r^2). r^2 value should be < 0.99.

Range:

The range is the interval between the upper and the lower levels of analyte (inclusive) that have been demonstrated to be determined with precision, accuracy and linearity using the method as written.

If the relationship between response and concentration is linear, the range may be estimated using a calibration curve.

Ruggedness:

Ruggedness, according to the USP, is the degree of reproducibility of the results obtained under a variety of conditions, expressed as %RSD. The ruggedness of an analytical method is the degree of reproducibility of test results obtained by the analysis of the same samples under a variety of conditions such as different laboratories, different analysts, different instruments, different lot of reagents, different elapsed assay times, different assay temperatures, different days, etc.

Robustness:

ICH defines robustness as a measure of the method's capability to remain unaffected by small, but deliberate variations in method parameters. Robustness can be partly assured by good system suitability specifications. The evaluation of robustness should be considered during the development phase and depends

on the type of procedure under study. It should show the reliability of analysis concerning deliberate variations in method parameters.

Examples of typical variations are:

• Stability of analytical solutions

• Extraction time

In the case of liquid chromatography, examples of typical variations are

• Influence of variations of pH in a mobile phase

• Influence of variations in mobile phase composition

• Different columns (different lots and/or suppliers)

• Temperature

• Flow rate.

In the case of gas-chromatography, examples of typical variations are

• Different columns (different lots and/or suppliers)

• Temperature

• Flow rate.

System Suitability Test:

System suitability test is commonly used to verify the resolution, column efficiency and repeatability of the chromatographic system to ensure its adequacy for a particular analysis.