OVERVIEW OF VALIDATION AND BASICS CONCEPTS OF PROCESS VALIDATION


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ABSTRACT
Quality is the primordial intention to any industry and its products manufactured. Multiple views on obtaining such quality are the current interest in the pharmaceutical industry. Validation is the art of designing and practicing the designed steps alongside with the documentation. Validation and quality assurance will go hand in hand, ensuring the through quality for the products. Process Validation emphasize on process design elements and maintaining process control during commercialization and communicate that process validation is an ongoing program and align process validation activities with product lifecycle. Process validation also emphasizes the role of objective measures and statistical tools and analyses and emphasizes knowledge, detection, and control of variability and gives assurance on consistent of quality/productivity throughout life cycle of product. Process validation also emphasizes the role of objective measures and statistical tools and analyses and emphasizes knowledge, detection, and control of variability and gives assurance on consistent of quality/productivity throughout life cycle of product additionally a view of validation against the quality assurance, drug development and manufacturing process has been discussed.

KEYWORDS: Quality, Validation, Process Validation, Protocol, Prerequisite.

INTRODUCTION
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.[1]

Validation is a concept that has evolved in united states in 1978. 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 cGMP.[2]

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. The development of a drug product is a lengthy process involving drug discovery, laboratory testing, animal studies, clinical trials and regulatory registration. Process controls include raw materials inspection, in-process controls and targets for final product. The purpose is to monitor the online and off-line performance of the manufacturing process and then validate it. Even after the manufacturing process is validated, current good manufacturing practice also requires that a well-written procedure for process controls is established to monitor its performance.[3]

Validation mainly based on, FDA regulations describing current good manufacturing practice (cGMP) for finished pharmaceuticals are provided in 21 CFR parts 210 and 211. The cGMP regulations require that manufacturing processes be designed and controlled to assure that in-process materials and the finished product meet predetermined quality requirements and do so consistently and reliably. Process validation is required, in both general and specific terms, by the cGMP regulations in parts 210 and 211.

**History of validation**

The concept of validation was first proposed by two FDA officials, Ted Byers and Bud Loftus, in the mid 1970’s in order to improve the quality of pharmaceuticals (Agalloch 1995). It was proposed in direct response to several problems in the sterility of large volume parenteral market. The first validation activities were focused on the processes involved in
making these products, but quickly spread to associated process of pharmaceutical.

U.S.F.D.A. was the pioneer in advocating the concept of process validation, but till 29th September 1978 the definition of process validation did not appear in any part of literature of U.S.F.D.A. no cGMP regulations talked anything about process validation.[5]

Definitions[6-8]
ICH Definition
“Process Validation is the means of ensuring and providing documentary evidence that processes within their specified design parameters are capable of repeatedly and reliably producing a finished product of the required quality.”

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

Validation Set Up[14]
To establish the desired attributes. These attributes include physical as well as chemical characteristics. In the case of parenteral, these desirable attributes should include stability, absence of pyrogens, and freedom from visible particles.

Acceptance specifications for the product should be established in order to attain uniformity and consistently the desired product attributes, and the specifications should be derived from testing and challenge of the system on sound statistical basis during the initial development and production phases and continuing through subsequent routine production.

The process and equipment should be selected to achieve the product specification. For example; design engineers; production and quality assurance people may all be involved. The process should be defined with a great deal of specificity and each step of the process should be challenged to determine it adequacy. These aspects are important in order to assure products of uniform quality, purity and performance.
Table 1: Validation Team and Responsibilities.[15]

