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BASIC ASPECTS OF PHARMACEUTICAL PROCESS VALIDATION OF SOLID DOSAGE FORMS: QUALITY ASSURANCE POINT OF VIEW

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ABSTRACT

The purpose and interest of this overview on pharmaceutical process validation of immediate release tablets, is to highlight the critical process parameters to be validate during the activity of validation of solid dosage form. It is the most common dosage form for orally administration of drug. The Process validation should confirm that the control strategy is sufficient to support the process design and the quality of the product. This validation review covers the solid dosage form of process validation. The process is developed in such a way that the required parameters are achieved and it ensures that the output of the process will consistently meet the required parameters during routine production, the process is validated. A manufacturer can assure through careful design of the device, processes, process controls and process variable that all manufactured units will meet specifications and have uniform quality. This review provides information on objectives and benefits of process validation, types of process validation, major phases in validation and regulatory aspects. Guidelines and strategy for process validation of solid dosage formvalidation and regulatory aspects. Guidelines and strategy for process validation of solid dosage form are also discussed.

KEYWORDS: Pharmaceutical Process Validation, Process Validation Stages, Validation Acceptance Criteria.

INTRODUCTION

Validation is an integral part of quality assurance; it involves the systematic study of systems, facilities and processes aimed at determining whether they perform their intended functions adequately and consistently as specified. A validated process is one which has been demonstrated to provide a high degree of assurance that uniform batches will be produced that meet the required specifications and has therefore been formally approved. Validation in itself does not improve processes but confirms that the processes have been properly developed and are under control.[1] The objective of the design and manufacture of the immediate release 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. Numerous features are required to ensure product quality and the validation is one of them. 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. In most cases, end-product testing plays a major role in assuring that quality assurance goals are meet. A validated process is one which has been demonstrated to provide a high degree of assurance that uniform batches will be produced that meet the required specifications and has therefore been formally approved. Validation in itself does not improve processes but confirms that the processes have been properly developed and are under control.[2]

Process Validation Definition[3]

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''

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".

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."

The Regulatory Basis For Process Validation[4]
Once the concept of being able to pre-directs process performance to meet user requirements evolved, FDA regulatory officials established that there was a legal basis of requiring process validation. The ultimate legal authority is in section 501(a)(2)(B) of the FD&C Act, which states that a drug is deemed to bead ultimate differ the methods used in or the facilities or controls used for its manufacture, processing, packing or holding do not conform to or administrated in conformity with CGMP. The CGMP regulations for finished pharmaceuticals 21CFR 210 and 211 were promulgated to enforce the requirements of the act which states 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 purport or are represented to possess.

Objective of Process Validation[5]
1. To reduce variation between various batches.
2. To provide a high degree of assurance of quality of the product.
3. To decrease the risk of defect costs and regulatory noncompliance.
4. To ensure the consistency of the manufacturing operation and reproducibility of the Process.
5. To demonstrate the robustness of the process.

Advantages of Process Validation[6,7]
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.

Elements of Validation[8]
Design Qualification (DQ): It is documented review of the design, at an appropriate stage of stages in the project, for conformance to operational and regulatory expectations.
1. GMPs and regulatory requirements
2. Performance criteria
3. Facility air flow, movement flow & pressure regimes
4. Reliability& efficiency
5. Commissioning requirements
6.Construct ability & installation of equipment
7. Maintenance& access to critical equipment & instrumentation
8. Safety& environment impact

Installation Qualification (IQ): It is documented verification that all aspects of a facility, utility or equipment that can affect productquality adhere to approved specifications and are correctly installed. Important IQ considerations are:
1. Installation conditions (wiring, utilities, and functionality)
2. Calibration, preventative maintenance, cleaning schedules
3. Safety features
4. Supplier documentation, prints, drawings and manuals
5. Software documentation
6. Spare parts list
7. Environmental conditions (such as clean room requirements, temperature and
Humidity)
8. Equipment design features (i.e. materials of construction clean ability)

