

## Pharmaceutical Validation: criteria exposure pharmaceutical importance

<sup>1</sup>Shailesh Pradhan\*, <sup>2</sup>Chandrakant Sahu, <sup>3</sup>Hitesh Bhoi, <sup>4</sup>Sachin Bishwal, <sup>4</sup>Bharti Pradhan,

<sup>1</sup>M.Pharma, Department of Pharmaceutical Quality Assurance, Columbia institute of pharmacy, Raipur (C.G.)

<sup>2</sup>M.Pharma, Department of Pharmaceutical Quality Assurance, Columbia institute of pharmacy, Raipur (C.G.)

<sup>3</sup>M.Pharma, Department of Pharmacology, Columbia institute of pharmacy, Raipur (C.G.)

<sup>4</sup>M.Pharma, Department of Pharmaceutical chemistry, Royal college of pharmacy, Raipur (C.G.)

<sup>4</sup>M.Pharma, Department of Pharmacology, Columbia institute of pharmacy, Raipur (C.G.)

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### ABSTRACT

Pharmaceutical validation is main processes for development and manufacturing of any pharmaceutical product. It is establishing documented evidence which provides a high degree of assurance that a specified process will consistently produce a product meeting its pre-determined specifications and quality characteristics. Process validation is a systemic approach to indenting, measuring, evaluating, documenting and revaluation the critical steps in the manufacturing process to ensure reproducible quality products. Pharmaceutical equipment validation in pharma industries is quite simple to proceed. The various stages of the process are thoroughly investigated and documented in accordance with approval from pharmaceutical industry. Validation of analytical method is adopted to confirm that the employed analytical procedure for a specific tests meet the intended requirements. Guidelines from the USP, ICH, FDA etc., can provide a framework for validations of pharmaceutical methods. Cleaning validation is documented evidence with high degree of assurance that one can consistently clean a system or piece of equipment to predetermined and acceptable limits.

**Key word:-**Validation, Quality assurance, Process validation, Parameters of Analytical methods, Equipment validation, Cleaning validation

### I. INTRODUCTION

The word validation simply means assessment of validity or action of proving effectiveness. Validation is a team effort where it involves people from various disciplines of the plant.

The word validation simply means assessment of validity or action of proving effectiveness. Validation is a team effort where it involves people from various disciplines of the plant.

This principle incorporates the understanding that the following conditions exist: Quality, safety, and efficacy are designed or built into the product. Quality cannot be adequately assured merely by in-process and finished product inspection or testing each step of a manufacturing process is controlled to assure that the finished product meets all quality attributes including specifications.

### Relative Terms/ elaboration

#### ACCORDING TO EUROPEAN COMMISSION

1991 –Validation-“Act of proving, in accordance of GMPs that Any...” process actually leads to expected results.

2000 -“Documented evidence that the process, operated within established Parameters, can perform effectively and reproducibly to produce a Medicinal product meeting its predetermined specifications and quality attributes”.

#### ACCORDING TO US FDA

“Process validation is establishing documented evidence which provides a high degree of assurance that a specified process will consistently produce a product meeting its pre-determined specifications and quality characteristics.

### ACCORDING TO WHO

“The documented act of proving that any procedure, process, equipment, material, activity or system actually leads to expected result.”

### REQUIREMENT 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.

### TYPES OF VALIDATION

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

1. Process validation
2. Equipment validation
3. Analytical method validation
4. Cleaning validation

#### 1. PROCESS VALIDATION\

Process validation is a basic factor for drug product safety and quality and thus a fundamental component of the quality assurance. Process validation is a systemic approach to indenting, measuring, evaluating, documenting and reevaluation the critical steps in the manufacturing process to ensure reproducible quality products.

Process validation is a quality assurance function that helps to ensure drug product quality by providing documented evidence that the manufacturing process consistently does what it is suppose to do.

Process validation is widely practiced by pharmaceutical, biotechnological, medical device and herbal industries.

### TYPES OF PROCESS VALIDATION:

#### (A) Prospective Validation:

- Conducted prior to the distribution of either a new product or a product made under a modified production process, where the modifications are significant and may affect the products characteristics.
- It is a preplanned scientific approach and includes the initial stages of formulation development, process development, setting of process specifications, developing in-process tests sampling plans, designing of batch records, defining raw material specifications, completion of pilot runs, transfer of technology from scale-up batches to commercial size batches, listing major process is executed and environmental controls.
- In Prospective Validation, the validation protocol is executed before the process is put into commercial use. It is generally considered acceptable that three consecutive batches/runs within the finally agreed parameters, giving product of the desired quality would constitute a proper validation of the process. It is a confirmation on the commercial three batches before marketing.

