



INTRODUCTION AND GENERAL OVERVIEW OF PHARMACEUTICAL PROCESS VALIDATION: A REVIEW

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ABSTRACT

Drugs are critical elements in health care. They must be manufactured to the highest quality levels. End-product testing by itself does not guarantee the quality of the product. Quality assurance techniques must be used. In the pharmaceutical industry, process validation performs this task, ensuring that the process does what it purports to do. Validation is defined as the collection and evaluation of data, from the process design stages through commercial production, which establishes scientific evidences that a process is capable of consistently delivering quality product. It is also a regulatory requirement. Total Quality Management and specifications according to regulatory guidelines involved in the pharmaceutical production has a great impact significantly on the quality of products. The validation protocol includes inventory control and equipment inspections in the preliminary steps and in-process controls in the subsequent steps. Process controls are mandatory in good manufacturing practices (GMP). This review critically evaluates the need of pharmaceutical validation, the various approaches and steps involved, and other pertinent considerations.

KEYWORDS: Validation, Total Quality Management, Pharmaceutical Validation, Good Manufacturing practices

INTRODUCTION

In Pharmaceutical organizations, validation is a fundamental segment that supports a company 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 methods¹. Validation is defined as the collection and evaluation of data, from the process design stages through commercial production, which establishes scientific evidences that a process is capable of consistently delivering quality product. The purpose of setting validation parameters is to monitor the on-line and off-line performance of the manufacturing process, and hence, validate it. The foremost priority of regulatory agencies is to ensure the safety of general public health. The bioavailability of drugs is greatly influenced by the dosage form characteristics and it's imperative to ensure the consistent performance of the product from batch to batch. In order to check final quality of product, a series control test has been devised. It's understood that the central role of these final stage tests limited to measure the attributes of product produced before releasing into market². Quality control tests are tools to ensure not assure the quality of product. It has always been known that facilities and processes involved in pharmaceutical production impact significantly quality of products. Processes controls are mandatory in Good Manufacturing Practices (GMP). Pharmaceutical industries are concerned about validation for the assurance of quality, for cost reduction, Government regulation. Validation is required in order to move a product from development to commercial production in the product life cycle. The development of drug product is lengthy and costly process which involves drug discovery, various in vitro and in vivo studies clinical trials and regulatory requirements. For further enhancement of effectiveness and safety of the drug product after approval regulatory agencies such as United States Food and Drug administration (FDA) also require that the drug product be tested for its identity, safety, purity, quality and stability before it can be launched. For this very reason Pharmaceutical validation and process

controls are key areas which have to be addressed in judicious manner³.

DEFINITION OF VALIDATION

- Action of proving, in accordance with the principles of good manufacturing Practice, that any procedure, process, equipment, material, activity, or system actually leads to the expected result.
- Documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes and characteristics.
- Obtaining and documenting evidence to demonstrate that a method can be relied upon to produce the intended result within defined limits.

Action to verify that any process, procedure, activity, material, system, or equipment used in manufacture or control can, will, and does achieve the desired and intended results⁴.

JUSTIFICATION OF VALIDATION

Validation is basically good business practice. The objective is to achieve success in the first production of a new product.

Government regulation

Current good manufacturing practices (GMPs) have been established all over the world. The GMPs basically serve as guidelines but do not provide step-by-step directions on how to achieve them. However, the validation master plan and associated SOPs exactly define responsibilities: who, when, where, and how much is sufficient to demonstrate.

Assurance of quality

Validation provides confidence in the quality of products manufactured as the over quality of a particular process cannot be established due to the limited sample size. Validation leads to less troubleshooting within routine production. As a result, it reduces the number of customer complaints and drug recalls.

Cost reduction

Processes running at marginal levels often cause costs because of necessary re inspection, retesting, rework, and

rejection. Validation leads to the optimization of processes and results in minimization of those expenses⁵.

BACKGROUND OF VALIDATION

History

Since the mid-1970s validation has become an increasingly dominant influence in the manufacture and quality assurance of pharmaceutical products. In 1976 the FDA proposed a whole set of current GMP regulations which were revised several times.

