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## Aspects of Pharmaceutical Process Validation: A Review



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### ABSTRACT

Process validation plays a key role in the pharmaceutical manufacturing process as it delivers a high degree of assurance and evidence that the process, which is being carried out gives out the uniform results, that is; it meets the required specifications, which have been performed accurately. Process validation is an integral part of quality assurance and therefore its aim is to provide and ensure that the required quality is attained. Validation of the various steps used in the manufacturing of the pharmaceutical product is known as process validation. Process validation is the collection and analysis of the various data which is gathered throughout the design and manufacturing of a product alongside the documentation. Validation does improve processes but also confirms whether the process is properly developed and therefore decreases the risk of errors. The main aim of this work is to provide an outline and general review on process validation of Pharmaceutical product.



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## INTRODUCTION

The major objective of any pharmaceutical plant is to manufacture products of requisite attribute and consistent quality, 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.

Validation is an act of demonstrating and documenting that any procedure, process, and activity will consistently lead to the expected results. Validation is an essential part of GMP. It is, therefore, an element of the quality assurance program associated with a particular product or process. The concept of validation was first proposed by FDA Officials, Ted Byers, and Bud Loftus in order to improve the quality of pharmaceuticals. Pharmaceutical validation is a vast area of work and it practically covers every aspect of pharmaceutical processing activities.

Validation is proof that the process works and this must be done using scientific and statistical principles. This is done to establish the process capabilities and to confirm product acceptability. Process validation is documented evidence, which provides the high degree of evidence that a process will produce a product meeting its pre-determined specifications and quality attributes. The requirements of process validation appear of the quality system regulations. The main objective of process validation is to create a robust manufacturing process that consistently produces a drug product with a minimal variation that adheres to quality criteria of purity, identity, and potency. In the end, process validation also ensures a robust product that is highly reproducible over time.<sup>[1]</sup>

### Process Validation

Process Validation is defined as the collection and establishing the data evidence from the design stage from the beginning to the end of production.<sup>[2]</sup> USFDA exaggerated process validation as "Establishing documented evidence which provides the high degree of evidence that a specific process will consistently produce a product, meeting its predetermined specifications and quality characteristics."<sup>[3]</sup> Process validation may also be defined as the collection and evaluation of evidence, that is being followed by the process design stage throughout production, and establishes scientific evidence that a process is capable of consistently delivering standard quality products.<sup>[4]</sup>

## **The basic concept of Process Validation**

Pharmaceutical Process validation is the most important and recognized parameter of cGMP. The Necessity of process validation appears to be comprised of the quality system (QS) regulation. Process validation has a key role in assuring that the principles and goals like “products produced are fit for their intended use” are met. <sup>[5]</sup>

### **Importance**

1. Quality of product is assured.
2. Optimization of the process.
3. The cost of quality of a product is reduced.
4. The market recalls of a product is minimized.
5. The process is under controlled and the detailed study is possible. <sup>[6]</sup>

### **A need of Process Validation**

1. Introduction of a very new product.
2. Adulteration of process and equipment <sup>[7]</sup>
3. When process results cannot be fully verified during routine production by inspection and test, the process must be validated according to procedures.
4. Various routine end-product have insufficient sensitivity which is barely capable of meeting the desired safety and efficacy. <sup>[8]</sup>

### **Advantages**

1. It is a simple process, which deepens the understanding of the process.
2. Enhances regulatory compliance.
3. Enhances data and evaluation capabilities and therefore increase the confidence about process reproducibility and product quality.
4. Enhances the ability to statistically evaluate process performance and product

5. The risk of problems is decreased and thus assures the smooth running of processes.<sup>[9]</sup>

### Steps invalidating a process

1. Develop validation protocol
2. Conduct installation qualification (IQ)
3. Conduct operational qualification (OQ)
4. Conduct performance qualification (PQ)
5. Analyze Results and reach conclusions
6. Monitor and control process to ensure the process remains within established parameters under anticipated conditions
7. Investigate deviations from established parameters
8. Take corrective actions
9. Consider whether re-validation is necessary
10. Changes in process or product
11. Evaluate changes in process, product, procedures, equipment, Personnel, environment etc. to determine the effect of change<sup>[8]</sup>



### The basic principle for Process Validation

The basic principle for validation may be stated as follows:

- 1. Installation Qualification (IQ):** Establishing by objective evidence that all key aspects of the process equipment and ancillary system installation follow to the manufacturer approved specification and that the recommendation of the equipment by the supplier are suitably considered.<sup>[10]</sup>
- 2. Operational Qualification (OQ):** Establishing by objective evidence process control limits and activity level which result in a product that meets all pre-determined requirements.<sup>[11]</sup>

**3. Performance Qualification (PQ):** Establishing by objective evidence that the process, under anticipated conditions, consistently produces a product which meets all pre-determined requirements.<sup>[12]</sup>

