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PROCESS VALIDATION OF TABLETS: AN OVERVIEW

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ABSTRACT

To survive in competitive market and to be successful, it is necessary to achieve high level of product quality Validation is one of the important steps in achieving and maintaining the quality of the final product batch after batch. Without equipment, we cannot manufacture a product. By validating each step of production process we can assure that the final product is of best quality. This review provides information on objectives and benefits of process validation, types of process validation, major phases in validation and regulatory aspects.

Keywords: Validation,Equipments,Tablets.

Introduction

Validation is a systematic approach to identifying, measuring, evaluating, documenting and re-evaluating a series of critical step, in the manufacturing process that requires control to ensure a reproducible final product. It has become a necessary step to ensure better quality of medicinal product, throughout manufacturing, storage, handling and distribution. Quality cannot be inspected or tested into finished product. Thereby each step must be controlled to maximize probability that finished products meet all specifications. Process Validation is 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 Standards.[1]

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Process Validation has now become a part of Current Good Manufacturing Practices Regulations (cGMP), it is mandatory for manufacturers to go through Process Validation much more rigorously than earlier. Process Validation ensures improved levels of quality which inturn is bound to lead to reduced production costs by way of prevention of product failures. Thus Process validation also can be seen as a sound business proposition. By 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. Successfully validating a process may reduce the dependence upon intensive in-process and finished product testing.[2]

The FDA Guidelines on General Principles of Process Validation defines process validation as-"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"

According to EMEA, "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"[3]Considering the case of tablets, Tablets may be swallowed whole or being chewed. Some are dissolved or dispersed in water before

administration. Some are put in oral cavity, where the active ingredient is liberated at a predetermined rate. Implants or passeries may also be presented in form of tablet. Tablet may vary in shape and differ greatly in size and weight depending on the amount of medicinal substance and the intended mode of administration.

Objectives of process validation

- To introduce software verification and validation and to discuss the distinction between them.
- To describe the program inspection process and its role in V & V.
- To explain static analysis as a verification technique.
- To describe the Clean room software development process.[4]

Importance of process validation

- Government regulation
- Rapid automation
- Improved employee awareness
- Easier maintenance of equipments
- Increased output
- Reduction in quality cost
- Less failures of process thus less complaints
- Process optimization[5]

Types of process validation

Prospective validation

I. Establishing documented evidence prior to process implementation that a system does what it proposed to do based on preplanned protocols.

II. This approach to validation is normally undertaken whenever the process for a new formula (or within a new facility) must be validated before routine pharmaceutical production commences.

III. Validation of a process by this approach often leads to transfer of the manufacturing process from the development function to production.

Retrospective validation

I. Retrospective validation is used for facilities, processes, and process controls in operation use that have not undergone a formally documented validation process.

II. Validation of these facilities, processes, and process controls is possible using historical data to provide the necessary documentary evidence that the process is doing what it is believed to do.

III. This type of validation is only acceptable for well-established processes and will be inappropriate where there have been recent changes in the composition of product, operating processes, or equipment.

Concurrent validation

I. Concurrent validation is used for establishing documented evidence that a facility and processes do what they purport to do, based on information generated during actual imputation of the process.

II. This approach involves monitoring of critical processing steps and end product testing of current production, to show that the manufacturing process is in a state of control.

Revalidation

I. Revalidation means repeating the original validation effort or any part of it, and includes investigative review of existing performance data.

II. This approach is essential to maintain the validated status of the plant, equipment, manufacturing processes and computer systems. Possible reasons for starting the revalidation process include:

- The transfer of a product from one plant to another.
- Changes to the product, the plant, the manufacturing process, the cleaning process, or other changes that could affect product quality.
- The necessity of periodic checking of the validation results.
- Significant (usually order of magnitude) increase or decrease in batch size.
- Sequential batches that fail to meet product and process specifications.
- The scope of revalidation procedures depends on the extent of the changes and the effect upon the product.

Strategy for industrial process validation of solid dosage forms

The following points gives strategy for process validation:

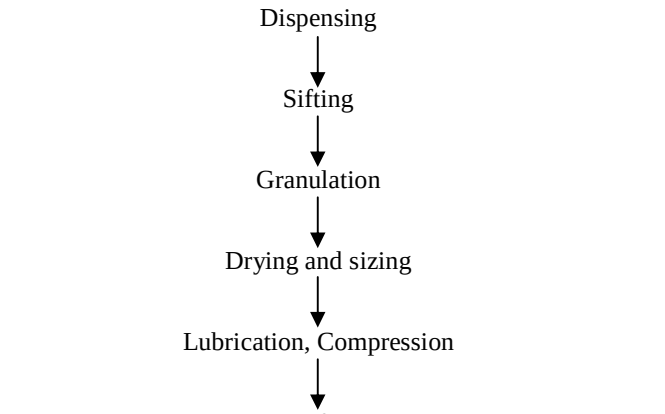
- The use of different lots of raw materials should be included. i.e., active drug substance and major excipients.
- Batches should be run in succession and on different days and shifts.
- Batches should be manufactured in the equipment and facilities designated for eventual commercial production.
- Critical process variables should be set within their operating ranges and should not exceed their upper and lower control limits during process operation. Output responses should be well within finished product specifications. [8]

Process overview

Guidelines for process validation of tablets

There are several important reasons for validating a product and /or process.

