ABSTRACT
A present review article focus on introduction and general overview on validation in pharmaceutical industry. The concept of validation was first proposed by Food and Drug Administration officials, Ted Byers and Bud Loftus in 1970 in order to improve the quality of pharmaceuticals. In drug development, pharmaceutical validation and process controls are important to assure that the drug product can meet standards for the identity, strength, quality, purity, and stability of the drug product. 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.

KEYWORDS: Validation process, cGMP, Food and Drug Administration, quality control.

INTRODUCTION
Definition of Validation
In March 2012, (1)
“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.” [1]
The prime goal of any pharmaceutical plant is to fabricate results of essential trait and quality reliably, at the most reduced conceivable expense. 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 to identifying, measuring, evaluating, documenting and re-evaluating a series of critical steps in the manufacturing process that require control to ensure a reproducible final product.[2-3]

Some other Definitions of Validation

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.” [4]

According to US FDA

In 1978,

“A validation manufacturing process is one which has been proved to do what it purports or is represented to do. The proof of validation is obtained through the collection and evaluation of data, preferably, beginning from the process development phase and continuing the production phase. Validation necessarily includes process qualification (the qualification of materials, equipment, system, building, personnel), but it also includes the control on the entire process for repeated batches or runs”. [5]

In 1987,

“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”.

In 2008,

“Process Validation is defined as the collection and evaluation of data, from the process design stage throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality products”.
In 2011,
“The revised guidance also provides recommendations that reflect some of the goals of FDA’s initiative entities “Pharmaceuticals CGMPs for the 21st century – A Risk-Based Approach,” particularly with regards to the use of technological advances in pharmaceutical manufacturing, as well as implementation of modern risk management and quality tools and concepts”.[6]

According to Europian Medical Agency 2014 guidance
“The documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes”.[7]

According to EMEA
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.”

According to European Commission
In 1991.
“Act of proving, in accordance of GMPs that Any” process actually leads to expected results.

In 2000
“Documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes”.[8]

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.$^{[9-10]}$

**REASON FOR PROCESS VALIDATION**

The possible reason of performing process validation may include:

• New product or existing products as per SUPAC changes.
• Change in site of manufacturing.
• Change in batch size.
• Change in equipment.
• Change in process existing products.
• Change in composition or components.
• Change in the critical control parameters.
• Change in vendor of API or critical excipient.
• Change in specification on input material.
• Abnormal trends in quality parameters of product through review during Annual Product Review (APR).
• Trend of Out of Specification (OOS) or Out of Trend (OOT) in consecutive batches.$^{[11]}$

**ADVANTAGES OF PROCESS VALIDATION$^{[12,13,14]}$**

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
8. Assurance of quality
9. Process optimization
10. Reduction of quality cost
11. Minimal batch failures, improved efficiently and productivity
12. Reduced testing in process and in finished goods
13. Government regulation (Compliance with validation requirements is necessary for obtaining approval to manufacture and to introduce new products)

**Why is validation required?[^15,16,17]**

- It would not be feasible to use the equipment without knowing whether it will produce the product we wanted or not.
- The pharmaceutical industry uses expensive materials, sophisticated facilities & equipment and highly qualified personnel.
- The efficient use of these resources is necessary for the continued success of the industry. The cost of product failures, rejects, reworks and recalls, complaints are the significant parts of the total production cost.
- Detailed study and control of the manufacturing process- validation is necessary if failure to be reduced and productivity improved.
- The pharmaceutical industries are concerned about validation because of the following reasons.
  - Assurance of quality.
  - Cost reduction.
  - Government regulation.

**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.[^18,19,20]

**TYPES OF VALIDATION**

1. **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).
2. **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.

3. **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.

4. **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.\[21,22,23]\n
**Stages of process validation**\[24,25,26,27\]

Stage 1 – **Process Design** :- The commercial manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities.
Constructing and Apprehending Process Knowledge and Understanding

- The functionality and limits of commercial manufacturing equipment should be considered in the process design.
- Design of experiments (DOE) studies can help to develop process knowledge by revealing relationships, including multivariate interactions, between the variable inputs and the resulting outputs.
- Risk analysis tools can be used to display possible variables for DOE studies.

Creating an Approach for Process Control

- Controls and consist of material analysis and equipment monitoring at significant.
- These controlled records are established in the Master formula records and control processing points.
- These controlled records are established in the Master formula records and control processing points.
- These controlled records are established in the Master formula records and control processing points.
- The calculated commercial production and control records should be carried forward to the next stage for confirmation.

Stage 2 – Process Qualification

During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.

- Element (1): Design of a facility and qualification of utilities and equipment - Ensure qualification of facility, utilities and equipment is completed & documented prior to initiate process qualification.

Element (2): Process Performance Qualification (PPQ)

- The PPQ combines the actual facility, utilities, equipment’s and the trained personnel with the commercial manufacturing controls.
- A company must successfully complete PPQ before commencing commercial distribution of the drug product.
- To understand the marketing process adequately, the manufacturer will need to consider the effects of scale.
- Strongly recommend firms employ objective measure (e.g. Statistical Metrics) wherever feasible and meaningful to achieve adequate assurance.
The increased level of inspection, testing, and sampling should continue through the process verification stage as correct, to establish levels and occurrence of routine sampling and checking for the particular product and process.

