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Review Article

A Review on process validation of solid dosage form

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Abstract

Objective: The purpose of this work is to perform a study on concurrent validation of levonorgestrel tablet BP 0.03mg that will deliver process validation approach as a quality assurance means. The process validation program will be investigated so that the plan will be designed to the character of the procedure under study. This can be performed by checking and controlling the various critical in process parameters.

Method: The samples from the three consecutive batches of levonorgestrel tablet 0.03mg are collected at the different stages of the manufacturing from dispensing, mixing, granulation process, drying process, blending process, compression process. Each and every parameter are analyzed and tested as per the specifications and all the data are recorded. The obtained results must be within the specified limit range.

Result: The results obtained from the evaluation of different parameters like bulk density, tapped density, friability, hardness, weight variation, and assay were found to be within specification limit range.

Conclusion: The conclusion of the concurrent process validation of levonorgestrel tablet BP 0.03mg is based on the result of the validation data of three consecutive batches. It is concluded that the manufacturing process used for levonorgestrel consistently producing the stable product meeting its predetermined specification and quality attributes.

Keywords: Concurrent process validation, Process validation, Levonorgestrel, Critical process parameter.

INTRODUCTION^{1,2}

The idea of approval was first presented by two Food and Drug Administration (FDA) authorities, Ted Byers and Bud Loftus, during the 1970's in order to improve the nature of drugs. The primary approval activities were zeroed in on the cycles engaged with making these items, however quickly spread to related cycles including ecological control, media fill and equipment sterilization and cleansed water production. The objective of the approval is to guarantee that quality is incorporated into the framework at every step, and not simply tried for toward the end, as such approval exercises will commonly remember preparing for creation material and working procedures, training of individuals included and checking of the framework while in production and turned into a significant piece of flow great assembling practices (CGMPs).

As indicated by FDA^{1,2}

Approval is archived program which gives a high degree of declaration that a particular cycle will continually deliver a product meeting its foreordained determinations and quality a scribes.

As per ICH^{1,2}

Cycle approval is the methods for guaranteeing and giving narrative verification that measures inside their predetermined plan boundaries are capable of consistently and dependably delivering a completed result of the required quality.

As indicated by USFDA³

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 characteristics.

OBJECTIVES OF PROCESS VALIDATION⁴

- ✓ The manufacturing process, in adding up to the individual equipment, must be validated.
- ✓ The rationale is to create a robust manufacturing process that time after time produces a drug product with minimal variation that adheres to quality criteria of purity, identity, and potency.

- ✓ The word validation simply means assessment of validity or action of proving effectiveness.
- ✓ The validation plan usually involves just a PQ section.
- ✓ Major changes after the initial validation will result in the need for subsequent revalidation. Just as equipment validation.
- ✓ In the end, process validation will ensure a robust product that is highly reproducible over time.

ADVANTAGES OF PROCESS VALIDATION^{5,6}

- ✓ Constant through output.
- ✓ Reduction in rejections and reworks.
- ✓ Reduction in cost of utility.
- ✓ Avoidance of capital expenditures.
- ✓ Fewer complaints about process related failure.
- ✓ Reduced testing in process and finished goods.
- ✓ More rapid and accurate investigations into process deviation.

STAGES OF PROCESS VALIDATION⁷

Process Validation is defined as the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality products. Process Validation involves a series of activities taking place over the lifecycle of the product and process.

The activities relating to validation studies may be classified into three stages.

Stage 1 - Process Design.

Stage 2 - Process Qualification.

Stage 3 - Continued Process Verification.

PHASE IN PROCESS VALIDATION⁸

The activities relating to validation studies may be classified into three.

Phase 1: Pre-Validation Qualification Phase:

This phase 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: Process Validation Phase:

It is designed to verify that all established limits of the critical process parameter are valid and that satisfactory. Products can produce even under the worst conditions.

Phase 3: 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 operating 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 resulted in requalification and revalidation.