- Manufacturers are required by law to confirm to GMP regulations.
- Good business dictates that a manufacture avoid the possibility of rejected or recalled batches.
- Validation helps to ensure product uniformity, reproductibility, and quality.



Dispensing

I. Ensure dispensing booth is clean and line check is given as per Standard operating procedure.
II. Ensure that balance is not due for calibrated. Check for zero error in the balance.
III. Check and ensure that the expire date of product to be released is later than that of batch expiry date.
IV. Check and ensure that the all materials are issued as per Batch Processing Report.

Sifting

I. Check and record the temperature and relative humidity in processing area i.e. 25 ±20° C & RH 45±5%.
II. Check and ensure visually all the equipment and equipment parts are cleaned.
III. Check and record the integrity of the sieves before and after sifting through out the processing activity.

Granulation

I. Add and dissolve ingredient into vessel.
II. Add the other ingredients into mixer and mix for 5 minutes using impeller at slow speed.
III. Collect, samples at 3,5 and 7 minutes at 5 different places and analyze it for uniformity in content.
IV. Add granulating solution and homogenize at slow speed for about 10 minutes.
V. Check the Loss of drying in the wet granules.

Table1: Shows control parameters for granulation process

Control Parameters		
Fixed	**Variable (Monitor)**	**Response (Test)**
Equipment	Mixing speeds Amount of granulation Fluid feed rate granulation Time Load	Drug distribution Water/ solvent Appearance (size) Power consumption (amp/torque)

Drying and sizing

Table 2: Shows control parameters for drying and sizing

Fixed	**Variable (Monitor)**	**Response (Test)**
Bowl charge	Inlet/ exhaust air temperature	Particle size distribution
Porosity of filter bags	Product temperature	Densities
Bowl sieve	Drying time	Loss on drying
	Air volume Humidity of incoming air (dew point) Humidity of exhaust air	Assay (for heat sensitive materials)

I. Check and ensure the integrity of the Fluidized bed drying bag.
II. Initially dry the wet granules with air for 10 minutes.
III. Check the Loss of drying of granules; it should not be not more than 1% at 70°C for 15 minutes.
IV. Check and ensure the dried granules are not stored above 25°C before the milling is started.
V. Check and ensure the integrity of the sieves before and after sieving.
VI. Pass the granules through 16 mm mesh sieve, break the oversize granules using mill fitted with 2mm screen.
VII. Collect the granules and analyse their flow properties
VIII. Check the weight of sifted and dried granules.

Milling

Table 3: Shows control parameters for milling

Variable	**Response**
Screen size Milling speed Feed rate	Particle size distribution Loose/ tapped densities

Powder blending

Table4: Shows control parameters for powder blending

Variable	**Response**
Blending time Blender speed Intensifier bar	Content uniformity Assay Particle size distribution Powder flow

Lubrications

Table 5: Shows control parameters for lubrications

Variable	Response
Blending speed Blending time Method of addition	Particle size distribution Loose / tapped densities Flow properties Tabletting characteristics (Friability, hardness)

I. Perform the pre mixing and final mixing as per Batch process report instruction
II. During the final mixing before i.e., before adding the remaining quantity of the lubricant mix for 15 minutes.
III. Collects sample at 5,10,15 minute's intervals form top, middle, bottom and
IV. Composite and subject it to analysis for assay.
V. After adding the remaining quantity of lubricant mix for 5 minutes.
VI. Collects sample at 3,5,7 minutes interval form top, middle, bottom and composite and subject it to analysis for assay and content uniformity.
VII. Check the weight of the final blend and record.

Compression

I. Check and ensure the temperature and relative humidity of the compression room is not more than 25°C and Relative Humidity not more than 50%.
II. Check and ensure the compression machine is cleaned.
III. Collect 40 tablets and inspect for Appearance, weight, thickness, friability and hardness every 1 hour.
IV. Tablets weight variation shall be XX mg. hardness shall be (IP) kg/cm^2, thickness.
V. Collect 40 tablets by "Bracketign" i.e. by increasing this speed of the compression machine form the target speed and by reducing from the targeted speed.
VI. Collect 10 tablets during initial, middle and end of the compression process and subjective it to analysis for content uniformity and perform the assay also.

