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A REVIEW ON PHARMACEUTICAL VALIDATION AND ITS IMPLICATIONS

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ABSTRACT

Validation is one of the important steps in achieving and maintaining the quality of the final product. If each step of production process is validated, we can assure that the final product is of the best quality. Validation is the art of designing and practicing the designed steps alongside with the documentation. Validation and quality assurance will go hand in hand, ensuring the thorough quality for the products. Process validation emphasize on process design elements and maintaining process control during commercialization and communicate that it is an ongoing program and align process validation activities with product lifecycle. The purpose of this review is to present an introduction and general overview on process validation of pharmaceutical manufacturing with special reference to the requirements stipulated by the US Food and Drug Administration (FDA).

KEY WORDS

validation, protocol, guidelines, quality, cGMP

INTRODUCTION

Pharmaceutical Process Validation is the most important and recognized parameters of cGMPs. The requirement of process validation appears as the quality system (QS) regulation. The goal of a quality system is to consistently produce products that are fit for their intended use. Process validation is a key element in assuring that these principles and goal are met. [1]

The concept of validation was first proposed by Food and Drug Administration officials in 1970 in order to improve the quality of pharmaceuticals. Process validation is assuring and documenting the process within their specified and designed criteria, therefore the manufactured product will meet its predetermined criteria and quality attributes with reproducible and constant result. [2] Assurance of product quality is derived from careful attention to number of factors including selection of quality parts and materials, adequate product and process design, control of the process, and in-process and end product testing. Due to the complexity of today's medical products, routine end product testing alone often is not sufficient to assure product quality for several reasons. Some end-products tests have limited sensitivity. [3] The principal objective of dosage form design is to achieve a predictable therapeutic response to a drug included in a formulation which is capable of large scale manufacture with reproducible product quality. Process Validation is one of the important steps in achieving and maintaining the quality of final product. It is the key element to assure the identity, purity, safety, efficacy and also maintaining the quality of final product. [4] The basic principle of quality assurance is that a drug should be produced that is fit for its intended use. In order to meet this principle, a good understanding of the processes and their performance is important. Quality cannot be

adequately assured by in-process and finished product inspection and testing but it should be built into the manufacturing processes. These processes should be controlled in order that the finished product meets all quality specifications. Process validation is intended to establish that the proposed manufacturing process is a suitable one and yields consistently a product of the desired quality. i.e. that the process is suitable and under control. [5]

WHY IS VALIDATION REQUIRED?

The pharmaceutical industry uses expensive materials, sophisticated facilities & equipment 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, and recalls, complaints are the significant parts of the total production cost. Detailed study and control of the manufacturing process- validation is necessary if failure to be controlled and productivity improved.

The pharmaceutical industries are concerned about validation because of the following reasons.

- ✓ Assurance of quality.
- ✓ Cost reduction.
- ✓ Government regulation [6]

RESPONSIBLE AUTHORITIES FOR VALIDATION [7,8]

The validation working party is convened to define, investigate, progress, collate, co-ordinate and ultimately approve the entire effort, including all of the documentation generate. The working part would usually involve the following staff members

·Production manager
·Head of Quality Control (Manager)
·Executive-QC
·Head of Engineering (Manager)
·Production executive
·Validation Executive
·Validation Manager
·Head of Quality Assurance (Manager)

Table 1: Responsible authorities for Validation

Department/Designation	Responsibility
Manager Production	Responsible for manufacturing of batches and review of protocol and report.
Manager QC	Responsible for samples collected
Executive QC	Responsible for analysis of samples collection and submission to QC
Manager Maintenance	Providing utilities and engineering support
Executive Production	Responsible for preparation of protocol and manufacturing of validation batches
Manager QA	Responsible for protocol authorization and preparation of summary report.

OBJECTIVES OF PROCESS VALIDATION [9]

1) The manufacturing process, in addition to the individual equipment, must be validated.
2) The goal is to create a robust manufacturing process that consistently produces a drug product with minimal variation that adheres to quality criteria of purity, identity, and potency.
3) A validation plan for the manufacturing process should be drafted and executed by engineers in order to satisfy guidelines. The validation plan usually involves just a PQ section.
4) Just as equipment validation, major changes after the initial validation will result in the need for subsequent revalidation.
5) In the end, process validation will ensure a robust product that is highly reproducible over time.

PREREQUISTE OF PROCESS VALIDATION: [1,10]

- Process Development Designee shall review the product development report, data from pilot scale, scale up batch and proposed master formula document of product intended for manufacturing.
- Process Development Designee shall review/ensure the availability analytical method transfer report to the plant and plant preparedness for conducting validation testing and routine testing; function shall co-ordinate with QC/QA in this regard.
- Process Development Designee shall prepare commercial/exhibit batch production and control records which include the operational limits and overall strategy for process control based on development report.
- The Process Validation is performed after the facility, utility, and equipment, and laboratory test

methods have been validated and released for process validation activities. Where compendia method is used only limited analytical method validation shall be conducted.