#### (B) Concurrent Validation:

A process where current production batches are used to monitor processing parameters. It gives of the present batch being studied, and offers limited assurance regarding consistency of quality from batch to batch.

Concurrent Validation may be the practical approach under certain circumstances. Examples of these may be when:

- A previous validated process is being transferred to a third party contract manufacturer or to another site.
- The product is a different strength of a previously validated product with the same ratio of active/inactive ingredients.
- The number of lots evaluated under the Retrospective Validation were not sufficient to obtain a high degree of assurance demonstrating that the process is fully under control. The numbers of batches produced are limited.
- Process with low production volume per batch and market demand.
- Process of manufacturing urgently needed drug due to shortage or absence of supply.

- In all above cases concurrent validation is valid, provided following conditions are appropriately.
- Pre-approved protocol for concurrent validation with rational.
- A deviation shall be raised with justification and shall be approved by plant head /head process owner/Head-QMS.
- Product behaviour and history shall be reviewed based on developmental/scale up /test batches.
- A detailed procedure shall be planned for handling of the marketed product if any adverse reactions observed in concurrent validation process.
- Concurrent validation batches shall be compiled in report and shall be approved all key disciplines.

**(C) Retrospective Validation:**

Retrospective Validation may be used for older products which were not validated by the fabricator at the time that they were first marketed, and which are now to be validated to confirm to the requirements of division 2, Part C of the Regulation to be Food and Drugs Act. Retrospective Validation is only acceptable for well established detailed processes and will be inappropriate where there have recent changes in the formulation of the products, operating procedures, equipment and facility.

Some of the essential elements for Retrospective Validation are:

- Batches manufactured for a defined period (minimum of 10 last consecutive batches).
- Number of lots released per year.
- Batch size/strength/manufacturer/year/period.
- Master manufacturing/packaging documents.
- List of process deviations, corrective actions and changes to manufacturing documents.
- Data for stability testing for several batches.
- Trend analysis including those for quality related complaints.

**(D) Revalidation:**

It is the repetition of a validation process or a part of it. This is carried out when there is any change or replacement in formulation, equipment plans or site location, batch size and in the case of sequential batches that do not meet product specifications and is also carried out at specific time intervals in case of no changes.

**2. EQUIPMENT VALIDATION**

The process of pharmaceutical equipment validation in pharma industries is quite simple to proceed. The various stages of the process are thoroughly investigated and documented in accordance with approval from pharma industry/company.

The process of procurement normally starts by the production of required documentation and user requirement specification. To perform validation project/plan, a form of change request should be taken from the existing facilities. As earlier the management agreed to proceed, the request is issued to perform validation project. Then with approved Validation Plan, the validation protocol can be started that required to verify that all the requirements documented in the user requirement specification and all cGMP requirements are fulfilled

**PHASES OF EQUIPMENT VALIDATION :**

The process of equipment validation is mainly divided into three phases:

**Phase-1:Pre-validation phase**

Pre-Validation Phase or the Qualification Phase, which covers all activities relating to product research and development, formulation, pilot batch studies, scale-up studies, technology transfer to commercial scale batches, establishing stability conditions, storage and handling of in-process and finished dosage forms, Equipment Qualification, Installation Qualification, Master Formula Record, Operational Qualification and Process Capability.

**Phase-2: Process validation phase**

Process Validation Phase (Process Qualification phase) designed to verify that all established limits of the Critical Process Parameters are valid and that satisfactory products can be produced even under the “worst case” conditions

**Phase-3: Validation maintenance phase**

Validation Maintenance Phase requiring frequent review of all process related documents, including validation audit reports to assure that there have been no changes, deviations, failures, modifications to the production process, and that all SOPs have been followed, including Change Control procedures.

At this stage the Validation Team also assures that there have been no changes/deviations that should have resulted in Requalification and Revalidation

## TYPES OF EQUIPMENT VALIDATION

### A. Design qualification (DQ)

The design qualification outline the key features of the system designed to address the user requirements, regulatory compliance and selection rationale of a particular supplier.

Caution should be taken when putting together a design qualification since it will have major

impact on installation, operation and performance qualification. The more function that are specified in design qualification, the more work have to be included in the Installation, operational and performance qualification processes.

