

## ***Pharmaceutical Process Validation***

***Sakshi S. Phadtare<sup>1</sup>, Sandhya R. Shinde (Kadam)<sup>2</sup>, Dr. Vivekkumar K. Redasani<sup>3</sup>***

*Student<sup>1</sup>, Asst. Professor<sup>2</sup>, Principal<sup>3</sup>*

*Department of B. Pharmacy*

YSPM'S, Yashoda Technical Campus NH4, Wadne, Satara, Maharashtra 415015

***Corresponding Author's Email: sakshisphadtare@gmail.com***

### ***Abstract***

*The primary goal of any industry and products it produces is quality. The pharmaceutical industry is currently interested in a variety of perspectives on achieving such quality, which is maintained by validation. Validation is documented proof that offers a high degree of assurance. One of subjects that the pharmaceutical industry is most familiar with these days is validation. This paper goes into great detail regarding the significance of pharmaceutical validation. Prioritizing quality is always essential while analyzing the products. The types of validation, equipment validation, process validation, cleaning, and analytical method validation are all covered in this article. The process of ensuring that the analytical technique used for a particular test is appropriate for its intended use is known as validation.*

***Keywords:*** *Validation, Process Validation, Prospective Validation, Retrospective Validation, Concurrent & Revalidation.*

## **INTRODUCTION**

Pharmaceutical validation is the most important and most recognized criteria. The primary goal of the pharmaceutical industry is to constantly produce products with the appropriate characteristics and quality at the lowest possible cost. In the pharmaceutical field, it is critical to ensure that the process will consistently yield results in addition to final product testing and compliance generates the intended results.

Validation is a concept that has been developing continuously since it was first formally recognized in the US in 1978. The quality system (QS) requirement has made process validation necessary. The objectives of validation are to keep the quality of the final product manufacturing process constant at every stage. In general every stage of a process is checked and confirmed. Process validation is often relevant in the production process and provides as a tool for manufacturers in understanding the requirements established down by the quality management system (QMS) for process validation. Standards set by the FDA that describes current good manufacturing practice (cGMP) for entire pharmaceuticals form the base for validation. These regulations can be accessed through 21 CFR parts 210 as well as 211.

### **Approval History**

In an effort to improve the quality of drugs, Ted Byers and Bud Loftus, two FDA officials, first proposed their concept of validation halfway through the 1970s.

Whereas the activity starting from focused on related processes to generate these chemicals, it soon expanded to include related pharmaceutical procedures.

### **Definition**

#### **WHO Definition**

- A formal procedure of demonstrating that a system, equipment, process, material, activity, or procedure effectively produces the intended result.¶

#### **ICH Definition**

- The process of validating and providing written evidence that processes operating within the limits of their intended design are able to consistently and consistently provide a final product of the required standard of quality is known as process validation.¶

#### **US FDA Definition**

- The act of documenting evidence that offers a high level of assurance that a given process will consistently yield a product that satisfies its predetermined specifications and quality attributes is known as process validation.¶

### **European commission**

- Proof written confirmation that the procedure, when followed within set parameters, can work efficiently and consistently to provide a medicinal product that satisfies its predefined requirements and quality standards.

### **Need of Validation**

The most important aspect of quality assurance is validation, which requires a methodical examination of systems, facilities, and procedures to determine if they appropriately and consistently carry out their intended functions.

- A validated process is one that has been officially authorized after it has been proven that it provides a high degree of assurance that uniform batches will be generated that fulfill the necessary criteria.
- Although validation verifies that processes have been designed correctly and are under acceptable control, it does not by itself improve processes.
- The pharmaceutical industry comprises highly skilled workers, complex facilities and technology, and expensive resources.
- Lower failure costs and better efficiency need careful examination and management of the manufacturing process batch validation.
- The industry's ongoing success depends on developing effective use of these resources.
- Reduced costs and quality assurance.