- All raw material and packaging material specification shall be from approved vendors and shall be approved by quality control.
- All the equipment and instrument to be utilized are calibrated and preventive maintenance programs are in place.
- Relevant SOPs are in place and training is completed on equipment, operation, manufacturing instruction and sampling strategy.
- Key process steps and process variables are identified, and their operating ranges have been established.
- All the master formula, manufacturing instruction, packaging instruction, testing procedure & specification shall be approved before execution of process validation batches.
- The cleaning of the area and equipment has been completed prior to the initiation of process validation.
- The validation team and operational team shall be trained from process engineer.

STRATEGY FOR VALIDATION OF METHODS [11,12]

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

1. The use of different lots of raw materials should be included. i.e., active drug substance and major excipients.
2. Batches should be run in succession and on different days and shifts (the latter condition, if appropriate).
3. Batches should be manufactured in the equipment and facilities designated for eventual commercial production.
4. 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.
5. 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.

PHASES OF PROCESS VALIDATION [13,14]

Pre-validation Phase or 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 and storage and handling of in-process and finished dosage forms, equipment qualification, installation qualification, master production document, operational qualification and process capacity.

Process Validation Phase (Process Qualification 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 case” conditions.

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

ELEMENTS OF PROCESS VALIDATION [15,16,17]

Qualification is pre-requisite of validation. The qualification includes the following:

1. Design Qualification (DQ)

The documented verification that the proposed design of the facilities, systems and equipment is suitable for the intended purpose.

In this qualification, compliance of design with GMP should be demonstrated. The principles of design

should be such as to achieve the objectives of GMP with regard to equipment. Mechanical drawings and design features provided by the manufacturer of the equipment should be examined.

2. Installation Qualification (IQ)

Establishing confidence that process equipment and ancillary systems are capable of consistently operating within established limits and tolerances. (FDA) The documented verification that the facilities, systems and equipment as installed or modified complies with the approved design and the manufacturer's recommendations.

Installation qualification should be carried out on new or modified facilities, systems and equipment. The following main points should be included in the installation qualification.

- Checking of installation of equipment, piping, services and instrumentation.
- Collection of supplier's operating working instructions and maintenance requirements and their calibration requirements.
- Verification of materials of construction.
- Sources of spares and maintenance.

3. Operational Qualification (OQ)

The documented verification that the facilities, systems and equipment, as installed or modified, perform as intended throughout the anticipated operating ranges. Operational qualification should follow IQ.

OQ should include the following:

- Tests developed from the knowledge of the processes systems and equipment
- Defining lower and upper operating limits. Sometimes, these are called 'worst case' conditions.

4. Performance Qualification (PQ):

"It is a documented verification that the equipment and ancillary systems as compared together can perform effectively and reproducibly based an approved method and specification." PQ is establishing confidence that the process is effective and reproducible, establishing confidence that a process in accordance with the design qualifications. Performance Qualification is documented proof that the equipment functions in your facilities exactly as intended. This is insured by verifying the suitability of the equipment under the actual operating conditions of the environment and according to its intended task (e.g., compliance with safety regulations for accident prevention, traceable data transmission). Performance Qualification reviews the critical parameters of the equipment using suitable test methods. These procedures are documented in form of test specifications. It is not mandatory to perform Performance Qualification on all equipments or instruments. However, Performance Qualification is to be performed for all the process equipments and the equipment that are critical. The question on whether not to carry out Performance Qualification is generally done on a case-to case basis.

TYPES OF PROCESS VALIDATION: [3,18,19,20]

1. Prospective validation
2. Concurrent validation
3. Retrospective validation
4. Revalidation

1. **Prospective Process Validation:** It is defined as the established documented evidence that a system does what it purports to do based on a pre-planned protocol. This validation usually carried out prior to distribution either of a new product or a product made under a revised manufacturing process performed on at least three successive production-sizes. (Consecutive batches)

These should be incorporated into the Batch manufacturing and packaging record or into appropriate standard operating procedures. Limits, frequencies and action to be taken in the event of the limits being exceeded should be specified.

Prospective validation should include, but not be limited to the following:

- Short description of the process.
- Summary of the critical processing steps to be investigated.
- List of the equipment/facilities to be used (including measuring, monitoring/recording equipment) together with its calibration status.
- Finished product specifications for release.
- List of analytical methods, as appropriate.
- Proposed in-process controls with acceptance criteria.
- Additional testing to be carried out, with acceptance criteria and analytical validation, as appropriate.
- Sampling plan.
- Methods for recording and evaluating results.
- Functions and responsibilities.
- Proposed timetable.

Batches made for process validation should be the same size as the intended Industrial scale batches. If it is intended that validation batches be sold or supplied, the conditions under which they are produced should comply fully with the requirements of Good Manufacturing Practice, including the satisfactory outcome of the validation exercise and the marketing authorization.

