Chapter1:PROCESS VALIDATION OF TABLETS

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❖ ABSTRACT

Gathering and evaluating data from the process design stage through production to establish scientific confirmation that a technique can dependably produce a quality medicinal substance is what validation is all about. The validation process ensures that quality is integrated throughout the system rather than being assessed at the end. It comprises the collection and evaluation of data that creates scientific proof that a process is capable of generating a quality pharmacological material on a consistent basis, beginning with the process design stage and continuing through production. Process validation is a critical component of quality assurance, according to cGMP. Validation and quality assurance will work together to assure the items' full quality. As a result, it was emphasized to review that provides a complete summary of validation. According to GMP, validation studies are required to be done as per predefined protocols. The purpose of this work is to present an introduction and general overview of process validation of the pharmaceutical manufacturing process with special reference to the requirements specified by the US Food and Drug Administration (FDA) of tablets.

Keywords: Process validation,tablets,quality,manufacturing process.

❖ INTRODUCTION

Pharmaceutical process validation is a significant element in assuring that these quality assurance goals are met. A manufacturer may develop a high level of confidence that all made units from subsequent batches will be acceptable by carefully designing and validating both the process and process controls. Validating a process successfully may reduce the need for extensive in-process and finished product testing. End-product testing is important in ensuring that quality assurance goals are satisfied in the majority of circumstances.

The term process validation can be defined as the gathering and assessment of data from the process design stage through commercial production that produces scientific proof that a process is capable of consistently producing a high-quality product. [1]

❖ BACKGROUND [2,4]

We have gained further expertise through regulatory monitoring, allowing us to enhance our industry advice on this topic. This revised guidance reflects FDA's current thinking on process validation and adheres to key principles first outlined in the 1987 guidance. The updated guidance also includes recommendations that reflect some of the goals of the FDA's initiative "Pharmaceutical CGMPs for the Twenty-First Century: A Risk-Based Approach," particularly regarding the use of technological advances in pharmaceutical manufacturing and the implementation of modern risk management and quality systems, tools and concepts. This revised guidance replaces the 1987 guidance.

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.

❖ PROCESS VALIDATION [6,7]

As per ICH: "Process Validation is the means of ensuring and providing documentary evidence that processes within their specified design parameters are capable of Repeatedly and Reliably producing a finished product of the required quality."

As per WHO: "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, following GMPs that any process actually leads to expected results. Documented evidence that the process, operated within established parameters, can perform effectively reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes.

As per USFDA: "Process validation is establishing documented evidence which provides a high degree of assurance that a specific process will continuously produce a product meeting its predetermined specifications and quality attributes."
The above definition is as per the 1987 guideline. The revised guideline was published in January 2011.As per the 2011 guideline
The FDA considers process validation necessary because,

- It makes good engineering sense.
- It results in fewer product recalls and troubleshooting assignments in manufacturing operations.
- It results in more technically and economically sound products and their manufacturing processes.

A. Process Validation and Drug Quality[2,4]

Effective process validation makes a substantial contribution to ensuring drug quality. The fundamental premise of quality assurance is that a medicine be manufactured that is suitable for its intended application.
This principle assumes the following conditions are met:
• Quality, safety, and efficacy are designed or built into the product.
• In-process and finished-product inspection or testing are insufficient to ensure quality.
• Each step of the production process is monitored to ensure that the finished product satisfies all quality attributes, including specifications.

B. Approach to Process Validation [5]

Process validation is defined for the purposes of this guidance as the collection and evaluation of data from the process design stage through commercial production that establishes scientific proof that a process is capable of consistently delivering a quality product. Process validation entails a series of activities that take place throughout the product and process's lifecycle.
This guidance describes process validation activities in three stages as shown in Figure 1.
• **Stage 1 –** Process Design: The commercial manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities.
• **Stage 2 –** Process Qualification: During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.
• **Stage 3 –** Continued Process Verification: Ongoing assurance is gained during routine production that the process remains in a state of control.

This guidance describes activities that are typical of each stage, but some activities may occur in multiple stages in practise.
Before any batch from the process is commercially distributed for consumer use, the manufacturer should have gained a high level of assurance in the performance of the manufacturing process, such that it will consistently produce APIs and drug products that meet the attributes of identity, strength, quality, purity, and potency.Data and information should show that the commercial manufacturing process can consistently produce acceptable quality products under commercial manufacturing conditions.
Manufacturers must:

• Recognize the origins of variation
• Determine the presence and extent of variation
• Recognize the effect of variation on the process and, ultimately, product qualities.
• Control the variation in proportion to the risk it represents to the process and product.