Important DQ consideration includes:

- GMP's and regulatory requirements.
- Performance criteria.
- Facility air flow.
- Reliability and efficiency.
- Commissioning requirements.
- Construct ability & installation of equipment.

### B. Installation qualification (IQ)

Documentary evidence to prove that the premises, supporting utilities and the equipment have been built and installed in compliance with their design specifications.

Important IQ consideration include:

- Installation conditions (wiring, utilities, and functionality).
- Calibration, Preventive maintenance, cleaningschedules.
- Safety features.
- Supplier documentation, prints, drawings and manuals.
- Software documentation
- Spare parts list.

### C. Operational qualification (OQ)

Operational qualification is a series of tests that measures the performance capability of the equipment. Operational qualification focuses on the equipment, rather than demonstrating performance capabilities relating to producing a particular product.

OQ considerations include:

- Process control limits (time, temperature, pressure, line speed, and setup conditions).
- Software parameters.
- Raw material specification.

- Process operating procedures.
- Material handling requirements.
- Process change control.
- Training.
- Short term stability and capability of the process.

### D. 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 requirement outlined in the design qualification.

PQ consideration includes:

- Actual product and process parameters and procedures established in OQ.
- Acceptability of the product.
- Assurance of process capability as established in OQ.
- Process repeatability, long term process stability.

## 3. ANALYTICAL METHOD VALIDATION

The process of validation of analytical method is adopted to confirm that the employed analytical procedure for a specific tests meet the intended requirements. Guidelines from the USP, ICH, FDA etc., can provide a framework for validations of pharmaceutical methods. Results from the method validation can be considered to judge its quality, reliability as well consistency pertaining to analytical results.

Analytical methods need to be validated, verified, or revalidated in the following instances:

- Before initial use in routine testing.
- When transferred to another laboratory

## NEED OF ANALYTICAL METHOD VALIDATION:

- Develop a validation protocol or operating procedure for the Validation
- Define the application, purpose and scope of the method
- Define the performance parameters and acceptance criteria
- Define validation experiments
- Verify relevant performance characteristics of equipment
- Qualify materials, e.g. standards and reagents
- Perform pre-validation experiments
- Adjust method parameters or/and acceptance criteria if necessary

- Perform full internal (and external) validation experiments
- Develop SOPs for executing the method in the routine
- Define criteria for revalidation

#### PARAMETERS OF ANALYTICAL METHOD OF VALIDATION:

1. Accuracy
2. Precision (repeatability and reproducibility)
3. Linearity
4. Range
5. Limit of detection (LOD)
6. Limit of Quantitation (LOQ)
7. Selectivity/ specificity
8. Robustness
9. System suitability

##### 1. Accuracy:

The accuracy of an analytical procedure expresses the closeness of agreement between the value which is accepted either as a conventional true value or an accepted reference value and the value found. This is sometimes termed trueness. Accuracy should be established across the specified range of the analytical procedure.

There are three ways to determine accuracy:

- A. Comparison to a reference standard.
- B. Recovery of the analyte spiked into blank matrix.
- C. Standard addition of the analyte.

It should be clear how the individual or total impurities are to be determined.

##### 2. Precision:

The precision of an analytical procedure expresses the closeness of agreement (degree of scatter) between a series of measurements obtained from multiple sampling of the same homogeneous sample under the prescribed conditions.

Precision may be considered at three levels: repeatability, intermediate precision and reproducibility.

**A. Repeatability:** Repeatability expresses the precision under the same operating conditions over a short interval of time. Repeatability is also termed intra-assay precision.

Repeatability should be assessed using:

- (a) A minimum of 9 determinations covering the specified range for the procedure (e.g., 3 concentrations/3 replicates each).

- (b) A minimum of 6 determinations at 100% of the test concentration.

**B. Intermediate precision:** Intermediate precision expresses within-laboratories variations: different days, different analysts, different equipment, etc. The extent to which intermediate precision should be established depends on the circumstances under which the procedure is intended to be used. The applicant should establish the effects of random events on the precision of the analytical procedure. Typical variations to be studied include days, analysts, equipment, etc. It is not considered necessary to study these effects individually. The use of an experimental design (matrix) is encouraged.

**C. Reproducibility:** Reproducibility expresses the precision between laboratories (collaborative studies, usually applied to standardization of methodology). Reproducibility is assessed by means of an inter-laboratory trial. Reproducibility should be considered in case of the standardization of an analytical procedure, for instance, for inclusion of procedures in pharmacopoeias. These data are not part of the marketing authorization dossier.

