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Research Article

Pharmaceutical Process Validation: A Mini Review

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ABSTRACT

Pharmaceutical Process Validation emphasizes on process design elements and maintaining process control during commercialization and communicate that process validation is an ongoing program and align process validation activities with product lifecycle. According to GMP validation studies are essential part of GMP these are required to be done as per predefined protocols, the minimum that should be validated include process, testing and cleaning as a result such control procedure stablish to monitor the output and validation of manufacturing processes that may be responsible for variability of drug product. The validation study provide the accuracy, sensitivity, specificity and reproducibility of the test methods employed by the firms, shall be established and documented. Thus the validation is an essential part of the quality assurance.

Key words: Master plan, Quality Assurance, Pharmaceutical Validation, Pharmaceutical Process Control.

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Introduction

Pharmaceutical Process Validation is the most important and recognized parameters of cGMPs. The concept of validation has expanded through the years to embrace a wide range of activities from analytical methods used for the quality control of drug substances and drug products to computerized systems for clinical trials, labelling or process control. Validation isfounded on, but not prescribed by regulatory requirements and is best viewed as an important and integral part of cGMP.[1] According to FDA, assurance of product quality is derived from careful and systemic attention to a number of importance factors, including: selection of quality process through in-process and end-product testing.[2] The concept of validation was first proposed by two Food and Drug Administration (FDA) officials, Ted Byers and Bud Loftus, in the mid 1970s in order to improve the quality of pharmaceuticals.[3]

Major Phases in Validation

The activities relating to validation studies may be classified into three:
Phase 1: This is the Pre-validation Qualification Phase which covers all activities relating to product research and development, formulation pilot batch studies, scale-up

Need of Pharmaceutical Validation

Validation is an integral part of quality assurance; it involves the systematic study of systems, facilities and processes aimed at determining whether they perform their intended functions adequately and consistently as specified. A validated process is one which has been demonstrated to provide a high degree of assurance that uniform batches will be produced that meet the required specifications and has therefore been formally approved. Validation in itself does not improve processes but confirms that the processes have been properly developed and are under control [4].
reliably. Process validation is required, in both general and specific terms, by the CGMP regulations in parts 210 and 211. The foundation for process validation is provided in § 211.100(a), which states that "[t] here shall be written procedures for production and process control designed to assure that the drug

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products have the identity, strength, quality, and purity they purport or are represented to possess..." (emphasis added). This regulation requires manufacturers to design a process, including operations and controls, which results in a product meeting these attributes 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: This is the Process Validation Phase. It 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: Known as the Validation Maintenance Phase, it 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 operating 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[5,6].

Process Validation

Process validation is the means of ensuring and providing documentary evidence that processes (within their specified design is beneficial to the manufacturer in many ways

1. It deepens the understanding of processes; decreases the risk of preventing problems and thus assures the smooth running of the process.
2. It decreases the risk of defect costs.
3. It decreases the risk of regulatory non-compliance.
4. A fully validated process may require less in-process controls and end- product testing.

Validation should thus be considered in the following situations:

1. Totally new process;
2. New equipment;
3. Process and equipment which have been altered to suit changing priorities; and
4. Process where the end-product test is poor and an unreliable indicator of product quality.

When any new manufacturing formula or method of preparation is adopted, steps should be taken to demonstrate its suitability for routine processing. The defined process should be shown to yield a product consistent with the required quality. In this phase, the extent to which deviations from chosen parameters can influence product quality should also be evaluated. When certain processes or products have been validated during the development stage, it is not always necessary to revalidate the whole process or product if similar equipment is used or similar products have been produced, provided that the final product conforms to the in-process controls and final product specification. There should be a clear distinction between in-process control and validation. In production, tests are performed each time on a batch to batch basis using specifications and methods devised during the development phase. The objective is to monitor the process continuously.Parameters are capable of repeatedly and reliably producing a finished product of the required quality. It would normally be expected that process validation be completed prior to the release of the finished product for sale (prospective validation). Where this is not possible, it may be necessary to validate processes during routine production (concurrent validation). Processes, which have been in use for some time without any significant changes, may also be validated according to an approved protocol (retrospective validation) [7-15] .

