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## PHARMACEUTICAL PROCESS VALIDATION OF SOLID DOSAGE FORMS: A REVIEW

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### ABSTRACT

The concept of validation was first proposed by Food and Drug Administration officials in 1970 in order to improve the quality of pharmaceuticals. Process validation is the key element in assurance of pharmaceutical product. It is the most important and recognized parameters of cGMP. This establishes the flexibility and strict quality control in the manufacturing process control in the attainment of desirable attributes in the drug products while preventing undesirable properties. Through this review the authors make an effort to explain, the overview of validation concept of conducting validation trials and provide an insight to its importance in the pharmaceutical industry.

**Key Words:** Validation process, cGMP, Food and Drug Administration, Quality control.

### INTRODUCTION

The main purpose of all pharmaceutical industries is to invent quality products consistently, at the lowest feasible cost. Validation plays a very important role in quality assurance and productivity improvement. 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 (Paruchuri R *et al.*, 2012; Nash RA and Wachter HA, 2003; Armbruster D, Feldsien T, 2000) The concept of validation was first proposed by two Food and Drug Administration officials, Ted Byers and Bud Loftus in the mid 1970's in order to improve the quality of pharmaceuticals ( Sharma A and Saini S, 2013).

USFDA defined process validation as "establishing documented evidence which provides high degree of assurance that a specific process will consistently produce a product meeting its pre determined specifications and quality characteristics (Herbert AL *et al.*, 1990)

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WHO guidelines Defines validation as Validation is documented act of proving that any procedure, process, equipment, material, activity or system actually leads to the expected results. Validation act of proving, in accordance of GMPs that any process actually leads to expected results. Documented evidence that the process, operated with in established parameters, can perform effectively reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes.

Validation establishes that the process equipment has the capability of operating within required parameters (Thaduvai R *et al.*, 2012). Validation in itself does not improve only processes but also confirms that the processes have been properly developed and are under control. Adequate validation is beneficial for industries in many ways (Parida R, 2010)

### OBJECTIVE OF PROCESS VALIDATION

- To reduce variation between various batches.
- To provide a high degree of assurance of quality of the product.
- To decrease the risk of defect costs and regulatory noncompliance.

- To ensure the consistency of the manufacturing operation and reproducibility of the process.
- To demonstrate the robustness of the process.
- A fully validated process may require less in-process controls and end product testing.
- To ensure the existence of all necessary quality assurance system within organization (Kaur G *et al.*, 2012; Kumar S, 2011)

#### ADVANTAGES OF PROCESS VALIDATION

1. It is simple process and moisture sensitive and heat sensitive products can also be processed.
2. Expanded real time monitoring and adjustment of process.
3. Decreases the risk of preventing problems and thus assure the smooth running of the process.
4. Enhanced ability to statistically evaluate process performance and product variables e.g. individuals; mean; range; control limits.
5. Enhanced data and evaluation capabilities and increased confidence about process reproducibility and product quality.
6. Improved ability to set target parameters and control limits for routine production, correlating with validation results.
7. Enhanced reporting capability (Kathiresan K *et al.*, 2010; Himanshu *et al.*, 2012)

#### FDA guidelines general principle of validation

Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specification and quality attributes." Validation is the most important and recognized parameters of cGMP.

According to the FDA's current Good Manufacturing Practices (cGMP) control procedure shall be established to monitor output and to validate performance of the manufacturing processes that drug products be produced with a high degree of assurance of meeting all the attributes they are intended to possess (Chows S, 1997; US FDA, 1987; Good Manufacturing Practices, 1992; A WHO guide to GMP, 1997; Kumar S *et al.*, 2011)

#### TYPES OF VALIDATION

##### Prospective Process 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). Concurrent Process 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 testing. This helps to generate and documented evidence to show that the production process is in a state of control (Pandita R *et al.*, 2012; Sharma S *et al.*, 2013)

##### Retrospective Process 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. 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.

##### 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 (Tandel MJ *et al.*, 2012; Nandhakumar L *et al.*, 2011)

#### STRATEGY FOR VALIDATION OF METHODS

There are following strategy for process validation

- Preparation of process flow charts and Identification of critical process variables.
- Preparing process validation protocol.
- Develop SOPs for executing the method routinely.
- Execution of validation protocol.
- Monitoring process validation batches.
- Doing in process testing during manufacturing.
- Selection two consecutive batches having same batch size & manufacturing formula.
- The Failure to meet the requirements of the Validation protocol with respect to process input and output control should be subjected to process prequalification and subsequent revalidation following a thorough analysis of process data and formal discussion by the validation team (Jatto E *et al.*, 2012).
- Document validation experiment and results in the validation report. Batch manufacturing record, in process and finished product specification, other related documents to BMR and specifications, Related SOPs and Batch packing record all documents are necessary for process validation.