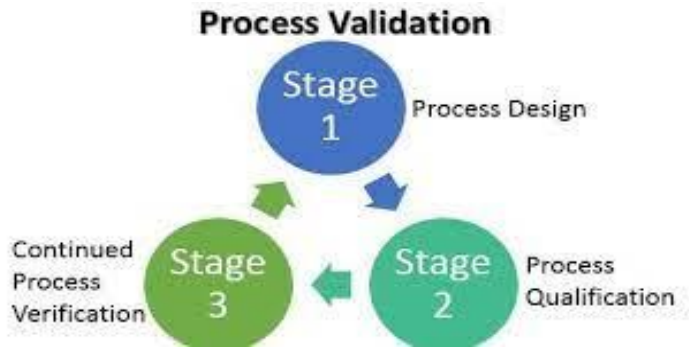

FIGURE 1: Stages of Process Validation

❖ OBJECTIVES OF PROCESS VALIDATION [8]

1. The manufacturing process must be validated along with the equipment.
2. The goal is to create a robust manufacturing process that consistently produces a drug product with the least variation that meets the quality criteria of purity, identity, and potency.
3. Process validation will ensure a robust product that is highly reproducible over time.
4. Engineers should draft and execute a validation plan for the manufacturing process to satisfy guidelines.
5. Major changes will result in the need for subsequent revalidation just as equipment validation, after the initial validation.

❖ REASONS FOR PROCESS VALIDATION [9]

The possible reason for performing process validation may include:

i. New products or existing products as per SUPAC changes.
ii. Change in process existing products.
iii. Change in composition or components.
iv. Change in the critical control parameters
v. Change in the vendor of API or critical incipient.
vi. Change in specification on input material.
vii. Change in a site of manufacturing.
viii. Change in batch size.
ix. Change in equipment.
x. Abnormal trends in quality parameters of product through review during Annual Product Review (APR).
xi. The trend of Out of Specification (OOS) or Out of Trend (OOT) in consecutive batches.

❖ THE REGULATORY BASIS FOR PROCESS VALIDATION [10]

When the concept of predicting process performance to meet user requirements emerged, FDA regulatory officials determined that requiring process validation had a legal basis.
The ultimate legal authority is found in section 501(a)(2)(B) of the FD&C Act, which states that a drug is considered to be defective if the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not administered in accordance with CGMP.

The 21CFR 210 and 211 CGMP regulations for finished pharmaceuticals were published to implement the act's requirements, which state that "there shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they require."

❖ TYPES OF PROCESS VALIDATION [11]

The guidelines on general principles of process validation mention four types of validation:
A) Prospective validation
B) Concurrent validation
C) Retrospective validation
D) Revalidation

A) Prospective process validation

Before the process is put into commercial use, an experimental plan known as the validation protocol is carried out (following the completion of the qualification trials). To generate validation support data, most validation efforts necessitate some degree of prospective experimentation. This type of process validation is typically performed in conjunction with the introduction of new drug products and manufacturing processes. The formalised process validation programme should never be initiated unless and until the following operations and procedures are satisfactorily completed:
1.The facilities and equipment used for process validation must meet CGMP criteria. (installation qualification completed)
2.The operators and supervisors who will be "running" the validation batch(es) are familiar with the process and its requirements.
3.The formula's design, selection, and optimization have been finished.
4.The qualification trials with ten sizes of pilot-laboratory batches have been completed, and the important processing stages and process variables have been determined, as well as the preliminary operating control limits for each critical test parameter.
5.Detailed technical information on the product and the production process, including documented verification of product stability, has been provided.
6.Finally, at least one qualification trial of a pilot-production (100 sizes) batch has been completed and demonstrates, upon inspection,that there were no significant deviations from the expected performance of the process.

