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A Review Article on Concurrent Process Validation

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ABSTRACT

Validation in simple form can be described as documented practice which delivers the evidence that any of the process, procedure, material, equipment, action or system truly shows the estimated result. Generally, validation is carried out; before any new method has been introduced for routine use, whenever there has been any change in the condition for which the method is further validated, eg: new instrument with different characteristics been used, whenever there is change in method, and the change has been made on the method which has not been mentioned in the original method. Process validation is expressed as the practice which involves the assortment and estimation of data during the different phases of pharmaceutical activities, starting from the procedure design phase during the course of production establishing the scientific indication that a procedure is efficient of steadily manufacturing quality outcomes. Concurrent process validation is quite similar to prospective process validation but differ in the aspect that the product will be sold by the operating firms throughout the qualification sequence among the public as its stated market value. In process supervising of critical processing phases and product testing lies under this validation which aids to produce the documented evidence showing the manufacturing procedure is proceed under a suitable state of control with quality characteristics. The validated documentation obtained from the concurrent process validation can be further used in the future to perform the retrospective process validation for the reference purpose.

Keywords*: Concurrent Process Validation, Retrospective Process, Revalidation Process.*

INTRODUCTION

Process validation is expressed as the practice which involves the assortment and estimation of data during the different phases of pharmaceutical activities, starting from the procedure design phase during the course of production establishing the scientific indication that a procedure is efficient of steadily manufacturing quality outcomes [1].

USFDA defined process validation as "the act of ascertaining documented confirmation which tends to delivers a high grade of assurance that a product will be manufactured through a specific procedure and the product thus produce will meet all its pre-determined descriptions mentioned and quality characteristics" [2,3].

FDA explains that the confirmation of product quality is attained from systemic consideration to different essential factors which includes: choosing of quality raw materials and other components, appropriate product and method design, and test or standardization of the procedure during testing of in process and end product [4]. Thus, elevated degree of certainty can be created through a careful and optimal design and by validating both process and the control systems of it, that the specified acceptable criteria will be attained by all distinct manufactured

entities of a particular batch or series of batches [5].

WHO guidelines has stated validation as documented act which proves or verify that any components, material, process or procedure, machine, system or activity will essentially direct to the estimated results. Validation authenticates that the procedure equipment has the ability of functioning within prerequisite parameters. Validations not only states that the process has been improved but also confirms that procedures have also been precisely developed, established and are within the expected control [6,7].

Validation is an act of verifying that the total GMPs has been followed effectively during the whole manufacturing procedure that expected results will be the outcome. Documented evidence which assures that the process which is performed with in ascertained factors can operate efficiently to manufacture a pharmaceutical product enduring its encoded specifications and quality aspects [8,9].

ADVANTAGES OF PROCESS VALIDATION [10]

1) As it is a simple practice and moisture sensitive; validation of heat sensitive manufactured good can be performed.
2) Real time monitoring can be expanded and process modification can be done.
3) Improved ability to statistically estimate process operation and product variables.
4) Ensure the smooth operation of the process by decreasing the possibility of arising problems.
5) Improve data and assessment proficiencies and improved conviction about product quality and process reproducibility.
6) Improved the reporting capability.
7) Enhanced ability to established estimated parameters and testing limits for repetitive production, associating with validation outcomes.

OBJECTIVES OF PROCESS VALIDATION

1) To decrease dissimilarity between different batches.
2) To minimalize the possibility of defect costs and monitoring noncompliance.
3) To validate the robustness of the process.
4) To offer a high notch of assurance that the products are of quality standard.
5) To certify the uniformity of the manufacturing operations and consistency of the process.
6) To declare the presence of all obligatory quality assurance system within association.
7) To reduce the in-process and end product testing in case of fully validated procedure.

