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A CONCISE REVIEW ON PROCESS VALIDATION OF CARBAMAZEPINE EXTENDED RELEASE TABLETS USP 100 mg

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Abstract: The aim of the work to establish scientific evidence by collection and evaluation of the data from the manufacturing of tablets which establishes scientific documented evidence that the process is capable of consistently delivering quality product and meeting the process parameter requirements as per predefined product specification and quality attributes. For achieving the quality product critical material attributes, critical process parameters and critical quality attributes are checked and controlled. The Samples are collected from the three consecutive batches are taken as per the pre-defined protocol which include the sampling plan from different manufacturing stages like dry mixing, drying, blending stage, compression stage and coating stage. Quality parameter are analyzed as per the pre-defined specified limits.

Keywords: Process performance qualification, critical material attributes (CMA) , critical process parameters (CPP), critical quality attributes (CQA), Protocol.

INTRODUCTION: [1, 2, 3]

VALIDATION- Action of proving and documenting that any process, procedure or method actually and consistently leads to the expected results.

PROCESS VALIDATION- The collection and evaluation of data, throughout the product life cycle, which provides documented scientific evidence that a process is capable of consistently delivering quality products. Process validation may take the form of Prospective, Concurrent or re-validation.

Process validation involves a series of activities taking place over the lifecycle of the product and process.

Process design → Process Performance Qualification → Continued process verification

(Process Validation)

Stage 1 – Process Design: The commercial manufacturing 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 evaluated to determine if the process is capable of reproducible commercial manufacturing.

Stage 3 – Continued Process Verification: Ongoing assurance is gained during routine production that the process remains in a state of control.

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 conditions, storage and handling of finished in-process and finished dosage forms. 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 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 facility
- New source of API or as assessed by change control procedure.
- After 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 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 assessing process. The main objective of this stage is to ensure that a process remain always in a validated condition with the help of following.

- Preventive maintenance, calibration and cleaning of facilities and equipment.
- Regular training of staff.
- Recognition and evaluation of changes (change control management).
- Evaluation of deviations, OOS, product defects & market complaints.
- Evaluation of the validation status in the context of Annual product review (may reveal necessity for revalidation)

Critical Process Parameters (CPP): A process input that, when varied beyond a limited range has a direct and significant influence on a critical quality attributes.

Critical Quality Attributes (CQA): Any physical, chemical or biological property of the drug substance or drug product.

Key Process Parameters (KPPs): An input process parameter that should be carefully controlled within a narrow range and is essential for process performance. A key process parameter does not affect product quality attributes. If the acceptable range is exceeded, it may affect the process (e.g. yield, duration) but not product quality.

Non-Key Process Parameters (Non- KPPs): An input parameter that has been demonstrated to be easily controlled or has a wide acceptable limit. Non-key operational parameters may have an impact on quality or process performance if acceptable limits are exceeded.

Quality Target Product Profile (QTPP): The QTPP shall consist of all relevant Quality requirements for the drug product Intended use in the:

- Clinical setting (e.g., dosage form and strength, route of delivery systems, container and closure system).
- Drug substance quality attributes appropriate to the drug product dosage form
- Being developed (e.g., physical, chemical, and biological properties)
- Drug product quality attributes appropriate for the intended marketed product (e.g. Purity/impurities, stability, sterility, physical, and chemical properties),

-Therapeutic moiety release or delivery, and attributes affecting Pharmacokinetic Characteristics (e.g., dissolution, aerodynamic performance) appropriate to the drug product.

Process Characterization (optimization): This refers to the normal behavior of a process when operating in a state of statistical control. It refers to the inherent ability of a process to produce similar parts for a sustained period of time under a given set of condition. It is also defined as the capability of a process to meet its purpose of process definition structure.

