JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

A Review Article on Concurrent Process Validation of solid Dosages Form

Priyanka jha, Mrs.Sunita Arya, Miss Gulbahar

ABSTRACT

Process Validation in pharmaceuticals is one of the important steps in accomplishing and maintaining the quality of final product. It gives a higher degree of assurance of pharmaceutical product. Validation simply can be described as documented practice which delivers the evidence that any of the equipment process, procedure, material, procedure and system truly shows the predetermined result. Process validation is expressed as the practice which involves the selection and estimation of data during the different phases of pharmaceutical activities, starting from the procedure design phase during the production process and establishing the scientific indication that a procedure is manufacturing quality outcomes. In process supervising of critical processing phases and product testing lies under this validation which assist 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: Validation, Process validation, Concurrent Process Validation

INTRODUCTION

Validation is an intergral part of Quality Assurance, It involves the systemic study of system, facilities, and process aims at determining whether they perform their intended functions adequately and consistently as specified. Validation in itself doesnot improve the process but conforms that the process have been properly developed and are under control. The concept of validation was first proposed by two FDA officials,Ted byers and bud loftus in 1979 in USA, to improve the Quality of Pharmaceuticals and later on it became an intergral part of current good Manufacturing Practices.

According to USFDA, the goal of validation is to “Establish documented evidence which provide a higher degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes”.

According to ISO “ validation is the confirmation by examination and the provision of objective that the evidence that the particular requirements for specific intended use are fulfiled”.

According to European commession”Action providing in accordance with the principles of GMP that any procedure, process, equipment, material, activity or system actually lead to the expected results” [13,14]

Process validation establishes the flexibility and limitations in the manufacturing process controls in the attainment of desirable attributes in the drug product while preventing undesirable properties. This is an important concept, since it serves to support the underlying definition of validation, which is a systematic approach to identifying, measuring, evaluating, documenting, and reevaluating a series of critical steps in the manufacturing process that require control to ensure a reproducible final product.[18]

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]

Concurrent validation is used for establishing documented evidence that a facility and processes do what they purport to do, based on information generated during actual imputation of the process. This approach involves monitoring of critical processing steps and end product testing of current production, to show that the manufacturing process is in a state of control.[11]

According to the FDA, assurance of product quality is derived from careful and systemic attention to a number of important factors, including: selection of quality components and materials, adequate product and process design, and (statistical) control of the process through in-process and end-product testing. Thus, it is through careful design (qualification) and validation of both the process and its control systems that a high degree of confidence can be established that all individual manufactured units of a given batch or succession of batches that meet specifications will be acceptable.

REASON FOR VALIDATION[13,14]

- It is regulated requirement stipulated in cGMP.
- Greater impact on product development process.
- Cost reduction.
- To Produce Zero defect product.
- End result of validation will be higher more uniform and reproducible.

ADVANTAGES OF PROCESS VALIDATION[19] .

- Real time monitoring can be expanded and process modification can be done.
- Upgrade the ability to statistically estimate process operation and product variables.
- Ensure the smooth operation of the process by decreasing the possibility of arising problems.
- Improve data and assessment ability and improved conviction about product quality and process reproducibility.
- Improved the reporting capability.
- Enhanced ability to established evaluate parameters and testing limits for repetitive production, associating with validation outcomes.

Process Validation is establishing documented evidence which provide a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality characterstics.[11]

The Process validation activities can be described in three stages.[9,10,11]

Stage 1 – Process Design: The commercial process is defined during this stage based on knowledge gained through development and scale-up activities. **Pre-validation phase or the qualification phase:** It 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, storage and handling of in-process and finished dosage forms, equipment qualification installation qualification, master production documents, operational qualification, process capability.

Stage 2 – Process Qualification: During this stage, the process design is confirmed as being capable of reproducible commercial manufacturing. Designed to verify that all established limits of the critical process parameters are valid and that satisfactory products can be produced even under the "worst case" conditions.

Stage 3 – Continued Process Verification/Validation Maintenance Phase: Ongoing assurance is gained during routine production that the process remains in a state of control. Validation requiring frequent review of all process related documents, including validation audit reports to assure that there have been no changes, deviations, failures, modifications to the production process, and that all SOPs have been followed, including change control procedures. At this stage the validation team also assures that there have been no changes/ deviations that should have resulted in requalification and revalidation.

TYPES OF VALIDATION [2-6,7,8]

The validation protocol is executed before the process is put into commercial use. During the product development phase, the production process should be broken down to individual steps. Each step is evaluated on the basis of experience or theoretical considerations to determine critical parameters that may affect the quality of the finished product. A series of experiments should be designed to determine the criticality of these factors. Each experiment should be planned and documented in fully authorized protocol. It is generally considered acceptable that is three consecutive batches within finally agreed parameters, giving product of the desired quality will constitute a proper validation of the process.

It is similar to prospective, except the operating firm will sell the products during its qualification runs, to the public as its market price. This validation involves in-process monitoring of its critical processing steps and product testing. This helps to generate documented evidence to show that the production process is in a state of control.

It is defined as the establishment of the documented evidence that the system does what it purports to do based on review and analysis of historical data. This is achieved by the review of historical manufacturing testing data to prove that the process has always remained in control.

Re-validation is usually performed to the confirmation of initial validation for a periodic review. Re-validation provides the evidence that changes in a process and /or the process environment that are introduced do not adversely affect the process characteristics and product quality. Documentation requirements will be the same as for the initial validation of the process. Re-validation becomes necessary in certain situations change in equipment, change in method of manufacturing. Re-validation divided in to two categories;
1) Re-validation after changes such as changes in the starting material, changes in packaging material, changes in the process, changes in equipment, changes in production area and support system, unexpected changes or deviations during manufacturing.
2) Periodic Re-validation.

