



**Review Article**

**AN OVERVIEW ON PHARMACEUTICAL PROCESS VALIDATION**

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**Abstract:** Validation is one of the important steps in achieving and maintaining the quality of the final Product. If each step of production process is validated we can assure that the final product is of best quality. Validation of the individual steps of the processes is called the process validation. Process Validation emphasise 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 & analyses and emphasizes knowledge, detection, and control of variability and gives assurance on consistent of quality/productivity throughout life cycle of product.

**Keywords:** Process Validation, process validation stages, process validation master plan, Quality Assurance and protocol

**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 and productivity improvement. Validation is a necessary part of a quality assurance program and is fundamental to an efficient production operation. Process validation establishes the flexibility and constraints in the manufacturing process controls in the attainment of desirable attributes in the drug product while preventing undesirable properties. This is an important concept, since it serves to support the underlying definition of validation, which is a systematic approach documenting, and re-evaluating a series of critical steps in the manufacturing process that require control to ensure a reproducible final product.<sup>1,2,3</sup>

**PROCESS VALIDATION DEFINITION**

**According to US FDA<sup>4</sup>**

"Process validation is establishing documented evidence which provides a high degree of assurance that a specific process (such as the manufacture of pharmaceutical dosage forms) will consistently produce a product meeting its predetermined specifications and quality characteristics".

**According to EMEA<sup>5</sup>**

**In March 2012,**

"Process validation can be defined as documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medical product meeting its predetermined specifications and quality attributes."

**OBJECTIVES OF PROCESS VALIDATION<sup>6</sup>**

1. The manufacturing process, in addition to the individual equipment, must be validated.

2. The goal is to create a robust manufacturing process that consistently produces a drug product with minimal variation that adheres to quality criteria of purity, identity, and potency.
3. A validation plan for the manufacturing process should be drafted and executed by engineers in order to satisfy guidelines. The validation plan usually involves just a PQ section.
4. Just as equipment validation, major changes after the initial validation will result in the need for subsequent revalidation.
5. In the end, process validation will ensure a robust product that is highly reproducible over time.

**REASON FOR PROCESS VALIDATION**

The possible reason of performing process validation may include:

1. New product or existing products as per SUPAC changes.
2. Change in site of manufacturing.
3. Change in batch size.
4. Change in equipment.
5. Change in process existing products.
6. Change in composition or components.
7. Change in the critical control parameters.
8. Change in vendor of API or critical incipient.
9. Change in specification on input material.
10. Abnormal trends in quality parameters of product through review during Annual Product Review (APR).
11. Trend of Out of Specification (OOS) or Out of Trend (OOT) in consecutive batches.

**Benefits of Process Validation<sup>7</sup>**

1. Consistent through output.
2. Reduction in rejections and reworks.
3. Reduction in utility cost.
4. Avoidance of capital expenditures.
5. Fewer complaints about process related failure.

6. Reduced testing process and finished goods.
7. More rapid and accurate investigations into process deviation.
8. More rapid and reliable start-up of new equipment.
9. Easier scale-up from development work.
10. Easier maintenance of equipment.
11. Improve employee awareness of processes.
12. More rapid automation.

### TYPES OF PROCESS VALIDATION<sup>7</sup>

#### (a) Prospective validation:

Prospective validation is defined as the Establishment of documented evidence that a system does what it purports to do based on a pre planned protocol. This validation is usually carried out prior to the introduction of new drugs and their manufacturing process. This approach to validation normally under taken when ever new formula, process or facility must be validated before routine pharmaceutical formulation commences. In fact validation of process by this approach often leads to transfer of the manufacturing process from the development function to product. The objective of Prospective validation is to prove or demonstrate that the process will work in accordance with a validation master plan or protocol prepared for pilot product trails.

#### (b) Retrospective validation:

Retrospective validation is defined as the establishment of documented evidence that a system does what it purports to do on review and analysis of historical information. The sources of such data are production, QA and QC records. The issues to be addressed here are changes to equipment, process, specification and other relevant changes in the past.

#### (c) Concurrent validation:

It is similar to the prospective, except the operating firm will sell the product during the qualification runs, to the public as its market price. This validation involves in process monitoring of critical processing steps and product t testing. This helps t o generate and documented evidence to show that the production process is in a state of control.