<table>
<thead>
<tr>
<th>Department</th>
<th>Designation</th>
<th>Responsibility</th>
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<tbody>
<tr>
<td>Research and development (R&amp;D)</td>
<td>Executive/Officer</td>
<td>To coordinate the entire validation process by scheduling meetings and discussions with production, quality control and quality assurance. Preparation of preliminary validation protocol, master formula record, monitoring the process, compiling and analyzing data and test results and preparing the final report. To review the preliminary validation documents.</td>
</tr>
<tr>
<td>Quality assurance</td>
<td>Officer</td>
<td>To coordinate the entire validation process by scheduling meetings and discussions with the team. Preparation of validation protocol, monitoring the process, compiling and analyzing data and test results and preparing the final report. To review of validation documents.</td>
</tr>
<tr>
<td>Production</td>
<td>Officer</td>
<td>To participate in performing the validation steps during manufacturing processes. To assist in collection of data.</td>
</tr>
<tr>
<td>Quality control</td>
<td>Officer</td>
<td>To test and report the test results.</td>
</tr>
<tr>
<td>Quality assurance</td>
<td>General manager Quality assurance</td>
<td>To approve the process validation protocol and report. To review of validation documents. To approve the process.</td>
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Methods

Types/Methods of validation[17,18]

Prospective validation

It is defined as the established documented evidence that a system does what it purports to do based on a pre-planned protocol. This validation usually carried out prior to distribution either of a new product or a product made under a revised manufacturing process. Performed on at least three successive production sizes (Consecutive batches).

In Prospective Validation, the validation protocol is executed before the process is put into commercial use. During the product development phase, the production process should be categorized into individual steps. Each step should be evaluated on the basis of experience or theoretical considerations to determine the critical parameters that may affect the quality of the finished product. A series of experiment should be designed to determine the criticality of these factors. Each experiment should be planned and documented fully in an authorized protocol.

All equipment, production environment and the analytical testing methods to be used should have been fully validated. Master batch documents can be prepared only after the critical
parameters of the process have been identified and machine settings, component specifications and environmental conditions have been determined.

Using this defined process a series of batches should be produced. In theory, the number of process runs carried out and observations made should be sufficient to allow the normal extent of variation and trends to be established to provide sufficient data for evaluation. 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.

In practice, it may take some considerable time to accumulate these data. Some considerations should be exercised when selecting the process validation strategy. Amongst these should be the use of different lots of active raw materials and major excipients, batches produced on different shifts, the use of different equipment and facilities dedicated for commercial production, operating range of the critical processes, and a thorough analysis of the process data in case of Requalification and Revalidation.

During the processing of the validation batches, extensive sampling and testing should be performed on the product at various stages, and should be documented comprehensively. Detailed testing should also be done on the final product in its package.

Upon completion of the review, recommendations should be made on the extent of monitoring and the in-process controls necessary for routine production. These should be incorporated into the Batch manufacturing and packaging record or into appropriate standard operating procedures.

Limits, frequencies and action to be taken in the event of the limits being exceeded should be specified.

Prospective validation should include, but not be limited to the following:

- Short description of the process.
- Equipment together with its calibration status.
- Finished product specifications for release. List of analytical methods Summary of the critical processing steps to be investigated.
- List of the equipment/facilities to be used (including measuring, monitoring/recording, as appropriate.
• Proposed in-process controls with acceptance criteria.
• Additional testing to be carried out, with acceptance criteria and analytical validation, as appropriate.
• Sampling plan.
• Methods for recording and evaluating results.
• Functions and responsibilities.
• Proposed timetable.

Batches made for process validation should be the same size as the intended Industrial scale batches. If it is intended that validation batches be sold or supplied, the conditions under which they are produced should comply fully with the requirements of Good Manufacturing Practice, including the satisfactory outcome of the validation exercise and the marketing authorization.

**Concurrent validation**

It is similar to prospective, except the operating firm will sell the product during the qualification runs, to the public at its market price, and also similar to retrospective validation.

• This validation involves in-process monitoring of critical processing steps and product testing. This helps to generate and documented evidence to show that the production process is in a state of control.
• In exceptional circumstances it may be acceptable not to complete a validation programme before routine production starts.
• The decision to carry out concurrent validation must be justified, documented and approved by authorized personnel.

Documentation requirements for concurrent validation are the same as specified for prospective validation.