### **Scope of Validation**

Pharmaceutical Validation is a broad area of study that essentially involves all aspects of pharmaceutical manufacturing, which explains the Scope.

It becomes quite difficult to validate. But a systematic examination of the pharmaceutical industry's activities will highlight the following areas, at the very least, that require the pharmaceutical validation.

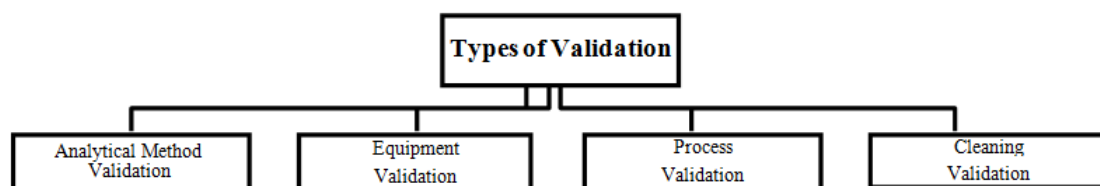
- Analytical
- Instrument Calibration
- Process Utility services
- Raw materials

- Packaging materials
- Equipment
- Facilities
- Manufacturing operations
- Product Design
- Cleaning
- Operators
- Importance of Validation
- Assurance of quality
- Time bound
- Process optimization

**Importance**

- Reduction of quality cost
- Nominal mix-ups, and bottle necks
- Minimal batch failures, improved efficiency and productivity
- Reduction in rejections
- Increased output
- Avoidance of capital expenditures
- Fewer complaints about process related failures
- Reduced testing in process and in finished goods
- More rapid and reliable start-up of new equipment
- Easier scale-up from development work
- Easier maintenance of equipment
- Improved employee awareness of processes
- More rapid automation

**Types of Validation**



## **ANALYTICAL METHOD VALIDATION**

Analytical validation is a procedure that has been found to be effective in laboratory experiments where the method's properties meet the needs of the intended use. All analytical methods that should be considered for use in analyzing the necessary clinical samples that require confirmation. Analytical methods validation is crucial, but for most, requires a lot of time in analytical development laboratories. It is crucial understand the possibilities readily available for achieving optimal performance with analytical resources in laboratory development work, as well as the necessity of this method in validation.

### **Why analytical procedures must be validated**

The analytical procedure is validated as they are regulatory requirements, sound science and quality control standard Code of Federal Regulations (CFR) 311.165c specifically states that its accuracy, sensitivity, specificity and reproducibility of the performed methods this organization must be established and documented. The management of the quality control unit would certainly like it ensure that the department needs an analytical procedure matters that its products are properly approved for its use that the product is safe for humans.

### **Methods must be validated if:**

- It must be designed for normal use.
- If the circumstances change, the order will be changed.

## **EQUIPMENT VALIDATION**

### **Qualification refers to the process of validating the equipment.**

The four categories of equipment validation are Performance Qualification (PQ), Operational Qualification (OQ), Installation Qualification (IQ), and Design Qualification (DQ). A DQ document contains the criteria of the client, each supplier's compliance with regulations, and the reasons behind their selection. Static credit of a facility or an item is specified in an IQ document to confirm that the unit has been installed correctly and that the producer's installation criteria have been followed.

It is important to verify that the equipment can deliver the operational ranges specified in the purchase order after installation. It refers to this definition as OQ. The PQ is focused on demonstrating that the process is being examined and functions as intended.

## **CLEANING VALIDATION**

Validating the cleanup process is important for ensuring that the cleaning methods effectively minimize any residue. Pharmaceutical sector cleaning and production equipment is the primary use for production equipment and cleaning validation. Expliciting the concept Cleaning processes is an analytical research that uses validation.

This should also clarify the development of acceptance standards as well as chemical and microbiological parameters, including sampling technique selection and detection limit.

The reasons for evaluating the cleaning methods-

1. It is a need of customer.
2. It safe guards the purity of the product.
3. This is a regular requirement in the API for product production
4. Pharma products & API are pompous to pharmaceuticals & microbial contamination.