Considerations for the duration of the intensified sampling & checking period could include (not limited to):
- Volume of production
- Process Complexity
- Level of process understanding
- Experience with similar products and process

Stage 3 – Continued Process Verification

Ongoing assurance is gained during routine production that the process remains in a state of control.

- Manufacturers should monitor product quality of commercial batches after completion of Phase I and Phase II of process validation. This will provide evidence that a state of control is maintained throughout the product life-cycle.
- Periods of enhanced sampling and monitoring may help to increase process understanding as part of continuous improvement.
- Process trends such as the quality of incoming materials or components, in-process and finished product results and non-conformances should be collected and assessed in order to verify the validity of the original process validation or to identify required changes to the control strategy.
- The extent and frequency of ongoing process validation should be reviewed periodically and modified if appropriate throughout the product life-cycle.
- Continued process validation (CdPV) should not be confused with product quality review.

Table provides a summary of the new approach to process validation.

<table>
<thead>
<tr>
<th>Product life-cycle</th>
<th>Process validation</th>
</tr>
</thead>
<tbody>
<tr>
<td>stage I</td>
<td>stage II</td>
</tr>
<tr>
<td>Process design</td>
<td>Qualification</td>
</tr>
<tr>
<td>- Pilot scale (and scale-up batches where appropriate) - Risk assessment to identify critical quality attributes and process control parameters</td>
<td>- Premises - Utilities - Equipment</td>
</tr>
<tr>
<td>- Periodic review of trends - May include sampling and testing</td>
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</tr>
</tbody>
</table>
6. STRATEGY FOR VALIDATION OF METHODS\[^{28}\]\n
The validity of a specific method should be demonstrated in laboratory experiments using samples or standards that are similar to the unknown samples analyzed in the routine. The preparation and execution should follow a validation protocol preferably written in a step by step instruction format as follows:

- Develop a validation protocol or operating procedure for the validation.
- Define the application purpose and scope of method.
- Define the performance parameters and acceptance criteria.
- Define validation experiments.
- Verify relevant performance characteristics of the equipment.
- Select quality materials, e.g. standards and reagents;
- Perform pre-validation experiments;
- Adjust method parameters and/or acceptance criteria, if necessary;
- Perform full internal and external validation experiments;
- Develop SOPs, for executing the method routinely;
- Define criteria for revalidation.
- Define type and frequency of system suitability tests and/or analytical quality control (AQC) checks for the routine; and
- Document validation experiments and results in the validation report.

REGULATORY BASIS FOR PROCESS VALIDATION\[^{29,30}\]\n
The concept of process validation from its beginnings in the early 1970s through the regulatory aspects associated with current good manufacturing practice (cGMP) regulations and the application thereof to various analytical, quality assurance, pilot plant, production and sterile product and solid dosage forms considerations. In the early 1990s, the concept of preapproval inspection (PAI) was born and had as one of its basic tenets the assurance that approved validation protocols and schedules were being generated and that comprehensive development, scale-up, biobatch and commercial batch validation data were required in order to achieve a successful regulatory PAI audit.
There are several important reasons for validating a product or process. First, the manufacturers are required by law to confirm to cGMP regulations. Second, good business dictates that a manufacturer avoids the possibility of rejected or recalled batches. Third, validation help to ensures product uniformity, reproducibility and quality. But the original focus of validation was directed toward prescription drugs, the FDA modernization act of 1997 expanded the agency’s authority to inspect establishment manufacturing over the counter (OTC) drugs to ensure compliance with cGMP.

FDA has the authority and responsibility to inspect and evaluate process validation performed by manufacturers. The cGMP regulations for validating pharmaceutical (drug) manufacturing require that drug products be produced with a high degree of assurance of meeting all the attributes they are intended to possess. 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. The foundation for process validation is provided in § 211.100(a), which states that “here shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity. This regulation requires manufacturers to design a process, including operations and controls, which results in a product meeting these attributes.

**VALIDATION TEAM**

A multidisciplinary team is primarily responsible for conducting and supervising validation studies. Personnel qualified by training and experience in a relevant discipline may conduct such studies. The working party would usually include the following staff members such as;

**Responsible authorities for validation**

<table>
<thead>
<tr>
<th>Department/ Designation</th>
<th>Responsibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manager Production</td>
<td>Responsible for manufacturing of batches and review of protocol and report.</td>
</tr>
<tr>
<td>Manager QC</td>
<td>Responsible for analysis of samples collected</td>
</tr>
<tr>
<td>Executive QC</td>
<td>Responsible for samples collection and submission to QC</td>
</tr>
<tr>
<td>Manager Maintenance</td>
<td>Providing utilities and engineering support</td>
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<tr>
<td>---------------------</td>
<td>---------------------------------------------</td>
</tr>
<tr>
<td>Executive Production</td>
<td>Responsible for preparation of protocol and manufacturing of validation batches</td>
</tr>
<tr>
<td>Manager QA</td>
<td>Responsible for protocol authorization and preparation of summary report</td>
</tr>
</tbody>
</table>

**TYPES OF DOCUMENTATION IN VALIDATION PROCESS**\(^{[32,33,34]}\)

- 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.

