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A REVIEW ON PROCESS VALIDATION OF SOLID DOSAGE FORM

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ABSTRACT

The purpose of this work is to perform a study on process validation of Artesunate tablet 200mg that will deliver a process validation approach as a quality assurance aspect. The process validation program shall be scrutinized 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 process parameters and critical quality attributes. Samples from the three consecutive batches are taken as per the sampling plan from different manufacturing stages like dry mixing, wet mixing, drying, blending stage and compression stage. Every parameter is analysed as per the specification and all the data are recorded. All the obtained results must comply with the specification limits.

KEYWORDS

Process validation, Artesunate tablet, Critical process parameters and Critical quality attributes.

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INTRODUCTION[1-3]

The Food and Drug Administration defines process validation as" The establishing documented evidence that provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics''. Dosage form must be manufactured to the highest quality levels. The main idea of dosage form design is to achieve foreseeable therapeutic use to a drug included in a formulation that is capable of large-scale manufacturing with repeatable product quality, safety, and potency. Various processes involved in the development of a drug product into a dosage form are drug finding, lab test, regulatory registration, etc. Before releasing the product into

the market various product quality features like identity, chemical, physical stability, suitable preservation against microbial contamination if appropriate, strength, quality, purity, uniformity of dose of drug, stability, acceptability to users including prescriber and patient as well as suitable packing, labelling and validation are required. Process validation and process controls are two important key parameters that can ensure the above-said parameters in the manufacturing process. In a pharmaceutical manufacturing company, validation is a primitive tool that supports a company's commitment to quality of the finished product. Validation is a tool of quality assurance that provides a high degree of assurance that the equipments used, system, software; manufacturing process, and test method are in a validated condition.

Process validation is critical to ensure product quality, safety, efficacy, delivery, and cost.

Phases of Process validation

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

Process validation activities are categorized into three stages, which are

Stage 1: Process Design

Stage 2: Process Qualification

Stage 3: Continuous Process Verification

Process Design

Covers all the activities relating to the product research and development, formulation, pilot batch studies, scale-up studies, transfer of technology to commercial scale batches, establishing stability storage criteria, storage and handling of finished in-process and finished dosage.

For new product / Scale-up studies or optimization studies to be carried out before starting process Batch Monitoring /Validation studies. Scale-up Batch manufacturing record shall be prepared by the Manufacturing department. During Scale-up/ Optimization studies various process parameters shall be challenged and optimized Necessary corrections shall be done in master documents with reference to the recommendations given in Scale-up/ Optimization report.

Process Performance Qualification (Process Validation)

This phase is designed to verify that all established limits of the critical process parameters are valid and satisfactory products can be produced even under the worst condition. Process Validation shall be done under the following aspects:

New product (new formula)

New manufacturing procedure or process.

New resources i.e. equipment and area

New origin of active pharmaceutical ingredients or as evaluated by quality management tools.

After a major change in manufacturing formula/process, facility or equipment's used for manufacturing.

After completion of Scale-up/ optimization studies and incorporation of necessary changes to the master documents, process Validation studies are to be carried out. Process Exhibit batch monitoring/Validation protocol shall be prepared by the validation team. Based on the complexity of the process a minimum of three consecutive batches shall be taken for process validation studies. Intended numbers of batches shall be mentioned in the product-specific process Evaluation/Validation protocol. Process Evaluation/Validation batches shall be of the same size as intended production scale batches and if not, a reduced batch size corresponding to at least 10% of the intended batch size for full-scale production. A process shall be considered Qualified when the three consecutive validation batches give consistent results within the specified acceptance criteria.

Continued Process Verification

During this final phase, continual assurance that the process remains in a state of control (the validated state) during routine production shall require frequent review of all process-related documents, including validation reports to assure that there have

been no changes, deviations failure, modification to the process, Product stability program, change control process and the Annual Product Review are the vehicles for monitoring and continued evaluation of the process. The main objective of this stage is to ensure that a process remains always in a validated condition with the help of the following:

Preventive maintenance, calibration, and cleaning of facilities and equipment.

Well organized training of staff or employees.

Recognition and evaluation of changes (change control management).

Evaluation of deviations, OOS, product defects and market complaints.