TYPE OF PROCESS VALIDATION^{6,9,10}

There are four types of process validation which are as follows:

- a) Prospective Process Validation
- b) Concurrent Process Validation
- c) Retrospective Process Validation
- d) Process Revalidation

(a) Prospective process Validation:

Prospective process validation is primary & essential process for approving the product that it is suitable for commercialisation or not. During prospective validation, critical parameters that may affect the quality of the finished product are assessed. Sequence of trial should be designed to determine the criticality of these factors. All equipment, production environment and the analytical testing methods to be used should be fully validated. Preparation of Master batch documentation will be initiated after identification of critical parameters, machine settings, component specifications and environmental conditions of the process. Conducted prior to the distribution of either a new product or a product made under a modified production process, where the modifications are significant and may affect the products characteristics. It is a pre-planned scientific approach and includes the initial stages of formulation development, process development, setting of process specifications, developing in-process tests sampling plans, designing of batch records, defining raw material specifications, completion of pilot runs, transfer of technology from scale-up batches to commercial size batches, listing major process is executed and environmental controls. In Prospective Validation, the validation protocol is executed before the process is put into commercial use. It is generally considered acceptable that three consecutive batches/runs within the finally agreed parameters, giving product of the desired quality would constitute a proper validation of the process. It is confirmation on the commercial three batches before marketing.

(b) Concurrent process validation:

Concurrent process validation is done between the routine manufacturing process. A process where current production batches are used to monitor processing parameters. It gives of the present batch being studied, and offers limited assurance regarding consistency of quality from batch to batch. Concurrent Validation may be the practical approach under certain circumstances.

(c) Retrospective process validation:

Retrospective validation is applicable to processes that are steady and in regular use which have not undergone a formally documented validation process. Documentary proof for the validity of the processes can be provided by utilizing the historical data. Retrospective validation is only acceptable approach for well-established detailed processes that include operational limits for each critical step of the process and will be inappropriate where there is a change in operating procedures, product formulation, equipment and facility. Data from batch documents, process control charts, annual product quality review reports, maintenance log books, process capability studies, finished product test results, including trend analyses, and stability results acts as a source for retrospective validation. Conducted for a product already being marketed, and is based on extensive data accumulated over several lots and over time. Retrospective Validation may be used for older products

which were not validated by the fabricator at the time that they were first marketed, and which is now to be validated to confirm to the requirements of division 2, Part C of the Regulation to be Food and Drugs Act. Retrospective Validation is only acceptable for well established detailed processes and will be unsuitable where there have recent changes in the formulation of the products, operating procedures, equipment and facility. Retrospective validation needs the preparation of a protocol and reporting of the results for the data review, which leads to a conclusion and recommendation. Batches manufactured for a defined period (minimum of 10 last consecutive batches).

(d) Process re-validation:

Process re-validation required when there is a change in any of the critical process parameters, formulation, primary packaging components, raw material fabricator, major equipment or premises. Failure to meet product and process specifications in batches would also require process re-validation. Re-Validation becomes necessary in certain situations.

STEPS INVOLVED FOR PROCESS VALIDATION OF SOLID DOSAGE FORM¹¹⁻²¹

- 1) Dry mixing
- 2) Wet granulation
- 3) Wet milling
- 4) Drying
- 5) Milling
- 6) Lubrication and Blending
- 7) Tablet compression
- 8) In process testing
- 9) Finish product testing

Critical parameters of each stage:

1) Dry mixing

- Dry mixing time
- Shifting sieve size
- Impeller setting during mixing
- Chopper setting during mixing
- Speed of mixing machine

2) Wet granulation

- Binder addition rate
- Concentration of binder
- Time of mixing
- Granulation time
- Impeller setting during paste preparation

3) Wet milling

- Milling speed
- Milling screen size
- Milling sieve size

4) Drying

- Inlet air temperature
- Exhaust air temperature

- Total drying time

5) Milling

- size
- Sieve Screen size
- Milling speed

6) Lubrication and blending

- Pre-blending time
- Pre-blending speed
- Final-blending time
- Final-blending speed

7) Tablet compression

- Punch size and shape
- Upper punch
- Lower punch
- Compression machine speed
- Compression force

8) In process testing

- Uniformity of mixing
- Moisture content of granules
- Weight of tablet
- Hardness
- Thickness
- Disintegration time

9) Finish product testing

- Tablet appearance
- Hardness
- Weight of tablet
- Thickness
- Friability
- Assay
- Uniformity of content

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CONFLICT OF INTEREST:

The authors declare no conflict of interest.

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