#### (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 plan 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.

### STAGES OF PROCESS VALIDATION<sup>8-11</sup>

Process Validation is defined as the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product. Process Validation involves a series of activities taking place over the lifecycle of the product and process. The activities relating to validation studies may be classified into three stages:

**Stage 1 – Process Design:** “Focusing exclusively on qualification efforts without also understanding the manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities. It covers all activities relating to product research and development, formulation, pilot batch studies, scale-up studies, transfer of technology to commercial scale batches, establishing stability conditions, storage and handling of in-process and finished dosage forms, equipment qualification, installation qualification, master production documents ,operational qualification, process capability. Also this is the stage in which the establishment of a strategy for process control is taking place using accumulation knowledge and understanding of the process.”

**Stage 2 – process Qualification:** During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing. It confirms that all established limits of the Critical Process Parameters are valid and that satisfactory products can be produced even under “worst case” conditions. GMP compliant procedures must be followed in this stage and successful completion of this stage is necessary before commercial distribution of a product.

**Stage 3 – Continued Process Verification:** ongoing assurance is gained during routine production that the process remains in a state of control. The validation maintenance stage requires 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. A successful validation program depends on the knowledge and understanding and the approach to control manufacturing processes. These include the source of variation, the limitation of the detection of the variation, and the attributes susceptible of the variation.



Figure 1: Three model of process validation according to FDA Guidance for Industry – Process Validation

**BASIC PRINCIPLE FOR PROCESS VALIDATION**<sup>12,13</sup>

The basic principle for validation may be stated as follows:

**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.

**IQ considerations are:**

Equipment design features (i.e. material of construction cleanliness, etc.)

Installation conditions (wiring, utility, functionality, etc.)

Calibration, preventative maintenance, cleaning schedules.

Safety features.

Supplier documentation, prints, drawings and manuals.

Software documented.

Environmental conditions (such as clean room requirements, temperature, and humidity).

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

**OQ considerations include:**

Process control limits (time, temperature, pressure, line speed, setup conditions, etc.)

Software parameters.

Raw material specifications

Process operating procedures.

Material handling requirements.

Process change control.

Training.

Short term stability and capability of the process, (latitude studies or control charts).

Potential failure modes, action levels and worst-case conditions.

The use of statistically valid techniques such as screening experiments to optimize the process can be used during this phase.

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

**PQ considerations include:**

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

**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.

**VALIDATION MASTER PLAN**<sup>11</sup>

The validation master plan should provide an overview of the entire validation operation, its organizational structure, its content and planning. The main elements of it being the list/inventory of the items to be validated and the planning schedule. All validation activities relating to critical technical operations, relevant to product and process controls within a firm should be included in the validation master plan. It should comprise all prospective, concurrent and retrospective validations as well as re-validation.

The Validation Master Plan should be a summary document and should therefore be brief, concise and clear. It should not repeat information documented elsewhere but should refer to existing documents such as policy documents, SOP's and validation protocols and reports.

**The format and content should include:**

Introduction: validation policy, scope, location and schedule.

Organizational structure: personnel responsibilities.

Plant/process/product description: rational for inclusions or exclusions and extent of validation.

Specific process considerations that are critical and those requiring extra attention.

List of products/ processes/ systems to be validated, summarized in a matrix format, validation approach.

Re-validation activities, actual status and future planning.

Key acceptance criteria.

Documentation format.

Reference to the required SOP's.

Time plans of each validation project and sub-project.

**VALIDATION PROTOCOL**<sup>15,16</sup>

A written plan of actions stating how process validation will be conducted; it will specify who will conduct the various tasks and define testing parameters; sampling plans, testing methods and specifications; will specify product characteristics, and equipment to be used. It must specify the minimum number of batches to be used for validation studies; it must specify the acceptance criteria and who will sign/approve! Disapprove the conclusions derived from such a scientific study.

An ideal validation protocol contains the followings:

- 1) Objective and General Information.
- 2) Background I revalidation activities.
- 3) List of equipment's and their qualification status.
- 4) Facilities qualification.
- 5) Manufacturing formula & manufacturing procedure narrative.
- 6) Process flow diagram
- 7) Label claim
- 8) Process flow chart.
- 9) List of critical processing parameters and critical excipients.
- 10) Sampling, tests and specification.
- 11) Acceptance criteria

**CONCLUSION**

From the study it can be stated that pharmaceutical Process Validation is the most important and recognized parameters of cGMP. The cGMP regulation require that manufacturing processes be designed and controlled to assure that in-process materials and finished product meet predetermined quality requirements and do so consistently and reliably. The product should be designed robustly enough to withstand variations in the manufacturing process and the manufacturing process should be capable and stable to assure continued safe products that perform adequately. Process validation involves a series of activities taking place over the lifecycle of the product and process.

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