Legal requirements

In several major countries GMP regulations are considered official law and noncompliance is prosecutable. Additional compliance policies, guides, and guidelines are not legally binding. However, the pharmaceutical industry follows them as a part of good management and business practice.

Market requirements

The demands in the health care industry are greater than ever because customers (government, physicians, pharmacists, patients, and health insurance companies) are more interested in product safety, efficacy, and potency and asking value for money. Pharmaceutical products' quality must be consistent and meet the health and regulatory requirements. The pharmaceutical industry has the obligation to validate GMP to their process to be in compliance with GMP requirements⁶.

THE BASIC CONCEPT OF PROCESS VALIDATION

1. Requalification or revalidation
2. Calibration, verification, and maintenance of process equipment
3. Establishing specifications and performance characteristics
4. Selection of methods, process, and equipment to ensure the product meets specifications
5. Qualification or validation of process and equipment
6. Testing the final product, using validated analytical methods, in order to meet specifications
7. Challenging, auditing, monitoring, or sampling the recognized critical and key steps of the process

ESSENTIAL OF PHARMACEUTICAL VALIDATION

- To reduce batch to batch variations.
- To achieve reproducible products of the same quality, purity and strength.
- To assure safety and efficacy and to minimize hazardous effects.
- To reduce the chance of product recall from market.
- To save the cost that arises because of lengthy investigation procedures in case of product variances.

VALIDATION SHOULD BE CONSIDERED IN THE FOLLOWING SITUATION

- Totally new process
- New equipment
- Process and equipment which has been altered to suit changing priorities
- Process where the end product test is poor and unreliable indication of product quality

PRINCIPLES OF VALIDATION

The basic principle is characterized by harmony between the results obtained and requirements, which includes/ supports.

- Specified requirements and objectives
- Available means
- Choices which are justified in relation to objectives
- Each stage should begin when the previous stage is over.

Certain dispositions have to be taken into account as to

- How restrictions should be defined?
- How norms should be dealt with?
- How modifications should be dealt with?

Controlling the evolution will involve

- Setting data for decision making.
- Evaluation before decision making.
- Justifying the decision.

The following scheme may be suggested

- Aim versus objective.
- Process as a whole and flow diagram.
- Challenging the critical process variables.
- Validation protocol.
- Protocol versus report: procedures, sampling, testing, reporting and results.
- Evaluation and recommendations including frequency for re validation⁷.

VALIDATION:-Done by Whom?

The Consultant:-Individual or group of person who are responsible for the validation work.

The Task Force Concept:- Individual from the various department (may be from QA, Production, Engineering and R&D).

The Dedicated group:-A specific team who is just working on validation⁸.

TYPES OF VALIDATION

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.

Equipment Validation

Validation of equipments 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.

Process Validation

It would normally be expected that process validation be completed prior to the distribution of a finished product that is intended 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).Fig 1

Process validation is "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: In prospective validation, the validation protocol is executed before the process is put into commercial use. It is defined as the establishment of documented evidence that a system does what it purports to do based on pre-planned protocol. This validation is usually carried out prior to the introduction of new drugs and their manufacturing process. This approach to validation is normally undertaken whenever a new formula, process or

facility must be validated before routine pharmaceutical formulation commences.

Retrospective Validation: In many establishments, processes that are stable and in routine use have not undergone a formally documented validation process. Historical data may be utilized to provide necessary documentary evidence that the processes are validated. 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.

Concurrent Validation: It is similar to prospective, except the operating firm will sell the product during the qualification runs, to the public at its market price. This validation involves in process monitoring of critical processing steps and product testing.

Revalidation: It is the repetition of a validation process or a specific part of it. This is carried out when there is any change or replacement in formulation, equipment, plant or site location, batch size and in the case of sequential batches that do not meet product and process specifications.

Conditions for Revalidation:-

- Change in critical components (raw material)
- Change of replacement of equipment
- Change in location or site
- Significant increase or decrease in batch size.
- Sequential batches that fail to meet product and process qualification.

