PROCESS VALIDATION OF ORAL SOLID DOSAGE FORM: TABLET
– AN OVERVIEW

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ABSTRACT
Establishing documented evidence which provides a high degree of assurance that a specific process for manufacturing of tablets will consistently produce a product meeting its pre-determined specifications and quality attributes. It mainly involves the steps to be followed to evaluate and qualify the acceptability of the manufacturing process of Tablets. The process is limited to the three batches manufactured of specific batch size with specified equipments and control parameters for Tablets. The results suggest providing documentary evidence that all the manufactured Tablets were evaluated as per specifications. The steps involved such as Blend uniformity results between 90%-110%, compression assay results between 95%-105% were found within acceptable limits. Other tests related to compression such as hardness, thickness, disintegration, dissolution and for coatings such as weight gain, dissolution were found within acceptable limit.

KEYWORDS: Solid dosage form; Validation; Process validation; Tablet.

INTRODUCTION[1]
“Quality assurance” is a wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the object of ensuring that pharmaceutical products are of the quality required for their intended use. Quality assurance therefore incorporates GMP and other factors, including those outside the scope of this guide such as product design and development. The objective of the design and manufacture of the compressed tablet is to deliver orally the correct amount of drug in the proper form, over a period of time and in the desired location, and to have its
chemical integrity protected to that point. The prime objective of any pharmaceutical plant is to manufacture products of requisite attribute and quality consistently, at the lowest possible cost. Numerous features are required to ensure product quality, such as chemical and physical stability, suitable preservation against microbial contamination if appropriate, uniformity of dose of drug, acceptability to users including prescriber and patient, as well as suitable packing, labeling and validation. It is through careful design and validation of both the process and process controls that a manufacturer can establish a high degree of confidence that all manufactured units from successive lots will be acceptable. Successful validation of a process may reduce the dependence upon intensive in-process and finished product testing.

The system of quality assurance appropriate to the manufacture of pharmaceutical products should ensure that:

- Pharmaceutical products are designed and developed in a way that takes account of the requirements of GMP and other associated codes such as those of good laboratory practice (GLP) and good clinical practice (GCP).
- Production and control operations are clearly specified in a written form and GMP requirements are adopted
- Managerial responsibilities are clearly specified in job descriptions
- Arrangements are made for the manufacture, supply and use of the correct starting and packaging materials
- All necessary controls on starting materials, intermediate products and bulk products and other in-process controls, calibrations and validations are carried out
- The finished product is correctly processed and checked, according to the defined procedures.
- Pharmaceutical products are not sold or supplied before the authorized persons have certified that each production batch has been produced and controlled in accordance with the requirements of the marketing authorization and any other regulations relevant to the production, control and release of pharmaceutical products
- Satisfactory arrangements exist to ensure, as far as possible, that the pharmaceutical products are stored by the manufacturer, distributed and subsequently handled so that quality is maintained throughout their shelf-life.
- There is a procedure for self-inspection and/or quality audit that regularly appraises the effectiveness and applicability of the quality assurance system.
- Deviations are reported, investigated and recorded.
• There is a system for approving changes that may have an impact on product quality.
• Regular evaluations of the quality of pharmaceutical products should be conducted with the objective of verifying the consistency of the process and ensuring its continuous improvement.

- Terminology of Validation\textsuperscript{2,3,4}

The definitions given in the two regulatory documents may be compared as follows

1) Validation
Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes. (FDA) Action of proving in accordance with the principles of Good Manufacturing Practice that any procedure, process, equipment, material, activity or system actually leads to the expected results. (EC).

2) Process Validation
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. (EC).

3) Prospective Validation
Validation conducted prior to the distribution of either a new product, or product made under a revised manufacturing process, where the revisions may affect the product’s characteristics. (FDA) Validation carried out before routine production of products intended for sale. (EC).

4) Concurrent Validation
Validation carried out during routine production of products intended for sale. (EC - not specifically defined in FDA).

5) Retrospective Validation
Validation of a process for a product already in distribution based upon accumulated production, testing and control data. (FDA) Validation of a process for a product which has been marketed based upon accumulated manufacturing, testing and control batch data. (EC).

6) Re-Validation
A repeat of the process validation to provide an assurance that changes in the process/equipment introduced in accordance with change control procedures do not adversely affect process characteristics and product quality. (EC - not specifically defined in FDA).

7] Cleaning Validation
Cleaning validation is documented evidence that an approved cleaning procedure will provide equipment that is suitable for processing medicinal products. (EC - not specifically defined in FDA).

8] Validation Protocol
A written plan stating how validation will be conducted including test parameters, product characteristics, production equipment and decision points on what constitutes acceptable test results. (FDA - not specifically defined in EC).

9] Worst Case
A set of conditions encompassing upper and lower processing limits and circumstances including those within standard operating procedures which pose the greatest chance of process or product failure when compared to ideal conditions. Such conditions do not necessarily induce product or process failure. (FDA) A condition or set of conditions encompassing upper and lower processing limits and circumstances within standard operating procedures which pose the greatest chance of product or process failure when compared to ideal conditions. Such conditions do not necessarily induce product or process failure. (EC).