**4. Re-Qualification:** Modification to, or relocation of equipment should follow a satisfactory review and authorization of the documented change proposal through the change control procedures. Minor changes or changes having no direct impact on final or in process product quality should be handled through the documentation system of the entire preventive maintenance program.<sup>[13]</sup>

### Types of Validation

1. Prospective Validation
2. Concurrent Validation
3. Retrospective Validation
4. Revalidation

#### 1. Prospective Validation:

It is defined as the established documented evidence that a system does what it significances to do based on pre-planned protocols. 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.<sup>[14]</sup>

#### 2. Concurrent Validation:

It is stated as the validation, which is carried out during the normal production, and this method can only be successful if the development stage has resulted in the proper understanding of the fundamentals of the process. It also consists of close and intensive monitoring of the steps and critical points for at least first three production three batches.

#### 3. Retrospective Validation:

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

In this type of validation is assumed that the composition, procedures, and equipment remain unchanged.<sup>[15]</sup>

#### 4. Re-Validation:

Re-validation is the repetition of the process and a portion of it. This process is carried out when there is a change or replacement in the formulation, equipment, plant or site location etc. and in sequential batches that do not meet the desired specification and affect process characteristics and product quality. This is done to maintain the validated status of the plant and 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 fulfill the needs for revalidation.<sup>[16]</sup>

#### Approaches to Process Validation

Process Validation involves a series of activities taking place over the life cycle of the product and process. All the activities of the process validation were divided into three stages as follows:

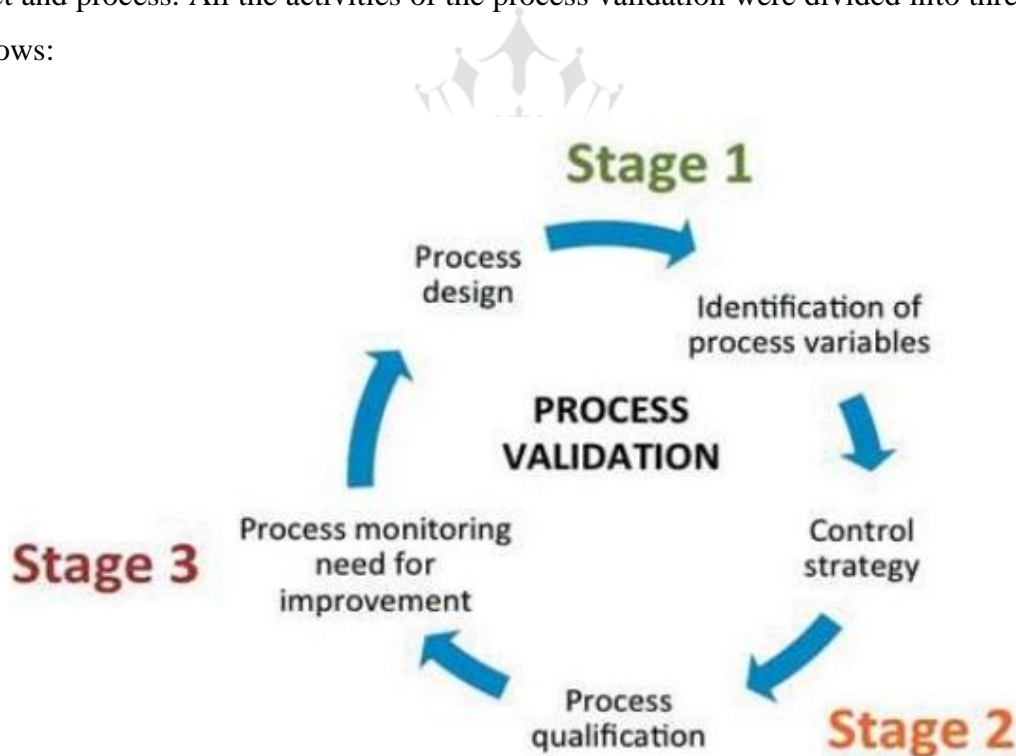


Figure 1: Flowchart of approaches to Process Validation

**Stage 1 Process Design:** The Commercial manufacturing process defined during this stage based on the knowledge gained through development and scale up activity.

**Stage 2 Process Qualification:** During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.

**Stage 3 Continued Process Verification:** Ongoing assurance is gained during routine production that the process remains in a state of control.<sup>[17]</sup>

A successful validation program depends upon information and knowledge from product and process development. This knowledge and understanding is the basis for establishing an approach to the control of the manufacturing process that results in products with the desired quality attributes.<sup>[18]</sup>

### Phases in Process Validation

The activities relating to Validation Studies may be classified into 3 Phases

**Phase 1: Pre-Validation Qualification Phase-** This Phase covers all activities relating to product, research and development, formulation, stability conditions, storage and handling of in-process and finished dosage form

**Phase 2: Process Validation Phase-** It is designed to verify all the limit of the critical process parameter is valid. Products can be produced even under worst conditions.