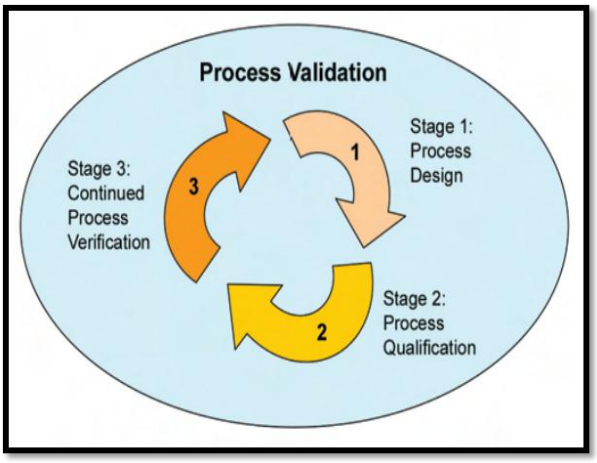
Operational Qualification (OQ): It is documented verification that all aspects of a facility, utility or equipment that can affect product quality operate to Intend throughout all anticipated ranges. OQ considerations include:
1. Process controllimits (time, temperature, pressure, line speed and setup conditions)
2. Software parameters
3. Raw material specifications
4. Process operating procedures
5. Material handling requirements
6. Process change control
7. Training

8. Short term stability and capability of the process.
9. Potential failure modes, action levels and worst-case conditions.

Performance Qualification (PQ): It is documented verification that all aspects of a facility, utility or equipment perform as intended in meeting predetermined acceptance criteria.

PQ considerations include.
1. Actual product and process parameters and procedures established in OQ
2. Acceptability of the product
3. Assurance of process capability as established in OQ
4. Process repeatability, long term process stability.

Three Stages of Process Validation[9]
Process validation involves a series of activities taking place over the lifecycle of the product and process.
Stage 1 – Process Design: The commercial 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 confirmed as being capable of reproducible commercial manufacturing.
Stage 3 – Continued Process Verification: On-going assurance is gained during routine production that the process remains in a state of control.



Types of process validation[10]
1]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.

2] 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.

3] Concurrent Validation: Validation carried out during routine production of products intended for sale.

4] 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.

5] 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.

Process Validation Phases[11]
The activities relating to validation studies may be classified into three.
Phase1: This is the Pre-validation Qualification Phase which covers all activities relating to
product research and development, formulation pilot batch studies, scale-up studies, transfer of technology to commercial scale batches, establishing stability conditions and storage, and handling of in-process and finished dosage forms, equipment qualification, installation qualification master production document, operational qualification and process capacity.
Phase 2: This is the process validation phase. It is designed to verify that all established limits of the critical process parameter are valid and that satisfactory. Products can be produced even under the worst conditions.
Phase 3: Known as the validation maintenance Phase, it requires frequent review of all process related documents, including validation of audit reports, to assure that there have been no changes, deviations failures and modifications to the production process and that all standard crepitating procedures (SOPs), including change control procedures, have been followed. At this stage, the validation team comprising of individuals representing all major departments also assures that there have been no changes/deviations that should have resultedin requalification and revalidation. A careful design and validation of systems and process controls can establish a high degree of confidence that all lots or batches produced will meet their intended specifications. It is assumed that throughout manufacturing and control, operations are conducted in accordance with the principle of good manufacturing practice (GMP) both in general and in specific reference to sterile product manufacture.

Strategy for Validation of Methods[12]
The validity of a specific method should be demonstrated in laboratory experiments using samples or standards that are similar to the unknown samples analysed 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

Industrial Process Evaluation and Selection for Tablets[13]

Determine the unit operations needed to manufacture the tablets.

1. Mixing or Blending Mixing or blending ensures production of uniform mixture of active pharmaceutical ingredients and excipients that do not segregate post blending. So this step is carefully scrutinized and validated. Parameters to consider.

- Mixing or blending technique
- Mixing or blending speed
- Mixing or blending time:
- Drug uniformity
- Excipient uniformity
- Equipment capacity/load.