## **PROCESS VALIDATION**

This form of validation presents written evidence, which offers a greater degree of assurance that the procedure will continuously result in a product that satisfies all predefined quality standards and attributes. The process validation also assures the repeatability of the process and decreases the risk of manufacturing problems which lead to an increase in output of predetermined quality.

### **It is beneficial to the manufacturer in many ways:**

- It deepens the understanding of processes, decreases the risk, preventing problems and thus assures the smooth running of the process.
- It lowers the possibility of defect expenses.
- It lowers the risk of regulatory non- compliance.
- A fully validated process may require less in-process Controls and end- product testing.
- Totally new process.
- New equipment.
- Procedure and equipment that have been modified to meet different priorities.
- A methods where the final product test is inadequate and and inaccurate measure of product quality.

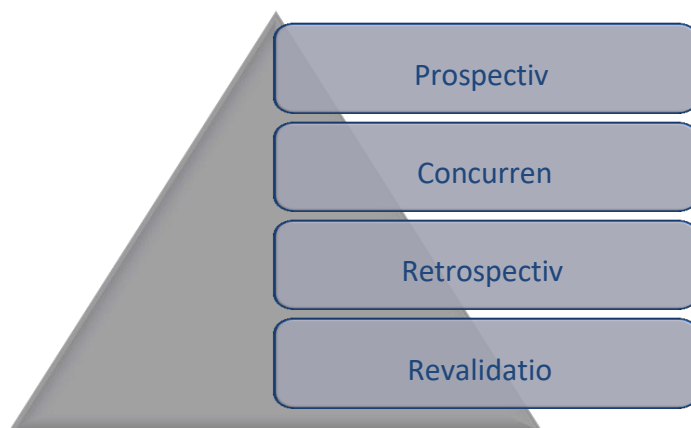
**Concept of Validation**

- Calibration, verification and maintenance of process equipment. Requalification or revalidation.
- Establishing specifications and performance characteristics.
- Election of methods, process and equipment to ensure the product meets specifications.
- Process and equipment qualification and validation.
- Testing the final product, using validated analytical methods, in order to meet specifications.
- Challenging, auditing, monitoring or sampling the recognized critical key steps of the process.

**Reasons for Validation**

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

**Types of Process Validation**



*Fig. 1 Types of Process Validation*

**Prospective Validation**

It is defined as definite, documented evidence that the system does what it promises, based on a pre-developed protocol. This validation is usually done before a new product or a product made according to a modified manufacturing process is marketed. This is done on at least three consecutive production volumes (consecutive batches). The purpose of prospective validation is. To prove or demonstrate that the process is working according to the validation protocol developed for pilot production. Prospective validation should usually be done before the drug is distributed and sold. In Prospective validation, a validation protocol is performed before the process is put into commercial use.

**Concurrent Validation**

Processing parameters are monitored using current manufacturing batches in this process. Concurrent validation is a method of using data produced during the process's actual implementation to develop documented proof that a process performs as intended. It gives details about the batch that is currently being studied and offers a low degree of assurance about the consistency of quality across batches. Concurrent validation might be the most appropriate course of action in some situations.

**Examples of these may be when.**

- A previous validated process is being transfer validation third party contract manufacturer or to another site.
- There are only a limited number of batches made.
- The product is an alternative strength of a previously validated product with the same ratio of active/inactive chemicals.
- The procedure used to manufacture pharmaceuticals that are in high demand because of a lack of availability

**Retrospective Validation**

It is defined as established documented evidence that the system does what it is intended to do when it reviews and analyzes historical data. This type of process validation applies to a product that is already distributed. Retrospective validation is only accepted for established processes and is not appropriate if they're having been recent changes to the product formulation, work methods or equipment. Previous information need to be used as a basis for

validating these techniques. Retrospective validation typically requires data from 10 to 30 consecutive sets. The consistency of the process must be checked, but fewer sets can be checked in justified cases.