#### TYPE OF DOCUMENTATION IN VALIDATION PROCESS

##### Validation: Type of documentation

- Validation master plan (VMP)

- Validation protocol (VP)
- Validation reports (VR)
- Standard operating process (SOPs)

#### **Validation master plan**

An approved written plan of objectives and actions stating how and when a company will achieve compliance with the GMP requirements regarding validation.

VMP is a summary intention document stating the scope of the validation and outlining the methods to be used to establish the performance adequacy. The validation master plan should provide an overview of the entire validation operation, its organizational structure, its content and planning. The main elements of its being the list/inventory of the items to, relevant to product and process controls within a firm should be included in the validation master plan. It even holds the calibration and qualification of equipments, summary and conditions of Validation Protocol (Guidelines, 1997).

#### **Process validation protocol**

- Protocol approval sheet
- Table of content
- objective and Scope
- Validation team and responsibility
- Steps for validation and acceptance criteria
- Process validation plan
- Evaluation of formulation ingredients
- Evaluation of active raw material
- Evaluation of equipment
- Responsibility
- Manufacturing process flow chart
- Product details
- Equipment detail
- Critical process parameters
- In-process specification
- Sampling procedure and testing plan
- Revalidation criteria
- Change control
- Deviations
- Stability
- Conclusion
- Report and conclusion (South African, 1996; Evans P K, 1998)

#### **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 study.

- Reference to protocol.
- Details of material.
- Equipment.
- Programmes and cycles used.
- Details of procedures and test methods.
- Results (compared with acceptance criteria).
- Recommendations on the limit and criteria to be applied on future basis (Good Manufacturing, 1992; Rockville M D, 1987)

#### **SOP (Standard Operating Procedure)**

Standard Operating Procedures (SOPs) are issued to specifically instruct employees in areas of responsibility, 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. The general aspects covered under the SOPs are the Preparation and maintenance of work area like washing and sterilization, decontamination and testing area. Even the work done in the laboratory were documented, for example, the laboratory operations involving the receipt of reagents, standards, preparation of reagents, labelling and storage, test procedures, reference material, identification, handling, storage and use deviations, errors. Even the details of the equipments and their maintenance were also involved (Lambert J, 2004; <http://www.pharmainfo.net/reviews/guidelines>)

#### **FLOW CHART OF PROCESS VALIDATION OF SOLID DOSAGE FORM**

(TABLET)  
 RAW MATERIAL DISPENSING  
 RM QUANTITY VERIFICATION  
 SIFTING  
 DRY MIXING  
 WET MIXING  
 DRYING  
 SIFTING OF DRIED GRANULES  
 MILLING  
 SIFTING OF LUBRICANT  
 LUBRICATION  
 COMPRESSION



#### **DIFFERENT TYPES OF ANALYSIS DURING PROCESS**

- Description [Physical Observation]
- Water content
- Content uniformity
- Dissolution
- Related substances
- Average fill weight

**Table 1. Control Parameters For Consideration In Solid Dosage Forms Development**

UNIT OPERATION	PROCESS VARIABLE
Dry mixing	Mixing time

Granulation	Load, speed, binder, Addition rate, Granulation time, Amperage, Reading of impeller & chopper
Extrusion	Screen Size, Speed of machine
Pelletization	Lot size, Friction plate, Speed of machine, Spheronization Run time.
Drying	Damper controller, Dryer inlet temperature, Total drying time, Loss on drying
Coating	Type of bed plate, Spray Nozzle Diameter, No. of spray gun, Peristaltic pump, Atomization Air Pressure, Spray Rate
Capsule filling	Standard fill weight, Mechanical pellet filling chamber, Machine Speed, Capsule separation vacuum, Compressed air pressure, Mini-filled capsule sorter, capsule Locking Length

## CONCLUSION

In pharmaceutical field, when a new drug is formulated, an accurate and reliable method of estimation is essential for its quality, identity, strength, purity, stability, effectiveness and safety. Quality is always a crucial requirement when we consider any product. Therefore drug must be manufactured to the highest quality levels. End product testing by itself does not promise the quality of the product. For this purpose, validation process is carried out, which is an integral part of pharmaceutical industry. . Process validation should result in fewer product recalls and trouble shooting. Appropriate and essential factors for validation process of solid dosage form must be considered fulfilling the requirement of quality assurance

of final product. In general, pharmaceutical validation and process control is to show the accuracy, sensitivity, specificity and reproducibility of the test methods employed by the firms, shall be established and documented. So finally, we can conclude that pharmaceutical validation and process control make available a certain assurance of batch to batch uniformity and quality of the product

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## CONFLICT OF INTEREST:

The authors declare that they have no conflict of interest.

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