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A REVIEW ON CONCURRENT PROCESS VALIDATION OF NORETHISTERONE ENANTHATE INJECTION 200 MG/ML

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ABSTRACT

Objective: The purpose of this work is to perform a study on the concurrent validation of norethisterone enanthate injection 200 mg/ml 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 as well as by evaluating the finish products.

Method: The samples from the three consecutive batches of norethisterone enanthate injection 200 mg/ml are collected at the different stages of the manufacturing from dispensing, mixing, filtration, filling and sealing as mentioned in the sampling plan for the individual processes. Each and every parameter are analyzed and tested as per the specifications and all the data are recorded. The obtained result must be within the specified limit range.

Result: The results obtained from the evaluation of different parameters like clarity of solution, filter integrity, sterility, bacterial endotoxin, visual particulate matter of filled ampoules, sealing quality and assay were found to be within specified limit range.

Conclusion: The concurrent process validation studies were executed for the three successive batches of norethisterone enanthate injection 200 mg/ml. Different parameters were checked and validated as per the specification. Any variation was not observed between the batches of concurrent process validation of the norethisterone enanthate injection 200 mg/ml.

Keywords: Concurrent process validation, Norethisterone enanthate, Critical parameter

INTRODUCTION [1, 2]

The concept of validation was first introduced by two Food and Drug Administration (FDA) officials, Ted Byers and Bud Loftus, in the mid 1970's in order to improve the quality of pharmaceuticals. The first validation activities were focused on the processes involved in making these products, but quickly spread to associated processes including environmental control, media fill and equipment sanitization and purified water production.

The goal of the validation is to ensure that quality is built into the system at every step, and not just tested for at the end, as such validation activities will commonly include training on production material and operating procedures, training of people involved and monitoring of the system whilst in production and became an important part of current good manufacturing practices (CGMPs).

According to FDA: Validation is documented program which provides a high degree of assertion that a specific process will constantly produce a product meeting its predetermined specifications and quality attributes.

According to ICH: Process validation is the means of ensuring and providing documentary proof that processes within their specified design parameters are capable of repeatedly and reliably producing a finished product of the required quality.

According to USFDA: Process validation is producing a documented proof that provides a high degree of assurance that a specified process will consistently produce a product meeting its predetermined specification and quality characteristics. Validation is a most excellent constituent of quality assurance scheme of a particular process. Validation is regarded as the requisite component of Good Manufacturing Practices (cGMP).

ADVANTAGES OF PROCESS VALIDATION [3]

- 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.
- More rapid and reliable start-up of new equipment.
- More rapid automation.

TYPES OF PROCESS VALIDATION: [4-5]

The four types of process validation:

1) Prospective process validation

2) Concurrent process validation

3) Retrospective process validation

4) Process Revalidation

1) Prospective process validation:

Prospective process validation is primary and essential process for approving the product that it is suitable for commercialization or not. During prospective validation, critical parameters that may affect the finished product are assessed. Sequence of trial should be designed to determine the criticality of this factor. All equipment, production environment and the analytical testing method 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 condition of the process. It is a pre-planned scientific approach and includes the initial stages of formulation development, process development, setting of process specification, 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.

2) 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 studies, and offers limited assurance regarding consistency of quality from batch to batch.

3) 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 procedure product formulation, equipment and facility. The 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 source for retrospective validation

4) Process Re-validation:

Process revalidation 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 specification in batches would also require

processes-validation becomes necessary in certain situations.

STAGES OF PROCESS VALIDATION [6]

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 three stages classified a process validation.

Stage 1 - Process Design.

Stage 2 - Process Qualification.

Stage 3 - Continued Process Verification .

PHASE IN PROCESS VALIDATION [7]

There are three phases of process validation

Phase 1: Pre-Validation Qualification Phase:

The phase is covers all activities relating to product research and development, formulation pilot batch studies, scale-up studies, transfer of technology to commercial scale batches, established stability condition 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 produced 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.

VALIDATION PROTOCOL: [8-9]

The detailed protocols for performing validations are essential to ensure that the process is adequately validated. Process validation protocols should include the following elements:

1. Objectives, scope of coverage of the validation study.
2. Validation team membership, their qualifications and responsibilities.
3. Type of validation: prospective, concurrent, retrospective re-validation.
4. Number and selection of batches to be on the validation study.

5. A list of all equipment to be used; their normal and worst case operating a Parameters.
6. Outcome of IQ, OQ for critical equipment.
7. Requirements for calibration of all measuring devices.
8. Critical process parameters and their respective tolerances.
9. Process variables and attributes with probable risk and prevention shall be captured.
10. Description of the processing steps: copy of the master documents for the product.
11. Sampling points, stages of sampling, method of sampling, sampling plans.
12. Statistical tools to be used in the analysis of data.
13. Training requirements for the processing operators.
14. Validation test method to be used in in-process testing and for the finished product.
15. Specification for raw and packaging material and test methods.
16. Forms and charts to be used for documenting results.
17. Format for presentation of results, documenting conclusions and for approval of study results.

VALIDATION MASTER PLAN: [10]

The all validation activities should be planned. The key elements of a validation programme should be clearly defined and documented in a validation master plan (VMP) or equivalent documents. The validation master plan should be a summary document and should therefore be brief, concise and clear. It should not repeat information documented elsewhere but should refer to existing documents such as policy documents, SOPs and validation protocols and reports. The format and content should include:

1. Introduction: validation policy, scope, location and schedule.
2. Organizational structure: personnel responsibilities.
3. Plant/process/product description: rational for inclusion or exclusions and extent of validation.
4. Specific process considerations that are critical and those requiring extra attention.
5. List of products/processes/ systems to be validated, summarized in a matrix format, validation approach.
6. Re-validation activities and actual status.
7. Key acceptance criteria.
8. Documentation format.
9. Reference to the required SOPs.
10. Time plans of each validation project and sub-project.

STEPS INVOLVED FOR PROCESS VALIDATION OF PARENTRAL DOSAGE FORM

1) Mixing
2) Filtration
3) Filling and Sealing
4) Visual inspection
5) In process testing
6) Finish product testing
7) Yield

Critical parameters of each stages:

1) Mixing

- Temperature
- Final volume
- Speed of stirrer
- Duration of stirrer
- Nitrogen gas flushing pressure
- Clarity of solution
- Assay

2) Filtration

- Pre filtration integrity
- Post filtration integrity
- Filter duration
- Pressure for filtration
- Clarity of solution
- Sterility

3) Filling and Sealing

- Filling machine peed
- Clarity
- Extractable wt
- Assay
- Visual particulatematter present
- Sealing quality
- Sterility
- Bacterial endotoxin test

4) Visual inspection

- Total quantity of goodampoules

5) In process testing

- Clarity
- Viscosity
- P^H
- Assay
- Sterility
- Bacterial endotoxin

6) Finish product testing

- Description
- Assay by HPLC
- Bacterialendotoxin test
- Sterility
- Related substance
- Extractable volume

7) Yield

- Filling yield
- Visual inspection yield

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