STRATEGY FOR INDUSTRIAL PROCESS ALIDATION OF SOLID DOSAGE FORMS

The strategy selected for process validation should be simple and straightforward. The following five points gives strategy for process validation:

- The use of different lots of raw materials should be included. i.e., active drug substance and major excipients.

- Batches should be run in succession and on different days and shifts (the latter condition, if appropriate).

- Batches should be manufactured in the equipment and facilities designated for eventual commercial production.

- Critical process variables should be set within their operating ranges and should not exceed their upper and lower control limits during process operation. Output responses should be well within finished product specifications. Failure to meet the requirements of the Validation protocol with respect to process input and output control should be subjected to process requalification and subsequent revalidation following a thorough analysis of process data and formal discussion by the validation team.

TYPE OF DOCUMENTATION IN VALIDATION[20]

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 the equipment and machinery used are also sum up in the validation master plan.[21]

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
- 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 proper 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 type 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]

STEPS INVOLVED FOR PROCESS VALIDATION OF SOLID DOSAGE FORM (TABLET) WITH THE CRITICAL PARAMETERS.

Mixing/ blending

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

Wet granulation

- Preparation of binder solution
- Binder solution addition
- Concentration of binder
- Time of mixing

- End point of granulation

Wet milling

- 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

REFERENCES

1. B. T. Loftus & R. A. Nash, 'Pharmaceutical Process Validation", Drugs and Pharm Sci. Series, Vol. 129, 3 rd Ed., Marcel Dekker Inc., N. Y.
2. Nash RA. and Watcher AH., "Pharmaceutical Process Validation"; third edition; Marcel & Dekker, Inc. New York, 2008, pp 1-31,159-190.
3. Potdar MA., "CGMP For Pharmaceuticals"; Pharma Med Press, Hyderabad, 2009, pp 413-493.
4. Potdar MA., "Pharmaceutical Facilities: Design, Layout & Validation"; Pharma Med Press, Hyderabad, pp 70-75
5. Sharma PP., "Validation In Pharmaceutical Industries: concepts, Approaches & Guidelines"; First edition; Vandana Publication PVT LTD. Delhi, 2007, pp 83-99,117,275-329
6. Libberman HA., Lechman L., and Schwartz JB., "Pharmaceutical Dosage Forms: Tablets"; Second edition; Marcel & Dekker, New York, 2005, pp 417-453
7. Pandharmise P., Kulkarni A., Naiyar S., Sharma D., and Kamble A., "Studies in Prospective Process Validation of Gliclazide Tablet 80 mg Dosage Formulation." *Int. J. PharmTech Res.* **2011**, 3, 1515-1520.
8. Rohokale BS., Jadhav VM., and KadamVJ., "Studies in Prospective Process Validation of Metformin HCl Tablet Dosage Formulation." *Int. J. PharmTech Res.* **2010**, 4, 1673-1678.
9. Chawla N., Rana AC., Saini S., and Singh G., "An Overview: Role of Process Validation In Tablets." *Int. J. Pharm.* **2012**, 1,113 – 119.
10. Wazade MB., Walde SR., and Ittadwar AM., "An Overview Of Pharmaceutical Process Validation And Process Control Variables OfTablets Manufacturing Processes In Industry." *Int. J. Pharm. Sci. Res.* **2012**, 9, 3007 – 3022.
11. https://kneat.com/article/the-four-types-of-process-validation
12. Sharma S, Khurana G, Gupta R. A Review on Pharmaceutical Validation CR Journals (Page 48–54) 2020. All Rights Reserved Page 54 Pharmaceutical Sciences Volume 1 Issue 1 and Its Implication. Indian J. Pharm. Biol. Res. 2013; 1 (3): 100-104.
13. Industrial Pharmacy,A Comprehensive approach by D.K Tripathi (671-699)
14. Pharmaceutical Process validation :An overview by M.D shoaib Ala etal:journal of advanced pharmacy education anmd research,Oct-Dec 2012,vol 2,issue 4(190-1960
15. Tandel MJ, Kumar J, Dedania R, Vadalia KR. Process Validation of Pyrazinamide Tablets: Review. International Journal of Advances in Pharmacy, Biology and Chemistry.
16. Prabhu Lakshamana, T.N.K. Suriyaprakash, K. Ruckmani, R. Thirumurugan, Concepts of process validation in solid dosage form (Tablet), Scholarena, 2014, 1(1), 1-12
17. Kaur G, Rana AC, Bala R, Seth N. An Overview: The Role of Process Validation inPharmaceutical Industry. International Research Journal of Pharmacy, 2012; 3(1): 25-27.
18. European medicines agency. Guideline on Process Validation (Draft), Geneva, Switzerland; 2012:10-11.
19. A WHO guide to GMP (1997); Requirements, part 2: Validation.
20. Good Manufacturing Practices for Pharmaceutical Products. WHO Expert Committee on Specifications for Pharmaceutical Preparations (1992).32nd Report, WHO Technical Report Series no.823. Geneva: WHO, 14-96.
21. Kathiresan K, Sreenu VS, Moorthi C, Reddy B, Kumar B, Reddy M, Yellamula P, Manavalan R. Cleaning Validation of Acetaminophen Tablets. International Journal of Chemical Environmental and Pharmaceutical research, 2010; 3(3): 503-506.