2. Wet Granulation Different types of wet granulation techniques can be used such as low shear (e.g., Hobart), high shear (e.g., Diosna, GEI-Collette) or fluid bed (e.g., Glatt, Fluid Air). Each technique will produce granules with different physical properties and will require monitoring of different processing parameters. Wet granulation parameters to be considered during development and validation are:

- Binder addition
- Binder concentration
- Amount of binder solution/granulating solvent
- Binder solution/granulating solvent addition
- Mixing time
- Granulation end point

3. Wet Milling The wet granulation might need to be milled to break up the lumps and enhance drying of the granulation. Wet granules that have a wide aggregate range can lead to inefficient drying (long drying times and partially dried large granules or lumps). Factors to consider are.

- Equipment size and capacity
- Screen size
- Mill speed
- Feed rate

4. Drying: The type of drying technique (e.g., tray, fluid bed, and microwave) required for the formulation needs to be determined and justified. The type of technique may be dependent on such factors as drug or formulation properties and equipment availability. Changing dryer techniques could affect such tablet properties as hardness, disintegration, dissolution, and stability. The optimal moisture content of the dried granulation needs to be determined. High moisture content can result in tablet picking or sticking to tablet punch surfaces and poor chemical stability as a result of hydrolysis. An over dried granulation could result in poor hardness and friability. Moisture content analysis can he performed using the conventional loss-on-drying techniques or such state-of-the-art techniques as near infrared (NIR) spectroscopy. Factors to be considered are: 1. Inlet/outlet temperature, 2. Airflow, 3. Moisture uniformity**5. Milling** The milling operation will reduce the particle size of the dried granulation. The resultant particle size distribution will affect such material properties as flow, compressibility, disintegration, and dissolution. An optimal particle size/size distribution for the formulation will need to be determined. Factors to consider in milling are.

- Mill type
- Screen size
- Mill speed
- Feed rate

6. Lubrication: Lubricants are added to reduce the friction during tablet ejection between the walls of the tablet and die cavity in which the tablet was formed. Factors like amount of lubricant added, grade of lubricant used, compatibility with other ingredients and mixing time must be considered.

7. Tablet Compression: Compression is a critical step in the production of a tablet dosage form. The materials being compressed will need to have adequate flow and compression properties. The material should readily flow from the hopper onto the feed frame and into the dies. Inadequate flow can result in "rat holing" in the hopper and/or segregation of the blend in the hopper/feed frame. This can cause tablet weight and content uniformity problems. 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:

- Tooling
- Compression speed
- Compression/ejection force

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

- Appearance

- Hardness
- Tablet weight
- Friability
- Disintegration
- Weight uniformity

8. Tablet Coating Tablet coating can occur by different techniques (e.g., sugar, film, or compression). Film coating has been the most common technique over recent years and will be the focus of this section. Key areas to consider for tablet coating include the following: Tablet properties.

- Equipment type
- Coater load
- Pan speed
- Spray guns:
- Tablet flow
- Inlet/outlet temperature and airflow
- Coating solution
- Coating weight
- Residual solvent level

9. In-process tests

- Moisture content of "dried granulation"
- Granulation particle size distribution
- Blend uniformity
- Individual tablet weight
- Tablet hardness
- Tablet thickness
- Disintegration
- Impurity profile

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10. Finished product tests

- Appearance
- Assay
- Content uniformity
- Tablet hardness
- Tablet friability
- Impurity profile
- Dissolution

These key test parameters are the yardsticks by which the major processing variables in solid dosage forms are evaluated. Some processing variables are:

- Mixing time and speed in blenders and granulators
- Solvent addition rates in granulators
- Time, temperature, and airflow conditions in dryers and coaters
- Screen size, feed rate, and milling speed in mills
- Machine speed and compression force in tablet presses.

  Process validation testing is generally done on the first three batches of product made in production-size equipment. Revalidation testing is only done when a "significant" change has occurred. A significant change is one that will alter the in-process or final product specification established during the validation program or a change in formula, process, or equipment.

Steps for Validation and Acceptance Criteria[13]

The following steps (Table 1) are used in industry for validation of tablets in wet granulation process.