**Elements to be considered for retrospective validation:**

- Batches manufactured during the defined period (ex – 10 last successive batches).
- Batches released per year.
- Batch size and strength.
- Master manufacturing and packaging records.
- Most current requirements for APIs and the final product.
- Corrective action list
- Process deviation list.

**Revalidation**

This type of validation is required when there are changes in the Critical Process Parameters, formulation, core packages, etc. This shows that changes in the process and its environment do not negatively affect the process characteristics or the product quality.

Non-compliance with process and product specifications also requires re validation.

All facilities, systems, equipment and processes must be regularly accessed to ensure their validity.

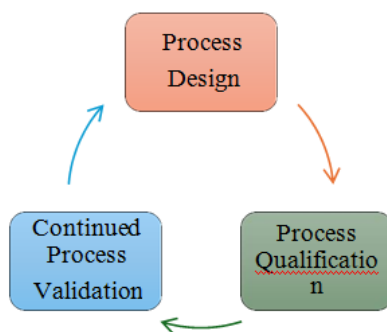
If no significant changes have been made to validated equipment, facilities, systems, etc. assessment with evidence that the process meets specified requirements meets the need for revalidation.

The following are examples some of the planned or unplanned changes that may require re-validation:

- Variations to the raw materials (physical characteristics that could have an impact on the process or final product, such as moisture, viscosity, density, and particle size distribution).
- 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).
- Must be qualified.
- Changes in the plant/facility.
- Variations revealed by trend analysis (e.g. process drifts)

**Stages of Process Validation**



***Fig.2 Stages of Process Validation***

**Process Design**

The explanation of focusing on only qualifying efforts without understanding the manufacturing process occurs at this level, which builds upon knowledge gained by development and increase activity. It covers all aspects of product development and research, including formulation, scale-up studies, technology transfer, commercial scale batches, pilot batch studies, acceptance of stability conditions, handling and storage of raw materials and finished goods, equipment qualification, installation qualification, master production documents, operational qualification, and process capability. Additionally, this is the only phase where a process control plan is accepted using both understanding and collected knowledge.

**Process Qualification**

In order to determine if the process is effective in reproducing commercial manufacturing, the process design is evaluated at this stage. It states that all of the recognized limits of the critical Process Parameters have to be accurate in order to deliver acceptable results even in the most difficult circumstances. Before the product is commercially distributed, it is important to successfully complete the GMP validation processes in this specific stage.

### **Continued Process Validation**

During the method production process, continuous assurance that the process remains under control is obtained. In order to ensure that there have been no modifications, deviations, failures, or changes to the production process, as well as that all SOPs—including changes in monitoring procedures—have been deleted, the validation of the periodic repair stage requires regular evaluation of all process-related documents and validation audit reports. A successful validation program depends on the knowledge, understanding, and industrial process control methodology. These consist of the variation's origin, its finding's limitations, and the characteristics that contribute to the variation.

### **Advantages of Process Validation**

1. Enlarge real time monitoring and modification of process.
2. Enlarged skill to statistically assess process performance and product variables. e.g., individuals; mean; range; control limits.
3. Enhanced data and evaluation capabilities and increased confidence about process reproducibility and product quality.
4. Improved ability to set target parameters and control limits for routine production, correlating with validation results.
5. Enhanced reporting capability.
6. Decreases the chances of the failure of the batches.
7. Reduces the production cost of the product.

### **CONCLUSION**

The study makes it clear that one of the most important and necessary steps in producing a high- quality product is process validation.

A set of procedures known as process validation must be followed at every stage of the product's development.

Also, process validation is carried out after the product is developed to ensure that it satisfies all pre- established specifications and that it should be developed under close supervision.

Also, process validation control is more crucial to achieving the intended results and producing a product with superior strength, purity, and stability. Additionally, the sector receives stability and depend ability for medication development from the process validation.

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