The Process validation activities can be explained in three stages:

Stage 1: Process Design

Based on information acquired through enlargement and scale-up actions, the commercial practice is defined during the process design stage. Accomplishments that elucidate a process appropriate for commercial manufacturing which steadily produce a good that encounter its quality aspect are included in this stage. This stage provides a key input to the studies that are carried without the application of good manufacturing practices, during the product development studies which ultimately helps in the various design stages such as anticipated dosage form, manufacturing route. All the findings that are executed during this stage are to be documented, acknowledged and verified internally for the purpose to use them in later stage of the lifecycle succeeding ICH Q10 recommendations. Various factors should be considered during the development, such as limitations of

commercial equipment, future variability which are highly chances to be raised from various sources such as materials (raw materials), personnel (procedures and operators), machine used (different equipment), control and measurement (testing systems and methods), and various environmental factors.

Stage 2: Process Qualification
Process qualification is the second stage where the evaluation of process design is performed to regulate whether it is efficient of reproducible commercial production.

Stage 3: Continued Process Verification
All the continual data assembled to sustain the quality of product are evaluated in the third stage *i.e.* CPV of process validation. Various data are included such as critical quality attributes, process tends and in process material attribute, critical quality attributes. From the routine production, continuing assurance is acquired that the process endures in a status of control.

DIFFERENT TYPES OF PROCESS VALIDATION [11]

1) Prospective Process Validation

Prospective process validation is executed after the completion of the R and D trial in order to produce the product for the commercial purpose. This is one of the crucial part of the process validation as most validation efforts depends on the prospective experimentation so that data that support the validation could be generated. This type of validation is generally connected with the introduction of new drug product into the market and involves the studies of all their manufacturing processes.

2) Concurrent Process Validation

This validation is quite similar to prospective process validation but differ in the aspect that the product will be sold by the operating firms throughout the qualification sequence among the public as its stated market value. In process supervising of critical processing phases and product testing lies under this validation which aids to produce the documented evidence showing the manufacturing procedure is proceed under a suitable state of control with quality characteristics. The validated documentation obtained from the concurrent process validation can be further used in the future to perform the retrospective process validation for the reference purpose.

3) Retrospective Process Validation

The retrospective validation is generally performed on the established product which does not face any sort of instability and are considered stable, when the prospective validation programs cannot be justified due to the resource limitation and on the basis of economic considerations alone.

Prior to commencing retrospective validation, where in the numbers of in-process or end-product test data of past manufacturing batches are exposed to the equipment, facilities, statistical analysis and sub systems involved in association with the manufacturing procedure must be practiced in conformance with CGMP necessities.

4) Revalidation

Revalidation basically refers to the repetition of the validation method. In any pharmaceutical plant revalidation is performed if any sort of changes is made in the batch size, formulation or when the consecutive batches of the manufacturing unit doesn't meet specification as stated in its product, when changes are made in the site location, equipment size and capacity or new advance equipment are introduced for the further processing or when new manufacturing methods and control are to be followed or changes are made in them.

STRATEGY FOR VALIDATION OF METHODS [12]

The various strategies for process validation of method are:

1) Preparing process flow charts and detecting the critical process variables.
2) Selecting the three sequential batches which possess same manufacturing formula and batch size.
3) Process prequalification should be carried out in case of failure to encounter the prerequisite of the validation protocol on the basis of process input and output control.
4) Proper documentation should be prepared for all the validation experiment and results by maintaining a validation report.
5) BMR, SOPs, finished and in process product specification along with other associated documents and batch packaging record should be maintained.
6) Prepare a relevant process validation protocol of the specified product.
7) In other to perform the task consistently and efficiently, SOPs should be prepared.
8) Accomplishment of validation protocol effectively.
9) Monitoring of all the respective process validation batches.
10) Carrying out the in process testing during manufacturing of the product.

TYPE OF DOCUMENTATION IN VALIDATION [13]

The various documentation to be prepared during the validation process are:

1) Standard operating process (SOPs)
2) Validation protocol (VP)
3) Validation master plan (VMP)
4) Validation reports (VR)

Validation Master Plan

Validation master plan (VMP) is the document that states all the details required for performing the validation procedure and the time scales required to complete the work along with the responsibilities related to the validation plan. It provides the brief knowledge on the validation work program of the company. WHO guideline states validation master plan as a high level document that creates the validation plan for the complete project and reviews the manufacturer's methodology. Validation master plan explains that any of the process, method or procedure is actually and consistently capable of producing the desired outcome or results. Calibration and qualification of the equipment and machinery used are also sum up in the validation master plan [14].

