QUALITY ASSURANCE

VALIDATION

Definition :

Each of the regulatory bodies have defined validation in different words . Some of the important definitions include :

European Commission , 1991:

" Validation is the act of proving , in accordance with GMPs , that any process actually leads to the expected results."

In 2000, this definition was modified to read as ;

" validation is documented evidence that the process within established parameters, can perform effectively & reproducibly to produce a Medicinal product meeting its predetermined specifications & quality attributes .

US FDA Definition :

"Process validation is established documented evidence which provides a high degree of assurance that a specified process will consistently produce a product meeting its predetermined specifications & quality characteristics.

ICH Definition :

" Process Validation is the means of ensuring & providing documentary evidences that processes within their specified design parameters are capable of repeatedly & reliably producing a finished product of the required quality."

WHO Definition :

" Validation is the documented act of providing that any procedure , process , equipment , material , activity or system actually leads to expected result ."

SCOPE OF VALIDATION :

Pharmaceutical manufacturers have to make sure their validation program covers all the important areas of pharmaceutical processing . The major areas include:

- Equipment's validation .
- Process validation.
- Cleaning validation.
- Analytical methods validation.

TYPES OF VALIDATION :

Validation can be done at different stages of the process . According , there are 3 main types of validation :

1. Prospective Validation – done before the process commences.
2. Concurrent Validation –done as the process is going on .
3. Retrospective Validation – done on already completed process.

1) Prospective Validation :

It is defined as established documented that a given system actually dose what it purports to do on the basis of a previously determined protocol.

Information in prospective Validation Protocol:

- Brief description of process to be validation.
- Summary of the critical manufacturing steps to be studied.
- Analytical test methods to be used & their validation status .
- Methods to record result & evaluate the data obtained.

2) Concurrent Validation:

concurrent validation involves monitoring of the critical processing & prospective & testing steps at the in –process stage. It is almost the same as prospective validation except that the manufacturer will sell the product manufactured during the validation run, provided they meet all the pre-determined quality requirements .Documentation for concurrent validation is same as that for prospective validation .

3) Retrospective Validation :

Retrospective validation is defined as establishing documented evidence that a system performs as purported , by reviewing the historical data that had been collected during the manufacturing & testing stages.

Elements to be considered for retrospective validation :

- Batches manufactured during the defined period .
- Batch size & strength .
- Process deviations list.
- Corrective actions list.
- Stability testing data for several batches.

REVALIDATION :

During the normal coarse of operations , it may become necessary to introduce changes in the process the quality . Occasionally , new equipment's may be installed in the utility system.

Often , due to wear & tear , over the course of time , there may be a drift from normal operating conditions . This makes it important for manufacturers to make sure they schedule a periodic revalidation of their system & process to confirm that they continue to perform as expected to meet the prescribed quality requirements.

Change that Necessitate Revalidation :

1. Change in raw materials which tend to affect product or process quality.
2. Change in vendor from whom APIs & other raw materials are produced .
3. Change in the primary container or other packaging material.
4. Any change in the facility .
5. Process change .

Validation Master Plan :

A validation Master Plan (VMP) is defined as the document that provides information about the company's validation programme. This document must contain details of validation to be done, & the timeframe for the studies to be performed .

The WHO guidelines define VMP as " a high –level document that establishes & umbrella validation plan for the entire project & summaries the manufacturer overall philosophy & approach .

Purpose of VMP :

1. It helps to manage to understand how much time will be required , personnel to be involved , & expenses expected to be incurred.
2. It informs members of the validation team about their jobs & responsibilities .
3. It helps auditors to understand the company approach to validation activities.

Elements of Good VMP :

- Company validation policy .
- Organizational structure.
- List of items to be validated.
- Change control procedure.
- Training requirements for validation team.
- Brief outline of system,equipments , facilities & processes to be validated.
- Formats for documenting protocols & test reports.

Contents of VMP:

1. Title page with document number & version information , & authorization in the form of approval signature .
2. Table of contents listing out critical areas of the VMP.
3. Glossary to define technical terms & abbreviations .
4. Managements approach to validation .
5. Services to be outsourced to outside vendors .
6. Change control procedure,
7. Risk management policy.

Analytical Method Validation :

Definition :

Analytical method validation is defined as the process of establishing ,through laboratory studies , that the procedures performance characteristics meet the requirements for its intended use.

Analytical method validation is not a one time activity . Methods need to be revalidated on a regular basis to ensure they are suitable to analyze materials in use at that point of time .

Steps in Analytical Methods Validation :

1. Planning analytical methods validation .
2. Writing the protocol & getting it approved .
3. Executing the approved protocol.
4. Analyzing validation data obtained .
5. Reporting results of validation .
6. Finalizing the analytical method procedure based on validation result.

Analytical Method Validation Parameters :

The analytical performance parameters that must be a part of validation programs include the following :

- Accuracy
- Precision
- Specificity
- Detection limit
- Quantitation limit
- Linearity
- Range robustness

Finalizing the Analytical Procedure :

following a successful analytical method validation , the final analytical procedure must be established & documented .

1. Rationale for the procedure & capabilities of the method . If the method is a revised one, advantages of the revision must be described.
2. Complete details of analytical procedure to allow the method to be replicated by anyone reading.

3.List of impurities that are permitted & their limits for impurity assay.
4.Validate data.
5.Revision history .
6.Signatures of authorized personnel

Analytical Methods Revalidation :

validated methods need to be validated in the following situations :

1. When a significant change has been introduced in the process of synthesizing the drug substance.
2. When a new impurity is encounted , changing the specificity profile of the method.
3. If change are made in excipients composition which can introduce new impurities.
4. When there is change in major equipment degradation profile of the API .

Calibration of pH meter :

1. Switch on the pH meter, & wait for enough time for it to warm up .
2. Remove the electrode from its storage solution , rinse with distilled water & blot dry using a piece of tissue paper . Avoid rubbing the electrode while drying to prevent damage to sensitive membrane that surrounds it.
3. Place the electrode tip into buffer solution of pH 7.00 & press the " Measure" or "calibrate " button, & wait for the display to stabilize .
4. Adjust the calibration button to make the display read 7 if required .
5. Remove the electrode from the buffer solution rinse with distilled water & blot dry using fresh tissue paper.
6. Place the electrode into buffer solution of either pH 4.01 or 9.20 & wait for the display to stabilize.
7. Adjust the calibration button to make the display read the pH as 4.01 or 9.20 depending on which buffer you have used.
8. Remove the electrode from the buffer
9. Place the dried electrode back into the storage solution.

Qualification of UV – Visible Spectrophotometer :

The UV Visible spectrophotometer is an instruments that is used to measure absorbance of solution over the ultraviolet & visible ranges of electromagnetic spectrum , generally between 200-800 nanometer.

Qualification of the UV – Visible spectrophotometer involves the following steps :

1) Design Qualification : The type & make of the instruments to be purchased must be chosen carefully depending on the specific requirements of the type of sample that will need to be measure.
2) Installation Qualification : the installation site must be away from dust, corrosive liquids or gases & direct sunlight. Remove the instruments from its packaging material
3) Operational Qualification : connect the instruments to the mains & switch it on . Follow the operating manual instructions
4) Performance Qualification : define the performance criteria that are most important to routine operations .define the acceptance criteria for these performance criteria selected.