The objective of prospective validation is to prove or demonstrate that the method can add accordance with a validation program or protocol ready for pilot-product (100 × sizes) trials.Sometimes 2 or 3 pilot-production (100 ×) batches are ready for validation functions. The first batch to be included in the sequence may be the already successfully concluded first pilot batch at 100 × sizes, which is sometimes ready below the direction of the structure operating directly accountable for pilot scale-up activities. Later, replicate batch manufacture is also performed by the pharmaceutical production operator.
The strategy selected for method validation ought to be easy and uncomplicated. The subsequent factors are conferred for the reader's consideration:

I. The use of various lots of components, such as APIs and major excipients, should be included.
II. Batches should be run sequentially on different days and shifts (the latter condition, if appropriate).
III. Batch production should take place in equipment and facilities designed for eventual commercial production.
IV. During process operation, critical process variables should be set within their operating ranges and should not exceed their upper and lower control limits. The output responses should fall well within the parameters of the finished product.
V. Failure to meet the requirements of the validation protocol concerning process inputs and output control should be subjected to requalification following a thorough analysis of process data and formal review by the CMC Coordination Committee.

B) Concurrent Validation

In-process monitoring of critical processing steps and current production end-product testing can provide documented evidence that the manufacturing process is under control. Such validation documentation can be obtained from the test parameters and data sources described in the retrospective validation section.

All of the in-process tests listed below are not required to demonstrate that the process is under control. The critical processing variables to be evaluated should be used to select test parameters.

Table 1:List of Test parameters of in process and End product testing

Test parameters	**Data source**

Average unit potency	End-product testing
Content uniformity	End-product testing
Dissolution time	End-product testing
Weight variation	End-product testing
Powder-blend uniformity	In-process testing
Moisture content	In-process testing
Particle or granule size distribution	In-process testing
Weight variation	In-process testing
Tablet hardness	In-process testing
pH value	In-process testing
Color or clarity	In-process testing
Viscosity or density	In-process testing

C) Retrospective Validation

The retrospective validation option is chosen for established products whose manufacturing processes are considered stable, and when prospective validation programmes cannot be justified solely on the basis of economic considerations and resource constraints. Before undertaking retrospective validation, which involves statistically analyzing numerical in-process and/or end-product test data from previous production batches, the equipment, facilities, and subsystems used in the manufacturing process must be qualified in accordance with CGMP requirements.

"Valid in-process specifications for such characteristics shall be consistent with drug product final specifications and shall be derived from previous acceptable process average and process variability estimates where possible and determined by the application of suitable statistical procedures where appropriate," states 21CFR 211.110(b).Retrospective validation can be performed in the following ways, using either data-driven computer systems or manual methods:

- For analysis, include data from at least the last 20-30 manufacturing batches. If there are fewer than 20 batches, include all manufactured batches and commit to acquiring the necessary number for analysis.
- Trim the data by removing test results from noncritical processing steps and removing all extraneous numerical data.
- Analyze and evaluate the resulting data statistically.
- Based on the study of retrospective validation data, reach a conclusion about the state of control of the manufacturing process.
- Issue a report of your findings (documented evidence). One or more of the following output values (measured responses), which are critical in terms of the specific manufacturing process being evaluated, are usually selected for statistical analysis.

1. Solid Dosage Forms
2. Individual assay results from content uniformity testing
3. Individual tablet hardness values
4. Individual tablet thickness values
5. Tablet or capsule weight variation
6. Individual tablet or capsule dissolution time (usually at t50%) or disintegration time
7. Individual tablet or capsule moisture content

D) Revalidation [10]

Conditions requiring revalidation study and documentation are listed as follows:

i. Changes in the source of active raw material manufacturers.
ii. Changes in packaging material (primary container/closure system).
iii. Changes in raw materials (physical properties such as density, particle size distribution, moisture, etc. that may affect the process or product).
iv. Changes in the process (e.g., mixing time, batch size).
v. Changes in the equipment (e.g. addition of automatic detection system).
vi. Changes of Equipment that involve the replacement of equipment on a "like for like" basis would not normally require a re-validation except that this new equipment must be qualified.

vii. Changes in the plant/facility.
viii. Variations revealed by trend analysis (e.g. process drifts).

Periodic Revalidation:

The decision to implement periodic revalidation should be based primarily on a review of historical data, i.e., data generated during in-process and finished product testing following the current validation, with the goal of confirming that the process is under control. Any trend in the data collected should be evaluated during the review of such historical data.
Additionally, during a scheduled revalidation, the following points should be checked:

1.Changes in master formula and procedures, batch size, and so on, if any, should be evaluated for their impact on the product.
2.To determine whether calibrations were performed in accordance with the established programme and time plan.
3.Revalidation confirms that preventative maintenance was carried out in compliance with the programme and timetable.
4.Update the necessary standard operating procedures (SOPs).
5.Confirming that the cleaning and hygiene schedule has been followed.
6.Are there any changes to the analytical control methods?