##### 3. Linearity:

The linearity of an analytical procedure is its ability (within a given range) to obtain test results which are directly proportional to the concentration (amount) of analyte in the sample. Linearity should be evaluated by visual inspection of a plot of signals as a function of analyte concentration or content. If there is a linear relationship, test results should be evaluated by appropriate statistical methods, for example, by calculation of a regression line by the method of least squares. The correlation coefficient, y-intercept, slope of the regression line and residual sum of squares should be submitted. A plot of the data should be included. In addition, an analysis of the deviation of the actual data points from the regression line may also be helpful for evaluating linearity.

For the establishment of linearity, a minimum of 5 concentrations is recommended.

##### 4. Range:

The range of an analytical procedure is the interval between the upper and lower concentration (amounts) of analyte in the sample (including these concentrations) for which it has been demonstrated



that the analytical procedure has a suitable level of precision, accuracy and linearity.

The following minimum specified ranges should be considered:

**(a) For the assay of a drug substance or a finished (drug) product:** normally from 80 to 120 percent of the test concentration;

**(b) For content uniformity:** covering a minimum of 70 to 130 percent of the test concentration, unless a wider more appropriate range, based on the nature of the dosage form (e.g., metered dose inhalers), is justified;

**(c) For Dissolution Testing:** +/-20 % over the specified range;

#### 5. Limit of detection:

LOQ is determined by the analysis of samples with known concentration of analyte and by establishing that minimum level at which the analyte can reliably detected, but not necessarily quantitated as precise value, under the stated experimental conditions. The detection limit is generally expressed in the concentration of analyte (ppm) in the sample.

A number of approaches are recommended by the ICH for determining the detection limit of sample, depending on instrument used for analysis, nature of analyte and suitability of the method. The acceptable approaches are-

- Visual evaluation.
- Signal-to-noise ratio.
- Standard deviation of the response.
- Standard deviation of the slope of linearity plot.

The formula for calculating LOD is-

$$LOD = 3.3 \delta/S$$

Where  $\delta$  = standard deviation of intercepts of calibration curves.

S = the slope of linearity plot.

#### 6. Quantitation Limit (LOQ):

The quantitation limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be quantitatively determined with suitable precision and accuracy.

The quantitation limit is a parameter of quantitative assays for low levels of compounds in sample matrices, and is used particularly for the determination of impurities and/or degradation products. Several approaches for determining the quantitation limit are possible, depending on whether the procedure is a non-instrumental or instrumental. Approaches other than those listed below may be acceptable.

- Based on Visual Evaluation.
  - Based on Signal-to-Noise Approach.
  - Based on the Standard Deviation of the Response and the Slope
- The quantitation limit (QL) may be expressed as:  
**QL=10/S**

Where  $\sigma$  = the standard deviation of the response,  
S = the slope of the calibration curve.

The slope S may be estimated from the calibration curve of the analyte.

#### 7. Specificity:

One of the significant features of HPLC is its ability to generate signals free from interference. Specificity refers to the ability of the analytical method to differentiate and quantify the analyte in complex mixtures. An investigation of specificity is to be conducted during the determination of impurities and validation of identification tests. An ICH guideline defines specificity as ability to assess unequivocally the analyte in the presence of other compounds that may be likely to be present. Typically these might be impurities, degradants, matrix, etc. The definition has the following implications:

- **Identification test:** Identification tests should be able to differentiate compounds of closely related structure which are expected to be present i.e., to assure identity of an analyte.
- **Purity test:** To ensure that the analytical procedure performed allows an accurate statement of content of the impurity of an analyte i.e. related substances, residual solvents content, heavy metals, etc.
- **Assay:** To arrive at an accurate result, this permits a correct report on the potency or content of analyte in a sample.

#### 8. Robustness:

The robustness of an analytical procedure is a measure of its capacity to remain unaffected by small, but deliberate variations in method parameters and provides an indication of its reliability during normal usage. 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 an analysis with respect to deliberate variations in method parameters.

Examples of typical variations are: Stability of analytical solutions; Extraction time.

## 9. System Suitability:

System suitability testing originally believed by the industry of pharmaceuticals to decide whether a chromatographic system is being utilized day today in a routine manner in pharmaceutical laboratories where quality of results is most important which is suitable for a definite analysis. The parameters used in the system suitability tests (SST) report are as follows:

- Number of theoretical plates or Efficiency (N).
- Capacity factor (K).
- Separation or Relative retention ( $\alpha$ ).
- Resolution (Rs).
- Tailing factor (T).
- Relative Standard Deviation (RSD).