10] Risk Analysis
Method to assess and characterise the critical parameters in the functionality of an equipment or process. (EC - not specifically defined in FDA).

11] System
A group of equipment with a common purpose. (EC - not specifically defined in FDA).

12] Change Control
A formal system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect the validated status of facilities, systems, equipment or processes. The intent is to determine the need for action that would ensure and document that the system is maintained in a validated state. (EC - not specifically defined in FDA).
13] **Design Qualification (DQ)**
The documented verification that the proposed design of the facilities, systems and equipment is suitable for the intended purpose. (EC - not specifically defined in FDA).

14] **Installation Qualification (IQ)**
Establishing confidence that process equipment and ancillary systems are capable of consistently operating within established limits and tolerances. (FDA) The documented verification that the facilities, systems and equipment as installed or modified complies with the approved design and the manufacturer’s recommendations. (EC).

15] **Operational Qualification (OQ)**
The documented verification that the facilities, systems and equipment, as installed or modified, perform as intended throughout the anticipated operating ranges. (EC - not specifically defined in FDA).

16] **Performance Qualification (PQ)**
The documented verification that the facilities, systems and equipment as connected together can perform effectively and reproducibly based on the approved process method and product specification. (EC).

17] **Process Performance Qualification**
Establishing confidence that the process is effective and reproducible. (FDA).

18] **Product Performance Qualification**
Establishing confidence through appropriate testing that the finished product produced by a specified process meets all release requirements for functionality and safety. (FDA - not specifically defined in EC).

- **Process Validation**[5,6]

**Purpose**
This guideline outlines general principles that FDA considers to be acceptable elements of process validation for the preparation of human and animal drug products and medical devices.

**Scope**
This guideline is issued under Section 10.90 (21 CFR 10.90) and is applicable to the manufacture of pharmaceuticals and medical devices. It states principles and practices of general applicability that are not legal requirements but are acceptable to the FDA. This guideline lists principles and practices which are acceptable to the FDA for the process validation of drug products and medical devices.

**Introduction**

Process validation is a requirement of the Current Good Manufacturing Practices Regulations for Finished Pharmaceuticals 21 CFR Parts 210 and 211 and of the Good Manufacturing Practice Regulations for Medical Devices 21 CFR Part 820 and therefore, is applicable to the manufacture of pharmaceuticals and medical devices.

**Concepts**

Assurance of product quality is derived from careful attention to a number of factors including selection of quality parts and materials, adequate product and process design, control of the process and in-process and end-product testing. Routine end-product testing alone often is not sufficient to assure product quality for several reasons.

**The FDA Defines Process Validation**

Process validation is establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality characteristics.

- **Types of Process Validation**\(^{[7,8]}\)
- **Prospective Validation**

Prospective validation includes those considerations that should be made before an entirely new product is introduced by a firm or when there is a change in the manufacturing process which may affect the product’s characteristics, such as uniformity and identity.

- **Concurrent Validation**

Concurrent validation is carried out during normal production. This method of validation can only be successful if the development stage has resulted in a proper understanding of the fundamentals of the process. It is carried out during normal production of products intended for sale. It should involve close and intensive monitoring of the steps and critical points for at least first three production scale batches. The in-process control results are used to provide
some of the evidence required for validation but these are no substitute for validation. Validation in the production unit mainly comprises of the determination and evaluation of the process parameters of the facilities applied for the scale-up to final batch size. The control of all critical process parameters, the results of the in-process controls, final controls and stability tests should prove the suitability of the important individual steps of a procedure.

- **Retrospective Validation**
  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. Validation of such processes should be based on historical data. The steps involved require the preparation of a specific protocol and the reporting of the results of the data review, leading to a conclusion and a recommendation.

- **Revalidation**[^9]
  Facilities, systems, equipment and processes, including cleaning should be periodically evaluated to confirm that they remain valid. 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 fulfils the need for revalidation.

**Table 1: Process Control Parameter.**

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Parameter</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Average weight</td>
<td>End product testing</td>
</tr>
<tr>
<td>2</td>
<td>Potency</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Content uniformity</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Dissolution time</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Blend uniformity</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Moisture content</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Weight variation</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Tablet hardness</td>
<td></td>
</tr>
</tbody>
</table>

- **Pre-Requisites for Successful Validation**[^10]
  - Understanding
  - Communication
  - Experience
  - Resources
  - Budget
  - Plan
  - Training
• Standard Operating Procedures (SOP’s)
• Quality Control Lab Support
• Various Approaches in Process Validation

1. Product/process design and development
2. Qualification of the commercial manufacturing equipment and its process
3. Maintenance of the process in a state of control during routine commercial production.