Pre-requisites for Process Validation

Before process validation can be started, manufacturing equipment and control instruments as well as the formulation must be qualified. The information on a pharmaceutical product should be studied in detail and qualified at the development stage, i.e., before an application for marketing authorization is submitted. This involves studies on the compatibility of active ingredients and recipients, and of final drug product and

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packaging materials, stability studies, etc. Other aspects of manufacture must be validated including critical services (water, air, nitrogen, power supply, etc.) and supporting operations such as equipment cleaning and sanitation of premises. Proper training and motivation of personnel are prerequisites to successful validation.

The Pharmaceutical Process Equipment The key idea of validation is to provide a high level of documented evidence that the equipment and the process conform to a written standard. The level (or depth) is dictated by the complexity of the system or equipment. The validation package must provide the necessary information and test procedures required to provide that the system and process meet specified requirements[14,15].

Validation of pharmaceutical process equipment involves the following:

Installation Qualification (IQ)

This ensures that all major processing and packaging equipment, and ancillary systems are in conformity with installation specification, equipment manuals schematics and engineering drawing. It verifies that the equipment has been installed in accordance with manufacturers recommendation in a proper manner and placed in an environment suitable for its intended purpose.

Operational Qualification (OQ): This is done to provide a high degree of assurance that the equipment functions as intended. Operational qualification should be conducted in two stages:
1. Component Operational Qualification, of which calibration can be considered a large part.
2. System Operational Qualification to determine if the entire system operates as an integrated whole.

Process Performance Qualification (PQ):

This verifies that the system is repeatable and is consistently producing a quality product . These exercises assure, through appropriate performance lists and related documen- tation, that equipment, ancillary systems and sub-systems have been commissioned correctly. The end results are that all future operations will be reliable and within prescribed operational limits. At various stages in a validation exercise there are needs for protocols, documentation, procedures, specifications and acceptance criteria for test results. All these need to be reviewed, checked and authorized. It would be expected that representatives from the professional disciplines, e.g., engineering, research and development, manufacturing, quality control and quality assurance are actively involved in these undertakings with the final authorization given by a validation team or the quality assurance representative[16]

Expert Evaluation

This is an evaluation of the entire study against the protocol requirements as outlined above. It should be prepared and the conclusion drawn at each stage stated. The final conclusions should reflect whether the protocol requirements were met. The evaluation should include an assessment of the planned calibration and maintenance programmes for the equipment and instrumentation to maintain the validated conditions. In addition, all process monitoring and control procedures required to routinely ensure that the validated conditions are maintained should be reported. The evaluation should be signed by authorized officers of the organization who were members of the team establishing the protocol and who have appropriate expertise in the area assigned to them. Overall approval of the study should be authorized by the head of the validation team and the head of the quality control department [17]

Validation Report

A written report should be available after completion of the validation. If found acceptable, It should be approved and authorized (signed and dated). The report should include at least the following:

- Title and objective of study;
- Reference to protocol;
- Details of material;
- Equipment;
- Programmes and cycles used;
- Details of procedures and test methods;
- Results (compared with acceptance criteria); and
- Recommendations on the limit and criteria to be applied on future basis.

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Conclusion

It is necessary, before approval of a new drug, that an accurate and reliable assessment for its effectiveness and safety for the intended indication and target patient population is demonstrated. Pharmaceutical Process Validation is the most important and recognized parameters of cGMP. It is necessary, before approval of a new drug, that an accurate and reliable assessment for its effectiveness and safety for the intended indication and target patient population is demonstrated. Generally, pharmaceutical validation and process control provide a certain assurance of batch uniformity and integrity of the product manufactured.

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