**Retrospective validation**

It is defined as the established documented evidence that a system does what it purports to do on the review and analysis of historical information. This is achieved by the review of the historical manufacturing testing data to prove that the process has always remained in control. This type of validation of a process for a product already in distribution.

Retrospective validation is only acceptable for well-established processes and will be
inappropriate where there have been recent changes in the composition of the product, operating procedures or equipment.

Validation of such processes should be based on historical data. The steps involved require the preparation of a specific protocol and the reporting of the results of the data review, leading to a conclusion and a recommendation.

The source of data for this validation should include, but not be limited to batch processing and packaging records, process control charts, maintenance logbooks, records of personnel changes, process capability studies, finished product data, including trend cards and storage stability results.

Batches selected for retrospective validation should be representative of all batches made during the review period, including any batches that failed to meet the specifications, and should be sufficient in number to demonstrate process consistency. Additional testing of retained samples may be needed to obtain the necessary amount or type of data to retrospectively validate the process. For retrospective validation, generally data from ten to thirty consecutive batches should be examined to access process consistency, but fewer batches may be examined if justified.

**Some of the essential elements for retrospective validation**

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.
- Current specifications for active materials/finished products.
- List of process deviations, corrective actions and changes to manufacturing documents.
- Data for stability testing for several batches.

**Revalidation**

Re-validation provides the evidence that changes in a process and/or the process environment that are introduced do not adversely affect process characteristics and product quality. Documentation requirements will be the same as for the initial validation of the process.

Facilities, systems, equipment and processes, including cleaning, should be periodically evaluated to confirm that they remain valid. Where no significant changes have been made to
the validated status, a review with evidence that facilities, systems, equipment and processes meet the prescribed requirements fulfils the need for revalidation.

Revalidation becomes necessary in certain situations. Some of the changes that require validation are as follows:

- Changes in raw materials (physical properties such as density, viscosity, particle size distribution and moisture etc that may affect the process or product).
- Changes in the source of active raw material manufacturer.
- Changes in packaging material (primary container/closure system)
- Changes in the process (e.g., mixing time, drying temperatures and batch size)
- Changes in the equipment (e.g., addition of automatic detection system). Changes of equipment which involve the replacement of equipment on a “like for like” basis would not normally require re-validation except that this new equipment must be qualified.
- Changes in the plant/facility.

**Basic concept of process validation**

Pharmaceutical Process Validation is the most important and recognized parameters of cGMPs. The requirement of process validation appears of the quality system (QS) regulation. The goal of a quality system is to consistently produce products that are fit for their intended use.\[19\]

Process validation is a key element in assuring that these principles and goal are met. The process validation is standardization of the validation documents that must be submitted with the submission file for marketing authorization. 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. According to FDA, Assurance of product quality is derived from careful and systemic attention to a number of importance factors, including: selection of quality process through in process and end product testing.\[20\]

The basic principle for validation may be stated as follows,\[21,22\]

**Installation Qualification (IQ)**

Establishing by objective evidence that all key aspects of the process equipment and ancillary system installation adhere to the manufacturer’s approved specification and that the
recommendation of the supplier of the equipment are suitably considered.

**Operational Qualification (OQ)**
Establishing by objective evidence process control limits and action levels which result in product that all predetermined requirements.

**Performance Qualification (PQ)**
Establishing by objective evidence that the process, under anticipated conditions, consistently produces a product which meets all predetermined requirements.

**Re – Qualification**
Modification to, or relocation of equipment should follow satisfactory review and authorization of the documented change proposal through the change control procedure. This formal review should include consideration of re qualification of the equipment. Minor changes or changes having no direct impact on final or in-process product quality should be handled through the documentation system of the preventive maintenance program.

**CONCLUSION**
Validation is the most widely used word in the areas of 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.

**REFERENCES**
23. Patel RC, Bhuva CK; Pharmaceutical Process Validation: Pharmatutor, ART - 1053