• MANUFACTURING PROCESS
• Process evaluation and selection
➢ Mixing or blending
• Wet granulation
• Prior granulation to have a uniform drug/excipients
• After milling the dried granulation to add other excipients
• Factors in creating a uniform mix or blend
• Bulk density
• Particle shape
• Particle size distribution
• Surface area

➢ Items to be consider
• Mixing or blending techniques
• Diffusion (tumble)
• Convection
• Pneumatic (fluid bed)
• Drug uniformity
• Excipient uniformity
• Lubricant
• Color
• Equipment capacity/load

➢ Wet granulation
• Binder addition
• Binder concentration
• Amount of binder solution/granulation solvent
• Binder solution/granulation solvent addition rate
• Mixing time
• Granulation end point

➤ Milling
• Mill type
• Screen size
• Mill speed
• Feed rate

➤ Drying
• Inlet/outlet temperature
• Airflow
• Moisture uniformity
• Equipment capability/capacity

➤ Tablet compression
• Tooling
• Shape
• Size
• Concavity
• Compression speed
• Compression/ejection force
• In-process test
• Appearance
• Hardness
• Tablet weight
• Friability
• Disintegration
• Weight uniformity

➤ Tablet coating
• Coating purpose
• Taste masking
• Stability
• Controlled release
• Product identification
• Safety material handling
• Tablet properties
• Hardness
• Shape
• Equipment type
• Coater load
• Pan speed
• Spray guns
• Application/spray rate
• Tablet flow
• Inter/outlet temperature flow
• Coating solution
• Coating weight
• Residual solvent level

• **In process test**
• Moisture content of dried granulation
• Granulation particle size distribution affects
• Tablet compressibility
• Hardness
• Thickness
• Disintegration
• Dissolution
• Weight variation
• Content uniformity
• Blend Uniformity
• Individual tablet/capsule weight
• Tablet hardness
• Tablet thickness
Disintegration

**Finished product test**
- Appearance
- Tablet mottling
- Picking of the monogram
- Tablet filming
- Capping of the tablets
- Tablet colored
- Assay
- Content uniformity
- Beginning
- Middle
- End
- Tablet hardness
- Tablet friability
- Dissolution

**Table 2: Assessment of Critical Process Parameter.**

<table>
<thead>
<tr>
<th>Process Steps</th>
<th>Critical Variables</th>
<th>Rational</th>
<th>Critical Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Sifting</td>
<td>1. Particle size distribution of sifted materials</td>
<td>-To ensure uniform Particle size distribution of sifted input material Security sifting</td>
<td>- Right sievenumber - Sieve integrity before and after use</td>
</tr>
<tr>
<td>2. Blending</td>
<td>1. Blending Time (with lubricant)</td>
<td>To obtain final blend uniformity for Compression</td>
<td>- Blending time - Speed of blender - Quantity to beblended - Assay - Bulk / Tap density - Sieve analysis Blend uniformity - Water by KF</td>
</tr>
<tr>
<td>3. Compression</td>
<td>1. Degree of pressure applied 2. Machine Speed (300,400 and 500 Tab/Min)</td>
<td>To meet the desired product specification till Compression</td>
<td>- M/C Speed - Average weight - Weight Variation - Thickness - Hardness - Friability - Disintegration Test</td>
</tr>
<tr>
<td>4. Coating</td>
<td>1. Pan Speed(RPM) 2. Inlet Air temp</td>
<td>To meet the desired final product specification</td>
<td>- RPM of coating pan - Inlet temp.</td>
</tr>
</tbody>
</table>
CRITICAL PROCESS PARAMETERS FOR COMMON SOLID DOSAGE FORM
UNIT OPERATION ARE

Blending
Blending time, rotation rate, agitator speed, room temperature, humidity.

Dry granulation (Roller compaction)
Roll speed, feed screw speeds, roll force/pressure, and roll separation/gap, room temperature/humidity.

Milling
Impeller speed, feed rate, room temp, humidity.

Fluid bed granulation
Granulation fluid mixing time, fluid mixing speed, fluid amount, fluid addition rate, fluid temperature, spray nozzle air volume, bed mixing time, supply air flow rate, dew point, product bed temperature, exhaust air temperature, filter shaking intervals.

Compression
Tablet weight, turret speed, main compression force, pre compression force, feeder speed, upper punch entry, room temperature, humidity.

Coating
Coating suspension mixing time, mixing speed, amount, spray rate, atomization, pressure, pan rotation speed, pre heat time, supply air flow rate, temperature, product bed temperature, exhaust air temperature. Monitoring the state of robustness.

CONCLUSION
Nowadays Validation is the art of designing and practicing the designed steps together with the documentation in pharmaceutical industry. Validation itself does not improve processes but confirms that the processes have been properly developed and are under control in achieving, maintaining the quality of the final product. Application of validation principles will ensure to maintain quality, consistency and reproducibility in product manufacturing process and safety of the pharmaceutical products required from regulatory agencies across the world. The multidisciplinary validation team must identify, study the product and process characteristics and incorporate the important required validation key parameters to ensure that that product will meet all quality, manufacturing, and regulatory requirements. Process validation in solid dosage form is a systematic approach in identifying, measuring, evaluating, documenting and re-evaluating the critical steps in the pharmaceutical solid dosage form manufacturing process with control to assure consistency in the quality of final product. From this review we can conclude that the pharmaceutical process validation and process controls are important steps in manufacturing of solid dosage form with consistent to meet the regulatory required standard such as identity, strength, quality, purity and stability in the final solid dosage form [tablet].

REFERENCES