❖ PROCESS VALIDATION OF TABLETS [12-17]

A tablet is a well-known solid pharmaceutical dosage form that comprises of an active ingredient and appropriate excipients. Excipients typically used in tablets include binders, glidants, lubricants, and so on. Excipients are used in tableting for a variety of objectives, such as disintegrants to improve breakdown, glidants to facilitate powder flow, and flavoring agents to add diverse flavors in the tablets. The step-by-step manufacturing procedure should be understood because it aids in establishing the crucial areas that require special attention in terms of producing problems during the process..

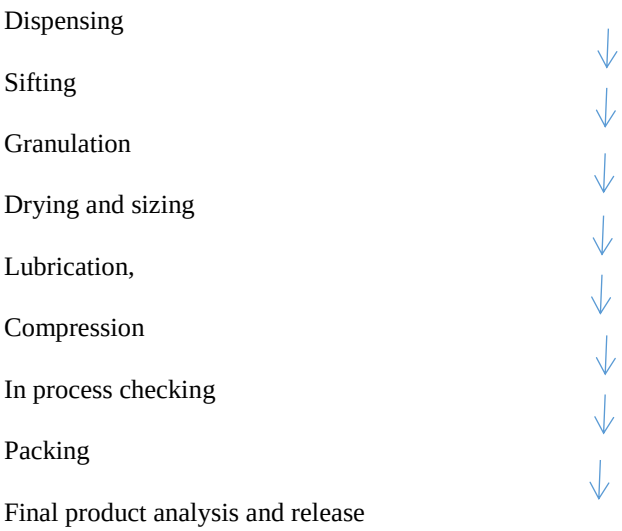

FIGURE 2:Process flow diagram for the manufacture of a tablet dosage form

■ Mixing Or Blending

Mixing is a critical step that is used at various stages of tablet manufacturing. Materials with similar physical properties can easily form a uniform mix or blend and do not segregate as quickly as materials with significant differences.

a) Mixing Or Blending Technique: To mix or blend materials, techniques such as diffusion, convection (planetary or high intensity), or pneumatic (fluid bed) are used. The technique used depends on whether the drug and excipients are mixed together for a direct compression formulation or if the lubricant (e.g., magnesium stearate) is added to the granulation.

b) Mixing or Blending Speed: Mixing the drug and excipient requires more vigorous mixing than mixing in the lubricant.

c) Mixing or blending time: The product's mixing or blending time will be determined by the mixing or blending technique and speed.

d) Drug uniformity: The content uniformity test is typically used to estimate the homogeneity of the drug throughout the mix or blend.

e) Excipient consistency: In addition to drug uniformity, excipient uniformity is required in the granulation or blend. There are two main excipients:

e) Lubricant Picking and sticky difficulties during compression can stem from uneven lubricant distribution. It may potentially cause tablet performance issues.

g) Color: The colourant must be equally dispersed in the mixture so that the tablets seem uniform (e.g., color, hue, and intensity).

h) Equipment capacity/load: The bulk density of materials or granules will affect the capacity of the equipment. Undercharging or overcharging a blender can result in poor drug or tablet lubricant distribution.

■ Wet Granulation

a)Binder Addition: Adding the binder dry eliminates the requirement to find the ideal binder concentration and a separate production for the binder solution during development and validation.

b) Binder Concentration: The ideal binder concentration for the formulation must be determined. If the binder is to be sprayed, the binder solution must be dilute enough to pass through the spray nozzle. It should also be concentrated enough to produce granules without over-wetting the materials.

c) Amount of Binder Solution/Granulating Solvent: Using an excessive amount of binder or solvent solution will over wet the materials, causing them to dry more slowly. The amount of binder solution needed is proportional to the concentration of binder.

d) Addition Rate of Binder Solution/Granulating Solvent: The rate or rate range at which the binder solution or granulating solvent can be applied to the materials should be correctly determined.

e) Mixing Time: Inadequate granulation can result in partial granules. These granules may exhibit poor flow and compression characteristics. Over mixing the granulation, on the other hand, can result in tougher granules and a decreased dissolving rate.