## 4. CLEANING VALIDATION

Cleaning validation is documented evidence with high degree of assurance that one can consistently clean a system or piece of equipment to predetermined and acceptable limits. Cleaning validation is primarily applicable to the cleaning of process manufacturing equipment in pharmaceutical industry. It is necessary to have effective cleaning programs in place because of regulatory requirements.

### Need of Cleaning Validation:

- Initial qualification of process/ equipment.
- Critical change in a cleaning procedure.
- Critical change in formulation.
- Significant change in formulation.
- Change in a cleaning process.
- Change in a cleaning agent.

### Contamination & Cross Contamination:

Generally cross contamination and contamination by a foreign material are two types of contamination.

Cross contamination is usually through an active ingredient from one product carrying over into subsequent manufactured.

### Mechanism of Contamination:

#### 1. Cross contamination with active ingredient:

One of the real dangers in cross contamination of active ingredients is that by being contaminated results in a multiple ingredient product instead of single active ingredient. Depending on medical effects, the contamination may enhance the action or negate the action or contaminant may have an entirely different medical effects.

**2. Microbiological contamination:** This form of contamination is particularly insidious because the contamination may develop at any time even after cleaning. A major contributing factor is the storage of equipment in a wet condition. This provides a natural medium in which bacteria can grow.

**3. Contamination by cleaning or sanitizing agents:** Some pharmaceutical operations may find it necessary to use fairly toxic materials for cleaning purpose for stubborn residues. This is particularly true in the manufacture of active pharmaceutical ingredients (APIs). As such, these materials represent a potential threat as contaminants. It seems obvious that one effective way of dealing with this potential problem is to use cleaning agents with the lowest toxicity that will still be effective in removing the residue in the given cleaning situation. The same factors also apply to sanitizing agents used to wipe down cleaned equipment.

**4. Contamination by miscellaneous other materials:** In addition to the usual expected or anticipated list of potential contamination in a pharmaceutical operation, many other less likely materials can also contaminate products. A partial list includes equipment parts such as excipients, bristles from brushes used in packaging filling equipment, paper filters, micron filters, fibers and rubber particles from gloves, cleaning aids such as brush bristles, cloth, and cotton fibers from rags and wiping materials, lubricants.

**Cleaning Agent selection:** Following cleaning agent are select for cleaning validation-

1. Water
2. Solvents
3. Commodity chemicals
4. Formulated cleaning agents

**1. Water:** It is the universal solvent. If water alone will effectively clean the product without undue time or physical effort to remove the residues, by all means employ water alone. For many, however the water alone requires an unacceptable increase in time to get the cleaning accomplished. For these individuals, one of the other approaches must be sought.

**2. Solvent:** These are typically applied in processes where solvent usage is already called for by the manufacturing process. For example, mother liquors are typically used as the solvents for cleaning of APIs. As the mother liquors is already known to dissolve the primary residue, there is little risk in employing it for cleaning.

**3. Commodity chemicals:** In this, chemicals such as NaOH can be used for cleaning as well. Like their solvent counterparts, there may be hazard issues, effluent issues associated with these materials. Their typically high alkalinity or low acidity, however, often makes them helpful in inactivation processes. However these chemicals lack the detergency of a formulated cleaning agent and they may be difficult to rinse, taking larger volumes of water to rinse free from systems than would a formulated cleaning agent.

**4. Formulated cleaning agent:** It is the largest class of cleaners. This category includes solvent based formulations and aqueous formulations. Typically formulated cleaning agents can include one or more alkalinity or acidity sources, surfactants builders, sequestrants, chelants and either a solvent or water. For industrial applications, unlike consumer-use products, these materials are formulated to be low foaming and therefore are more readily rinsable and are appropriate for high impingement or high turbulence cleaning.

## II. CONCLUSION-

Validation is the evidence document which is most widely used in pharmaceutical industry in drug development, manufacturing and specification of finished products. The consistency and reliability of a validated process to produce a quality product is the very important for an industry. Pharmaceutical Process Validation is the most important and recognized parameters of cGMP. The process validation is intended to assist manufacturers in understanding quality management system (QMS) requirements concerning process validation and has general applicability to manufacturing process. DQ, IQ, OQ, PQ are the most important factor for validation of all equipment and instrument which is used in pharmaceutical industry.

Validation of analytical method most important for quality control and assure the quality of product which are before and after manufacture in pharmaceutical industry. Requirement of validation is very necessary for any pharmaceutical company that manufacture drug product for human beings.

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