Purpose of VMP

1) Instruct the management regarding the validation plan on the basis of plan for time, manpower and capital, and the essentiality of the program.
2) Guide the associates of the validation team about their responsibilities and task to be performed.
3) Direct the GMP inspectors to recognize the firm approach to validation and organization of all validation activities.

VMP Procedure

- Scope and purpose
- Responsibility
- Validation policy
- Qualification of system, facilities, machine and utilities
- Validation
- Personal qualification
- Documentation format
- Requalification and revalidation
- Scheduling and planning
- Change of control
- Reference to prevailing documents

Validation Protocol

Validation protocol (VP) includes:

- Scope and objectives
- Responsible Personnel
- Description of SOPs

- Instruments or machinery to be used
- Calibration requirements
- Standard and criteria as appropriate
- Stages of validation
- Critical processes parameter
- Sampling, testing requirement and additional test
- Stress testing where appropriate
- Predetermined acceptance criteria
- Reviews
- Interpretation of results obtained
- Deviations
- Conclusion

Validation Reports [15]

An authorized report should be composed and made available after accomplishment of the validation and should be accepted and authorized by the quality assurance. The validation report should comprise of:

- Title of the study
- Objectives of study
- References to protocol
- Detail of raw materials
- Machine and utilities
- Programs and processes
- Specific procedures and testing approaches
- Results comprises of acceptable criteria
- Recommendation on the limit
- Recommendation on criteria to be concerned on future basis

Standard Operating Procedure (SOPs)

Standard Operating Procedures (SOPs) are the instruction that are released to guide employees in spaces of appropriate specifications, responsibility, work directions and required records. It is the integral part of the quality assurance which draws the attention on the procedures which are to be followed to assert the GMP compliance. The various attributes that lies under the SOPs is to provide step wise instruction to be performed when any sort of task has been carried out in the pharmaceutical plants. It includes steps to be followed during cleaning to prevent cross contamination in the working area, handling and operation of equipment and machinery, testing and controls, documenting and overall all the aspects of the organization [16,17].

Objectives of SOPs

1) To conduct the quality control and quality assurance.
2) To aid as a training document for educating the operators about the processing steps for which SOPs was prepared.
3) To present guidelines for timely and accurate collection of data.
4) To assist reliable conformance to quality system requirements and to aid data quality.
5) To maintain the uniformity of the operation.

STEPS INVOLVED FOR PROCESS VALIDATION OF SOLID DOSAGE FORM (TABLET)

1) **Mixing/ blending**

- Mixing of raw materials
- Mixing time
- Uniformity of drug
- Mixing technique: tumbling
- Speed of mixer
- Uniformity of excipient
- Capacity of equipment used

2) **Wet granulation**

- Preparation of binder solution
- Binder solution addition rate
- Concentration of binder
- Mixing of binder solution and mixture of powder
- Time of mixing
- End point of granulation

3) **Wet milling**

- Milling speed
- Feed rate
- Equipment capacity and size

- Size of screen

4) **Drying**
- Temperature
- Airflow
- Uniformity of moisture

5) **Milling**
- Milling speed
- Feed rate
- Equipment capacity and size
- Size of screen

6) **Lubrication**
- Time of mixing
- Lubricant used
- Quantity of lubricant

7) **In–process testing**
- Uniformity of mixing
- Moisture content of granules

8) **Tablet compression**
- Tooling set up
- Speed of compression
- Compression force

9) **In–process testing**
- Weight of tablet
- Hardness
- Thickness
- Impurity profile
- Disintegration time

10) **Finish product testing**
- Tablet appearance
- Hardness
- Weight of tablet
- Thickness
- Friability
- Assay
- Impurity profile
- Uniformity of content

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