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Review Article

A REVIEW ON PHARMACEUTICAL PROCESS VALIDATION

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ABSTRACT
Validation is one of the important steps in achieving and maintaining the quality of the final product. Validation of the individual steps of the process is called process validation. The process is developed in such a way that the required parameters are achieved and it ensures that the output of the process will consistently meet the required parameters during the routine production. If each step of the process is validated, we can assure that the final product is of the best quality. This review covers need of validation, principle of validation, types of validation, phases of validation, strategy for validation.

Keywords: Validation, Process validation, Consistent, Quality assurance.

INTRODUCTION

The concept of validation was first proposed 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[1]. The development of a drug product is a lengthy process involving drug discovery, laboratory testing, animal studies, clinical trials and regulatory registration. To further enhance the effectiveness and safety of the drug product after approval, the United States Food and Drug Administration (FDA) also require that the drug product be tested for its identity, strength, quality, purity and stability before it can be released for use. For this reason, pharmaceutical validation is important. The purpose is to monitor the performance of the manufacturing process and then validate it[2]. The validation protocol includes inventory control and equipment inspection in preliminary steps and in-process controls in subsequent steps. The purpose of setting validation parameters is to monitor the on-line and off-line performance of the manufacturing process. Thus, validation is an integral part of quality assurance[3].

VALIDATION

In pharmaceutical organizations, validation supports a company's commitment to quality assurance. Validation is a tool of quality assurance which provides confirmation of the quality in equipment systems, manufacturing processes, software and testing methods. Validation assures that products with pre-determined quality characteristics and attributes can be reproduced consistently within the established limits of the manufacturing process operation at the manufacturing site. Validation is required in order to move a product from development to commercial production[4].

Basic principle of validation[5]

- Quality, safety and efficacy must be designed and built into the product.
- Quality cannot be assured merely by in-process and finished product inspection or testing.
- Each step of the manufacturing process must be controlled to assure that the finished product meets all quality and design specifications.

Definitions:

USFDA defines validation as[6]

"Validation is establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics."

European Commission[7]

"Validation is the act of demonstrating and documenting that a procedure operates effectively. Process validation is the means of ensuring and providing documentary evidence that processes are capable of consistently producing a finished product of the required quality."

Benefits of validation[4,8]

- It deepens the understanding of processes.
- It decreases the risk of preventing problems and thus assures the smooth running of the process.
- It decreases the risk of defect cost.
- It decreases the risk of regulatory noncompliance.
- A fully validated process may require less in-process controls and end-product testing.
- A validated process is more efficient and produces less reworks, rejects and wastage.
- Enhanced ability to statistically evaluate process performance and product variables.e.g. Mean; range; control limits.
- Increased confidence about process reproducibility and product quality.

Need of validation[9]

- It would not be feasible to use the equipment without knowing whether it will produce the product we want or not.
- The pharmaceutical industry uses expensive materials, sophisticated facilities & equipments and highly qualified personnel.
- The efficient use of these resources is necessary for the continued success of the industry. The cost of product failures, rejects, reworks, recalls, complaints are the significant parts of the total production cost.
- Detailed study and control of the manufacturing process validation is necessary if failure cost is to be reduced and productivity is to be improved.

Government regulations

Validation is considered to be integral part of GMPs essentially worldwide, compliances with validation requirements is necessary for obtaining approval to manufacture and to introduce new products. The FDA's cGMP refer to the concepts of the validation in both sections, 21 CFR 210 and 211. 21 CFR 211.100 states: "There shall be

written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess." A generally stated requirement for process validation is contained in the medicinal device GMP regulations where deviations from specification could occur as a result of manufacturing process itself. There shall be written procedures describing any process controls necessary to assure conformance to specifications[3,9].

Types of validation[6,10,11,12]

I. **Analytical validation:** Analytical validation is the evaluation of product quality attributes through testing, to demonstrate reliability is being maintained throughout the product life cycle and that the precision, accuracy, strength, purity and specification has not been compromised.