**Phase 3: Validation Maintenance Phase-** It requires frequent review of all process related documents including audit reports, to assure that there have been changes, deviations and modifications to the production process and that all SOPs have been followed. At this stage, the validation team also assures that there have been no changes in re-qualification and re-Validation. All the operations conducted should be in accordance with the principle of GMP.<sup>[19]</sup>

### Strategy for Industrial Process Validation

The following 5 points give the strategy for Process Validation

1. The use of different lots of raw materials should be included that is active drug substance and major excipients.
2. Batches should be run in succession and on different days and shifts.

3. Batches should be manufactured in the equipment and facilities designated for eventual commercial production.
4. Critical Process Variables should be set within their operative ranges and should not exceed their upper and lower control limits during process operations. Output responses should be well within finished product specifications.
5. Failure to meet the requirements of the validation protocol with respect to process input and output control should be subjected to process Re-Qualification and Subsequent Re-Validation.<sup>[20]</sup>

#### **Documentation in the Validation Process:**

1. Validation master plan (VMP)
2. Validation Protocol (VP)
3. Validation Report (VR)
4. Standard Operating Procedure (SOPs)



#### **1. Validation Master Plan**

- A Validation master plan is a summary of an entire philosophy, intentions, and approaches to be used for establishing performance adequacy of the company.
- It is an approved written plan of objectives and actions stating how and when a company will achieve compliance with the GMP requirements regarding validation.<sup>[21]</sup>

#### **2. Validation Protocol**

- Validation protocol is a plan of action stating how process validation will be done, how the various task will be conducted and defines the testing parameters, sampling plans, testing methods, and specifications.<sup>[22]</sup>
- The validation protocol should be numbered, signed and dated and should contain the following information.

- Protocol Approval sheet



- Table of content
- Objective and scope
- Validation team and Responsibility
- Step for Validation and acceptance criteria
- Evaluation of formulation ingredients and active raw materials
- Product and equipment detail
- In-process specifications
- Sampling procedures and testing plan
- Re-Validation Criteria
- Change control
- Deviations
- Stability
- Report and Conclusion



### **3. Validation Reports**

- A written report should be available after completion of the validation. If found acceptable it should be approved and authorized (signed and dated)
- The report should include at least the following
  - Title and objective of the study
  - Reference to protocol
  - Details of material
  - Equipment
  - Program and cycle used

- Details of procedures and test methods
- Results (compared with acceptance criteria)
- Recommendations on the limit and criteria to be applied on the future basis

#### **4. Standard Operating Procedures (SOPs)**

- SOPs are issued to specifically instruct employees in areas of responsibilities, work instructions, appropriate specifications, and required records.
- These outline procedures must be followed to claim compliance with GMP Principles or other statutory rules and regulations.<sup>[23]</sup>
- The general format of the SOPs involves
  - Title
  - Code
  - Objective
  - Scope
  - Definitions
  - Description
  - Safety
  - Documentation
  - Effective date, review date, version no.
  - Footer; prepared by, reviewed by, approved by, authorized by
  - References<sup>[24]</sup>



## Outcomes of Process Validation

### 1. Assurance of Quality:

- Validation is an extension of the concept of quality assurance since close control of the process is necessary to assure product quality
- Without validated and control processes it is impossible to produce quality product consistently.

**2. Reduction of Quality cost:** All the Preventive cost (Cost incurred in order to prevent failures like quality planning, vendor approval system, training, maintenance, calibration, auditing and self-inspection), Appraisal cost (Cost of Inspection, testing and Quality evaluation), Internal Failure cost (Cost Associated with non-confirming materials) and External failure cost (Cost associated with a non-conformance conditions after the product has left the company's ownership) are reduced.

### 3. Process Optimization:

- The Optimization of the process means making the process effective, efficient, perfect or useful as possible at the minimum cost.
- Trained, qualified people are the key element in this process and thus have the greatest impact on improving efficiency and productivity<sup>[6]</sup>

**4. Safety:** It also results in increase operation safety ex: Gauges used on equipment that designed to operate to a certain temperature and pressure must be reliable i.e. they must be calibrated.<sup>[5]</sup>

## SUMMARY

Process Validation is an accurate and reliable method to ensure that the drug product will meet standards for quality, purity, identity, strength, effectiveness, evaluation, safety and efficacy. It is the full flashed quality control tool for the pharmaceutical industries. Pharmaceutical process validation is the most important and recognized parameters of cGMP. Process validation and process control provide a certain assurance of batch uniformity and integrity of the product manufactured. This paper summarizes the importance, phases, approaches, documentation, and benefits of Process Validation.

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