Process for process Validation

1. Validation master plan[13] shall be established for any validation activity in which the validation strategy are established.
2. Must be a protocol based study which shall be approved from all the CFTs before commencement of any validation activity.
3. Data shall be collected in the reports and summary conclusion shall be withdrawn.
4. The process is put into commercial use. During the product development phase the production process should be broken down into individual steps. Each step should be evaluated on the basis of knowledge sharing through technology transfer report to determine critical parameters that may affect the quality of the finished product.
5. All the equipment, production environment and the analytical testing methods to be used shall be pre validated/Qualified. As the critical parameters of the process have been identified and machine setting, raw material specifications & environment conditions determined.
6. Three consecutive batches/ runs within the finally agreed parameters shall be consider and acceptable for the product of desired quality constitute and the process is properly validated.
7. During the processing of the validation batches, extensive sampling and testing shall be performed on the product at various stages as per approved protocol and sampling plan and shall be documented comprehensively.
8. Upon completion of the review, recommendation should be made on the extent of the monitoring and in process controls necessary for routine production.
9. The strategy for validation shall also consider the use of different lots of active raw materials and/or major excipients, batches produced on different shifts, operating range of the critical processes (on the extremes of the specification) as specify in Validation
10. Risk assessment shall be done on manufacturing process for identify the impact on critical quality attributes of product i.e. Strength, Identity, Safety, purity and quality.
11. The impact on critical quality attributes of the product shall be evaluated in terms of the process control parameter define in the manufacturing process for the identification and mitigation of risk.

12. The degree of control measures for the manufacturing process shall be defining the type of risk (Low, Medium and High) on the critical quality attributes of product i.e. Strength, Identity, Safety, purity and quality.
13. Critical material attributes are defines for the consistency of the products.
14. On the basis of identified risk, Justification for manufacturing process risk assessment and risk mitigation plan shall be provided to minimize the risk from High to medium/ low or medium to low in validation.
15. Validated equipment, environment and analytical testing methods shall be used.
16. Process validation shall be performed using the defined process (within the pre define parameters) on a minimum of three consecutive batches / runs, giving product of the desired quality.
17. During the processing of the validation batch/run, extensive sampling and testing shall be performed on the product at various stages and documented comprehensively. Detailed testing shall also be done on the final product.
18. The batch sizes of the batches shall be the same as the intended batch size for full-scale production.
19. Comprehensive documentation of the batches/runs under validation shall be done.
20. Following parameter shall be challenged during the process characterization during Scale up /optimization batch, product design and risk assessment (but not limited to);

Manufacturing stage	Critical process parameters	Quality Attributes
Dry Granulation	Mixing Time Mixing Speed	Particle size, Bulk density, Tapped density, LOD, Blend Uniformity
Wet granulation	Amount of granulating agent Granulation time Impeller speed Impeller Amperage Chopper speed Chopper Amperage	Particle size, Bulk density, Tapped density,
drying	Inlet and outlet temperature Product/Bed temperature	LOD
Pre-Lubrication	Mixing time Blender Speed	Blend uniformity, LOD
Lubrication	Final blend Mixing time with lubricants Blender Speed	Blend uniformity, Particle size, LOD (water), BD, TD, Compressibility factor, Assay
Compression	Compression speed Pre-compression force Main-compression force Fill depth	Uniformity of weight, Content Uniformity, Average weight DT, Dissolution, Assay Hardness, Friability, Thickness
Coating	Pan Speed Nozzle Size, Number of Guns Spray Rate Inlet and Bed temperature Exhaust Temperature Distance between spray gun and tablet bed Atomization pressure Drying time	Uniformity of weight DT, Dissolution, Weight Gain, Content Uniformity, Average weight, Thickness

Process re-validation:

Conditions requiring revalidation study and documentation are listed as follows:

1. Change in a API or critical raw material and excipient.
2. Change or renewal in a critical change part of the equipment which may be product impacting.
3. Change in a facility and plant (usually location or site).
4. Increase or decrease in batch size (Scale Up/Down)
5. Successive batches that failed to meet product and process pre-defined specifications.

Conclusion- 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[13] 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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