II. **Equipment validation:** Validation of equipment is known as qualification. Equipment validation is divided into installation Qualification (IQ), Operational Qualification (OQ), and Performance Qualification (PQ). An IQ documents specific static attributes of a facility or item to prove that the installation of the unit has been correctly performed and that the installation specifications of the manufacturer have been met. After installation it must be ensured that the equipment can deliver operating ranges as specified in the purchase order. This is called OQ. The PQ's are concerned with proving that the process being investigated works as it is supposed to do.

III. **Process validation:** "A documented program which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specification and quality attributes". Process validation is divided into different types as follows:

Prospective validation: 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 into individual steps. Each step should be evaluated on the basis of experience or theoretical considerations to determine the 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 fully in an authorized protocol. It is generally considered acceptable that three consecutive batches within the finally agreed parameters, giving product of the desired quality would constitute a proper validation of the process.

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

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

Revalidation: It is the repetition of a validation process or a part of it. This is carried out when there is any change or replacement in formulation, equipment plan or site location, batch size and in the case of sequential batches that do not meet product specifications and is also carried out at specific time intervals in case of no changes.

Computer System Validation: Computer validation encompasses computers, which directly control process or system or collect analytical data. Computer validation includes the qualification of all software and hardware, which has an impact, direct or indirect, on the quality of a product.

Phases of validation[4,12]

Design Qualification (DQ)

It is established by document verification of the design of equipment and manufacturing facilities.

Installation Qualification (IQ)

It is established by document verification that all key aspects of the process equipment and ancillary system installation adhere to the manufacturer's approved specification and that the recommendations of the supplier of the equipment are suitably considered.

Operational Qualification (OQ)

It is established by document verification of process control limits and target range which result in product that meets all predetermined requirements.

Performance Qualification (PQ)

It is established by document verification that the equipment, under anticipated conditions, consistently produces a product which meets all predetermined requirements.

Process Validation Phases[4,8,10]

Validation related activities are grouped into three phases:

Phase 1 (Pre-validation phase or Qualification Phase): This phase 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 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 or Process qualification phase): This phase is designed to verify that all established limits of the critical process parameter are valid and that satisfactory. Products can be produced even under the worst conditions.

Phase 3 (Validation maintenance Phase): This phase 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 crepitating 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. A careful design and validation of systems and process controls can establish a high degree of confidence that all lots or batches produced will meet their intended specifications. It is assumed that throughout manufacturing and control, operations are conducted in accordance with the principle of good manufacturing practice (GMP) both in general and in specific reference to sterile product manufacture.

Strategy for validation

Development of an extensive process validation strategy early in product development is critical to the execution of a successful validation program, and should also be consistent with the FDA's Quality by Design initiative. Development and process support activities leading to process validation require the allocation of internal and external resources. Because of the nature of validation requirements, partnering with external experts in this area can prove to be an important decision to complete the program successfully. Time and

budgetary constraints do not allow the repetition of required activities, so all external resources need to be proven in their experience. The validation strategy is captured in a document that defines the process and activities related to each stage of process validation[13,14,15]. The validity of a specific method should be demonstrated in laboratory experiments using samples or standards that are similar to the unknown samples analyzed in the routine. The preparation and execution should follow a validation protocol preferably written in a step-by-step instruction format as follows[4,8]:

- Develop a validation protocol or operating procedure for the validation.
- Define the application purpose and scope of the method.
- Define the performance parameters and acceptance criteria.
- Define validation experiments.
- Verify relevant performance characteristics of the equipment.
- Select quality materials, e.g. standards and reagents.
- Perform pre-validation experiments.
- Adjust method parameters and/or acceptance criteria, if necessary.
- Perform full internal (and external) validation experiments.
- Develop SOPs, for executing the method routinely.
- Define criteria for revalidation.
- Define type and frequency of system suitability tests and/or analytical quality control (AQC) checks for the routine.
- Document validation experiments and results in the validation report.

CONCLUSION

Before the launch of the product in the market, it is necessary for the industry to ensure that quality is built into the system at every step. A process validation strategy which is developed at early stage of product development is necessary for a successful validation program. The validation helps to generate a method which produces the product consistently with the intended specifications and thus produces less wastage or rejects.

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