Coating

I. Check and ensure the coating pan and other equipment's are cleaned.
II. Check and ensure that the tablets is deducted, the speed of the coating pan inlet and exhaust air temperature, spray rate, spray type, temperature of the coating solution.
III. After coating is completed, samples are collected for dissolution testing and weight variation.

Labelling and packing

I. Check and record the temperature air the heating roller and sealing roller Check and record that the over printing instructions on labels and cartons.
II. Check and verify that price overprinted on label and carton is as per current price list.
III. After ensuring the proper labeling of tablets, check, for correctness of cartons packing for the same.

Finished product analysis and release

Finished product needs to be analyzed as per in-house specification product released only after predetermined specifications and quality attributes. Needs to be released only after pre-determined specifications [9-12]As a means of providing a broad overview of these validation criteria, the following checklist/guideline.

Check list of Validation and Control Documentation[13]

Table 6: Shows Check list of Validation and Control Documentation

Sr. No.	Selection of cGMP	Validation and control documentation
1	Introduction	Establishing of QA & PV functions
2	Organization and personnel.	Establishment and facility installation and qualification
3	Buildings and facilities	Plant and facility installation qualification Maintenance and sanitation Microbial and pest control
4	Equipment	Installation and qualification cleaning methods.
5	Air and water quality	Water treatment and steam systems air, heat, and vacuum handling.

6	Control of raw material, in-process material, product	Incoming components Manufacturing non-sterile products
7	Production and process controls	Process control systems (instruments and computers)
8	Packing and labeling controls	Depyrogenation, sterile packing, filling, and closing.
9	Holding and distribution	Facilities
10	Laboratory controls	Analytical methods
11	Records and reports	Computer systems
12	Returned and salvage drug products	Batch processing

Protocol for process validation

Protocol for title page in industry is shown in table 7 [14]

Table 7: Shows Check list of Validation and Control Documentation

NAME OF THE COMPANY	
PROCESS VALIDATION PROTOCOL	
Product:	Page no.:1 of
Protocol no:	Version no:
Product name:	
Label claim:	
Master Formula Record no:	
Effective date:	

Protocol approval is shown in table 8 below:[15]

Table 8: Shows Protocol approval

	Prepared by	**Checked by**			**Approved by**
Signature					
Date					
Name					
Department	**QA/R&D**	**R&D**	**Production**	**QC**	**Head QA**

Table of contents is shown in table 9 [16]

Table 9: Shows Table of contents

S.No.	**Title**	**Page No.**
1	Protocol approval sheet	
2	Table of contents	
3	objective	
4	scope	
5	Validation term and responsibility	
6	Steps for validation and acceptance criteria	
7	Process flow chart	
8	Procedure	
9	Form – A : Review of raw material/packing material	
10	Form – B : Evaluation of active raw material	
11	Form – C : Evaluation of inactive raw material	

12	Form – D : Qualification of equipment	
13	Form – E : Test instrument calibration	
14	Form – F : Dry mixing	
15	Sampling point diagram of RMG	
16	Form G-Wet mixing	
17	Form – H : Drying	
18	Sampling point diagram of FBD	
19	Form – I : Lubrication	
20	Sampling point diagram of RMG	
21	Form – J : Compression	
22	Form – K : Coating	
23	Form – L : Bulk packing	
24	Re validation criteria	
25	Change control	
26	Stability	
27	Deviations	
28	Conclusion	
29	Report and Approval	

8. Steps for validation and acceptance criteria in wet granulation process [4]

The steps for acceptance criteria are summarized in table 10:

Table 10: Shows Steps for validation and acceptance criteria in wet granulation process

Sr. No	Steps	Control Variable	Critical Parameters to be checked	Acceptance criteria
1	Dry mixing	Time …. Impeller speed.	Mixing time and 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	Kneading	Time Impeller speed & chopper speed	Mixing time and speed	Impeller speed : (slow/medium/high) Chopper speed: (slow/medium/high) Depending up on the formulation.
4	Drying	Inlet/outlet temperature & time	Inlet/outlet temperature & Drying time	Initial drying:……. C Drying time: ……min. Final drying: …… ^{0}C±5^{0}C Loss on drying : …….% below 3% or depending on formulation
5	Lubrication	Time Blender/granulator speed	Mixing time and speed	Mixing time: ……min. Speed: slow….rpm. Content uniformity: Physical parameters – for information.
6	Compression	Pressure and turret	Machine speed and	Average weight: mg±5%, 7.5%, 10%.

		speed	compression pressure	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… %
7	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: …….

Conclusion

Process validation is major requirement of cGMPs regulation for the process efficiency and sturdiness from the review validation data on pharmaceutical process validation and process control variables of tablets manufacturing processes in industry and it is the full fledged quality attributing tool for the pharmaceutical industries. The main goal in qualifying laboratory equipment is to ensure the validity of data. The current equipment qualification programs and procedures used within the pharmaceutical industry are based on regulatory requirements, voluntary standards,vendor practices, and industry practices.

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