**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
VALIDATION REPORT
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.

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.

**Critical Process Parameters**[^35,36]

<table>
<thead>
<tr>
<th>Processing Stage</th>
<th>Critical Process Parameter</th>
<th>Evaluation Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sifting</td>
<td>Sieve Size</td>
<td>Before and After Use Sieve Integity</td>
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<tr>
<td></td>
<td>Sieve Integrity</td>
<td></td>
</tr>
<tr>
<td>Dry Mixing</td>
<td>Mixing Time</td>
<td>Content Uniformity</td>
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<tr>
<td></td>
<td>Mixing Speed</td>
<td></td>
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<tr>
<td>Granulation</td>
<td>Binding Time</td>
<td>Check the Mixing Time</td>
</tr>
<tr>
<td></td>
<td>Mixing Speed</td>
<td></td>
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<tr>
<td></td>
<td>Load Size</td>
<td>Ampere (End Point)</td>
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<tr>
<td></td>
<td>Amount of Granulating Agent</td>
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<tr>
<td>Drying</td>
<td>Total Drying Time</td>
<td>LOD</td>
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<tr>
<td></td>
<td>Inlet and Outlet Temperature</td>
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<tr>
<td></td>
<td>Load Size</td>
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<tr>
<td>Sifting and Milling</td>
<td>Sieve Size</td>
<td>Sieve integrity</td>
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<td>Screen Type</td>
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<td>speed</td>
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<td>Knives direction</td>
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<td></td>
<td>Feed rate</td>
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<td>Lubrication</td>
<td>Mixing Time</td>
<td>Description</td>
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<td>Blender Speed</td>
<td>Assay for Blend Uniformity</td>
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<td>LOD</td>
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<tr>
<td>Compression</td>
<td>Compression Speed</td>
<td>Appearance</td>
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<td>Average Weight. and Uniformity of Weight</td>
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<td></td>
<td>Compression Force</td>
<td>Thickness and Diameter</td>
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<td>Granule Feed Rate</td>
<td>Hardness and Friability</td>
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<td>Disintegration Time</td>
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<tr>
<td>Coating</td>
<td>Spray Rate</td>
<td>Assay</td>
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<tr>
<td></td>
<td>Inlet and Outlet Temperature</td>
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<td></td>
<td>Air Pressure</td>
<td></td>
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<tr>
<td></td>
<td>Speed of Rotation of Coating Pan</td>
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<tr>
<td>Packaging</td>
<td>Forming and Sealing Temperature</td>
<td>Appearance of Tablet</td>
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<tr>
<td></td>
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<td>Sealing Quality (Knurling)</td>
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<td>Overprinting Quality</td>
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<td>Label Quality</td>
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<td>Leak Test</td>
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</tbody>
</table>
**DIFFERENT TYPES OF ANALYSIS DURING PROCESS**

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

*Pre-Requisites for Successful Validation*[^37]

There are some elements or tools that are required for conducting effective validations which are discussed in the following sections:

1) **Understanding:** The single most important element required is a good understanding of what validation is. This understanding activity must be anchored by sufficient years of practical experience and knowledge. It will permit sound and logical decisions even under most intense situations 12.

2) **Communication:** Communication is one of the best methods of improving understanding and is essential for any activity that requires more than one resource to complete as conducting effective validation involves multi-departments.

3) **Co-operation, Plan and Focus:** Multiple departments are involving and interacting during the validation process such as Quality Assurance, Production, Quality Control, Maintenance, project management, accounting etc so they should have a commendable co-operation, focus and plan in order to get good team synergy.

4) **Experience:** To get success in validation program well experienced validation team are required.

5) **Resources:** Resources means personnel who will plan and execute equipment on which validations will be performed on materials with which to conduct validations.

6) **Budget:** It is important to understand that a successful validation must be done to completion and it should not be limited by a budget as validations cost money.
7) **Standard Operating Procedures (SOP’s):** The SOPs capture activities that routinely occur within an organization so all the concerned department must be trained about SOPs and its implementation.

8) **Quality Control lab support:** During the validations, some laboratory testing will be required which are handled by the QC so well facilitated qc lab is required to get results in expected time.

9) **Permission to conduct preliminary runs.**

10) **Realistic completion dates.**

**CONCLUSION**

It is concluded that Process validation is a step to assure the identity, strength, purity, safety and efficacy of pharmaceutical drug products, and it is the most common word in the drug development, manufacturing and specification of finished 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. Continued awareness of validation requirements and a diligent application of validation principles will thus help to ensure that pharmaceutical products will be able to be developed and produced with the quality and reproducibility required from regulatory agencies across the world.

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