S.N.	Steps	Control Variable	Critical Parameters to be checked	Acceptance criteria
1	Dry mixing	Time Impeller speed	Mixing time Mixing speed	Mixing time:……min Impeller speed: ...(slow/medium/high)±5RPM. Content uniformity : 90%-110% RSD : ±5%
2	Binder preparation and addition.	Time Temperature, solvent used	Mode and time of addition	Depending up on the formulation.
3	Drying Inlet/outlet temperature & time	Inlet/outlet temperature & Drying time	Initial drying:…....°C Drying time: …….min.	Final drying : …….°C±5°C Loss on drying : …….% below 3% or depending on formulation
4	Lubrication	Time Blender/granulator speed	Mixing time and speed	Mixing time: ……min. Speed slow: ……..rpm. Content uniformity : Physical parameters – for information.
5.	Compression	Pressure and turret speed	Machine speed and compression pressure	Average weight: mg±5%,7.5%,10%. Uniformity of weight mg : Thickness : ……mm Hardness : …..KN or Kg/cm2 Disintegration time: NMT…..min. Friability : NMT……%w/w Assay : As per the

				label claim Dissolution:……%
6.	Coating	Pan speed and spray rate	Pan speed Inlet & outlet temperature Spray rate	Average weight : …..mg±5% Weight of 20 tablets :…..mg Thickness : …….mm Disintegration time: NMT….min. Assay : As per the label claim Dissolution: ……

Type of Documentation in Validation Process[14]

Validation: Type of documentation

1. Validation master plan (VMP)
2. Validation protocol (VP)
3. Validation reports (VR)
4. Standard operating process (SOPs)

1. Validation master plan: An approved written plan of objectives and actions stating how andwhen 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 themethods to be used to establish the performance adequacy. The validation master plan shouldprovide an overview of the entire validation operation, its organizational structure, its contentand planning. The main elements of its being the list/ inventory of the items to, relevant toproduct and process controls within a firm should be included in the validation master plan. Iteven holds the calibration and qualification of equipments, summary and conditions ofValidation Protocol.

2. Validation Protocol[15] The validation protocol should be numbered, signed and dated, and should contain as a minimum the following information.

- Title
- Objective & Scope
- Responsibility
- Protocol Approval
- Validation Team
- Product Composition
- Process Flow Chart
- Manufacturing Process Review of Equipments / Utilities
- Review of Raw Materials and Packing Materials Review of Analytical and Batch Manufacturing Records
- Review of Batch Quantities for Validation (Raw Materials)
- Review of Batch Quantities for Validation (Packing Materials)
- HSE Requirements
- Review of Process Parameters Validation Procedure
- Sampling Location
- Documentation
- Acceptance Criteria
- Summary
- Conclusion

3. Validation reports:[16,17] A written report should be available after completion of the validation.If found acceptable, it should be approved and authorized (signed and dated). The reportshould 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.

4. SOP (Standard Operating Procedure): Standard Operating Procedures (SOPs) are issued tospecifically instruct employees in areas of responsibility, work instructions, appropriatespecifications and required records. These outline procedures, must be followed to claimcompliance with GMP principles or other statutory rules and regulations. The general aspectscovered under the SOPs are the Preparation and maintenance of work area like washing andsterilization, decontamination and testing area. Even the work done in the laboratory weredocumented, 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 equipmentsand their maintenance were also involved.[18]

Change Control[19]

Process validation of a solid dosage form should includean SOP to reassess a process whenever there aresignificant changes in the process, equipment, facilities, reactants, process materials, systems, and so on that mayaffect the *critical* quality attributes and specifications ofthe solid dosage forms. Such changes should bedocumented and approved in accordance with the scopeof the change control SOP. The change control SOP should consist of the followingelements:

- Documentation that describes the procedure,review, approval, and basis for formal revalidationstudies
- Identification of the change and assessment of itslikely implication
- Requirements for monitoring change and testingneeds
- Assessment of information and justification for thechange
- Review and formal approval to proceed Identification of changes made to the physical andchemical composition of the solid dosage forms.
- Possible regulatory action and customer notification.

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