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. The validation approach to programmable logic controller (PLC) hardware and personal computers (PCs) is similar, both to one another and to the general overall approach to validation, in that the end user should define each requirement⁹.

PHASES OF VALIDATION

Design Qualification (DQ)

Document verification of the design of equipment and manufacturing facilities.

Installation Qualification (IQ)

Documented verification of equipment of system design and adherence to manufacturer's recommendations.

Operational Qualification (OQ)

Documented verification of equipment or system performance in the target operating range.

Process performance qualification (PQ)

Documented verification that equipment or systems operate as expected under routine productions the operation is reproducible, reliable and in a state of control¹⁰.

PROCESS/ PRODUCT VALIDATION

Validation is establishing documented evidence which provides a high degree of assurance that a specific system will consistently produce a product meeting its predetermined specifications and quality attributes.

Process Validation Phases

The activities relating to validation studies may be classified into three:

Phase1: This is the Pre-validation Qualification Phase which 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: 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 manufacture¹¹.

Stages of process validation

Stage 1 – Process design or process pre-qualification: The commercial 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 confirmed as being 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 control¹².

PROCESS VALIDATION PROTOCOL

- Protocol Approval Sheet
- Table of contents
- Scope and objective
- Validation term and responsibility
- Steps for validation and acceptance criteria
- Process flow chart
- Procedure
- For Review of raw material/packing material
- Evaluation of active raw material
- Qualification of equipment
- Test instrument calibration
- Revalidation criteria
- Reference document
- Product details
- Raw material for bulk manufacturing and their function
- Equipment detail
- Packing material detail
- Manufacturing process flow chart
- Critical process parameters
- In-process specification
- Sampling procedure and testing plan
- Re validation criteria
- Change control
- Deviations
- Stability

- Incidence
- Conclusion
- Report and Approval¹³

VALIDATION: Type of Documentation

- Validation master plan (VMP)
- Validation protocol (VP)
- Validation reports (VR)
- Standard operating procedures (SOPs)

Validation master plan (VMP)

- It is a document pertaining to the whole facility that describes which system, methods and processes will be validated and when they will be validated.
- Provide the format required for each particular validation document (IQ,OQ,PQ for systems; process validation, analytical assay validation)
- Indicate what information is to be contained within each document.
- Indicate why and when revalidation will be performed
- Who will decide validation will be performed
- Order in which each part of the facility is validated.

Validation protocol (VP)

- Objective of the validation and qualification study
- Site of the study
- Responsible personnel
- Description of the equipment
- SOPs
- Standards
- Criteria for the relevant products and processes

Validation reports (VR)

- Title
- Objective of the study
- Refer to the protocol
- Details of material
- Equipment
- Programmes and cycles use
- Details of Procedures and test methods¹⁴

STRATEGY FOR VALIDATION OF METHODS

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:

- 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.

CRITICAL FACTORS:- Critical factors which affect conducting effective process validation

- The quality system (infrastructure) should support the validation effort by way of document control, calibration, preventive maintenance, etc.
- All the critical points of the process should be clearly identified
- The process should run using the extremes of the system at the critical points (worst case).
- Adequate run (data) are required to provide statistical support to demonstrate product consistency.
- The execution of the protocol should follow the requirements of the validation document, where all deviations form the validation document well recorded and followed up properly.
- Before approving validation the area should be conformed for the requirement of validation¹⁵.

CONCLUSION

The goal for the regulators is to ensure that quality is built into the system at every step, and not just tested for an end, as such validation activities will commonly include training on production material and operating procedures, training of people involved and monitoring of system in production. In general, the entire process is validated a particular object within that process is verified. The regulations also set out an expectation that the different parts of production process are well defined and controlled, such that the result of that production will not substantially change over time. It is necessary, before approval of new drug, that an accurate and reliable assessment for its effectiveness and safety for the intended indication and target patient population is demonstrated.

In general, Pharmaceutical validation and process control provide a certain assurance of batch uniformity and integrity of batch manufactured.

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Figure 1 General view of process validation