Types of process validation: There are 4 types[4-6]

Prospective Process Validation

Concurrent Process Validation

Retrospective Process Validation

Process Re-validation

Prospective Process Validation

In prospective process validation, a preliminary plan called the validation protocol is executed before the process is put into commercial use. The majority of validation efforts require some degree of prospective experimentation to generate validation support data. This specific type of process validation is normally carried out in case of the introduction of new drug products and their manufacturing processes or introduction of new molecule or content. The harmonized process validation strategy should never be undertaken unless and until the following operations and procedures have been found completed satisfactorily:

The facilities and equipment which are used during the process validation are to be conducted to meet CGMP requirements.

The personnel who will be "running" the validation batch have proper knowledge of the process and its predefined requirements.

The design criteria, selection criteria, and optimization of the formula have been completed successfully.

The qualification trials using 10 times pilot-laboratory batches have been completed, in which the critical processing parameters and critical process variables have been identified, and the transitional operational control limits for each critical test parameter have been provided.

Detailed technical information on the product and the manufacturing process has been provided, including documented evidence of product stability.

At least one qualification trial of a pilot-production (100x) batch has been made and shows, upon scale-up, that there were no significant deviations from the expected performance of the process.

Concurrent process validation

Concurrent process validation is done between the routine manufacturing processes. 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 states of affairs.

Retrospective Validation

The retrospective validation is performed on established products whose manufacturing processes are considered stable and when on the basis of economic considerations alone and resources limitations, prospective validation programs cannot be reasonable. Prior to undertaking retrospective validation, wherein the numerical in-process and/or end-product test data of historic production batches are subjected to statistical analysis, the equipment, facilities, and subsystems used in connection with the manufacturing process must be qualified in conformance with CGMP requirements. The cornerstone for retrospective validation is stated in 21 CFR: "Valid in-process specifications for such peculiarity shall be consistent with drug product final specifications and shall be derived from previous tolerable process average and process variables calculated where possible and set on by the application of suitable statistical process control measures where are significant". The concept is also conceded in the FDA's Guidelines on General Principles of Process Validation. Using

Retrospective validation was conducted in the following manner

To collect the numerical data from the completed batch and incorporate assay results and values, finish products test results, and in-process results.

Categorize these results in a linear order according to batch records.

Take data from at least 20–30 batches for analysis.

Compress the data by removing test results from non-critical processing stages and deleting all unjustified information and resources.

Record the data for statistical analysis and evaluation.

Make conclusions as to the state of control of the manufacturing procedures based on the analysis of retrospective validation data and results.

Prepare and Issue a report of findings (documented evidence).

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 definite period (minimum of 10 batches).

Process re-validation

Conditions requiring revalidation study and documentation are listed as follows:

Change in a critical raw material and excipient.

Change or renewal in a critical change part of the equipment

Change in a facility and plant (usually location or site)

Notable increase or decrease in batch size

Successive batches that failed to meet product and process pre-defined specifications.

In some circumstances, requalification studies may be required prior to undertaking specific revalidation assignments. The FDA process validation guidelines refer to a quality assurance system in place that requires re-validation whenever there are changes in the packaging (assumed to be the primary container-closure system), formulation, equipment or processes which could impact on product effectiveness or product characteristics and whenever there are changes in product characteristics. Approved packing is normally selected after completing the packing performance qualification testing as well as product harmony and stability studies. Since in most instances (anomaly: transdermal delivery systems, distinctive tests, and medical devices) packaging is not familiarly involved in the manufacturing steps of the product itself, it contrasts with other factors, such as raw materials.

Benefits of process validation[7,4]

Reduction in rejections and reworks

Increased Outputs

Reduction in utility costs

Avoidance of capital expenditures

Fewer market complaints

Reduced in-process and finished goods testing

More rapid and accurate investigations into process deviations

Easy maintenance of the equipments and instruments

Improved employee consciousness of processes and program

More rapid automatic system

Process validation program can be made more effective and efficient through[8]

Good project management team

Robust scientific knowledge collection, management, and archiving

Uniform collection and assessment of information systems

Diminishing the burden of redundant information conference

Use of an integrated team approach

Suitably documented Project Plans

The support of senior management

Statistical assessment of data

Steps involved for process validation of solid dosage form[9-11]

Dry mixing

Wet granulation and Wet milling

Drying and Milling

Lubrication and Blending

Tablet compression

In process testing

Finish goods testing.

CONCLUSION

Process validation plays a vital role in the pharmaceutical industry to achieve and maintain the quality efficacy and safety of the final product. There should be a Validation program which is known as validation master plan[12] in Pharmaceutical Industry. The process validation team i.e. quality assurance, production, quality control and engineering should identify the important parameters of the process and product to ensure that the product meets its predetermined quality standards, manufacturing, and regulatory requirements.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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