■ Wet Milling

Sometimes wet milling of granules is needed before subjecting it for drying to dry them properly.

a) Equipment Size And Capacity: The mill should be large enough to de lump the entire batch within a reasonable time period to minimize manufacturing time and prevent the material from drying during this operation.

b) Screen Size: The screen needs to be small enough to de lump the material, but not too small to cause excessive heating of the mill, resulting in drying of the granulation.

c) Mill Speed: The speed should be sufficient to efficiently de lump the material without straining the equipment.

d) Feed Rate: The feed rate of the wet granulation is interrelated to screen size and mill size and speed.

■ Drying

The sort of drying process necessary for the formulation (e.g., tray, fluid bed, and microwave) must be determined. The technique used will depend on the qualities of the medicine or formulation as well as the availability of equipment. Tablet qualities such as hardness, disintegration, dissolving, and stability may be affected by changing dryer procedures. The dried granulation's moisture content must be optimized.

High moisture concentration can cause tablet picking or adhering to tablet punch surfaces, as well as poor chemical stability due to hydrolysis. Granulation that has been over-dried may have poor hardness and friability.

Parameters to be considered are:

A. Inlet/Outlet Temperature: The inlet temperature is the temperature of the air entering the dryer, while the outlet temperature is the temperature of the air leaving the unit. The intake temperature is crucial to the granulation's drying efficiency and should be set high enough to maximize drying without compromising the granulation's chemical/physical stability. The output temperature is an indicator of the granulation temperature, and it will rise toward the inlet temperature as the granulation's moisture content decreases (evaporation rate).
B. Airflow: There should be enough airflow to ensure that moisture-laden air is removed from the wet granulation. Inadequate air flow may cause drying to take longer and influence the chemical stability of the medication.
C. Moisture Uniformity: The moisture content of the granulation may vary.
D. Equipment Capability/Capacity: The load that can be efficiently dried within the unit needs to be known.

- **Dry Milling**

The dried granulation's particle size will be reduced throughout the milling process. The particle size distribution that results will have an impact on material qualities such as flow, compressibility, disintegration, and dissolution. It will be necessary to identify the appropriate particle size/size distribution for the formulation. The factors to consider in dry milling are the same as in wet milling..

- **Lubrication**

Lubricants are given to the tablets to prevent them from sticking and picking.
a) Lubricant Selection: The grade of the lubricant used, as well as its compatibility with other ingredients, should be thoroughly researched before selecting the proper one.
b) Lubricant Amount Added: How much lubricant is required? If there is too much lubricant on the tablet, it will develop a hydrophobic coating, causing dissolving issues.
c) Mixing Time: The ideal mixing time must be determined by rigorous batch testing because if not mixed long enough, problems such as chipping, capping, and so on can occur.

- **Tablet Compression**

Compression is an important step in the production of a tablet dosage form. As for the compressibility properties of the formulation, it should be examined on an instrumented tablet press.

Factors to consider during compression are as follows:
A. Tooling: The shape and size of the tooling should be examined based on the formulation properties and commercial specifications.
B. Compression speed: The formulation should be compressed at a wide range of compression speeds to determine the operating range of the compressor.
C. Compression/ejection force: The compression profile for the tablet formulation will need to be determined to establish the optimal compression force to obtain the desired tablet hardness.

The following in-process tests should be examined during the compression stage:

I. Appearance
II. Hardness
III. Tablet weight
IV. Friability
V. Disintegration
VI. Weight uniformity
VII. Tablet Coating

Table 2 : Summary table including steps, control variable and critical parameters to be checked in manufacturing of tablets.

Sr. No	Steps	Control Variable	Critical Parameters to be checked
1	Dry mixing	Time Impeller speed	Mixing time and speed
2	Binder preparation and addition	Time Temperature, solvent used	Mode and time of addition
3	Kneading	Time Impeller speed & chopper speed	Mixing time and speed
4	Drying	Inlet/outlet temperature & time	Inlet/outlet temperature & Drying time
5	Lubrication	Time Blender/ granulator Speed	Mixing time and speed
6	Compression	Pressure and turret Speed	Machine speed and compression pressure
7	Coating	Pan speed and spray rate	Pan speed Inlet & outlet Temperature Spray rate

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