2. Concurrent Process Validation: It is similar to the 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. This helps to generate and documented evidence to show that the production process is in a state of control.
- In exceptional circumstances it may be acceptable not to complete a validation programme before routine production starts.
- The decision to carry out concurrent validation must be justified, documented and approved by authorized personnel.
- Documentation requirements for concurrent validation are the same as specified for prospective validation.

3. Retrospective Process Validation: Retrospective validation is defined as the establishment of documented evidence that a system does what it purports to do on review and analysis of historical information. The sources of such data are production, QA and QC records. The issues to be addressed here are changes to equipment, process, specification and other relevant changes in the past. Retrospective validation is only acceptable for well-established processes and will be inappropriate where there have been recent changes in the composition of the product, operating procedures or equipment. The steps involved require the preparation of a specific protocol and the reporting of the results of the data review, leading to a conclusion and a recommendation. The source of data for this validation should include, but not be limited to batch processing and packaging records, process control charts, maintenance logbooks, records of personnel changes, process capability studies, finished product data, including trend cards and storage stability results. Batches selected for retrospective validation should be representative of all batches made during the review period, including any batches that failed to meet the specifications, and should be sufficient in number to demonstrate process consistency. Additional testing of retained samples may be needed to obtain the necessary amount or type of data to retrospectively validate the process. For retrospective validation, generally data from ten to thirty consecutive batches should be examined to assess process consistency, but fewer batches may be examined if justified. Some of the essential elements for Retrospective Validation Batches manufactured for a defined period (minimum of 10 last consecutive batches). Number of lots released per year.

- Batch size/strength/manufacturer/year/period.
- Master manufacturing/packaging documents.
- Current specifications for active materials/finished products.
- List of process deviations, corrective actions and changes to manufacturing documents.
- Data for stability testing for several batches.

4. 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 plans 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.

It provides the evidence that changes in a process and/or the process environment that are introduced do not adversely affect process characteristics and product quality. Documentation requirements will be the same as for the initial validation of the process. Where no significant changes have been made to the validated status, a review with evidence that facilities, systems, equipment and processes meet the prescribed requirements fulfils the need for revalidation. Revalidation becomes necessary in certain situations. Some of the changes that require validation are as follows:

- Changes in raw materials (physical properties such as density, viscosity, particle size distribution and moisture etc that may affect the process or product).
- Changes in the source of active raw material manufacturer.
- Changes in packaging material (primary container/closure system)
- Changes in the process (e.g., mixing time, drying temperatures and batch size)

- Changes in the equipment (e.g., addition of automatic detection system).
- Changes of equipment which involve the replacement of equipment on a "like for like" basis would not normally require revalidation except that this new equipment must be qualified.
- Changes in the plant/facility. A decision not to perform revalidation studies must be fully justified and documented.

VALIDATION PROTOCOL [21]

The validation protocol should be numbered, signed and dated, and should contain as a minimum the following information:

- ✓ Title
- ✓ Objective & Scope
- ✓ Responsibility
- ✓ Protocol Approval
- ✓ Validation Team
- ✓ Product Composition
- ✓ Process Flow Chart
- ✓ Manufacturing Process
- ✓ Review of Equipments / Utilities
- ✓ Review of Raw Materials and Packing Materials Review of Analytical and Batch Manufacturing Records
- ✓ Review of Batch Quantities for Validation (Raw Materials)
- ✓ Review of Batch Quantities for Validation (Packing Materials)
- ✓ HSE Requirements
- ✓ Review of Process Parameters Validation Procedure
- ✓ Sampling Location
- ✓ Documentation
- ✓ Acceptance Criteria
- ✓ Summary
- ✓ Conclusion

DOCUMENTATION [22,23]

Documentation at each phase of the process validation lifecycle is essential for effective communication in complex, lengthy, and multidisciplinary projects. Documentation is important so that knowledge gained about a product and process is accessible and comprehensible to others involved in each phase of the lifecycle. Information transparency and accessibility are fundamental tenets of the scientific method. They are also essential to enable organizational units responsible and accountable for the process to make informed, science-based decisions that ultimately support the release of a product to commerce.

A written protocol should be established that specifies how qualification and validation will be conducted. The protocol should be reviewed and approved. The protocol should specify critical steps and acceptance criteria. A report that contain references, the qualification and/or validation protocol should be prepared, summarizing the results obtained, commenting on any deviations observed, and drawing the necessary conclusions, including recommending changes necessary to correct deficiencies. Any changes to the plan as defined in the protocol should be documented with appropriate justification. After completion of a satisfactory qualification, a format release for the next step in qualification and validation should be made as a written authorization.

VALIDATION LIFE CYCLE

Validation is a continuing and evolving process. The validation process which extends from very basic to very broad theoretical and methodical investigation of how the system and processes perform. Its scope encompasses documentation revision control, training and maintenance of the system and process. Evidence of validation should be seen at the corporate level and be reflected in the management structure. Validation is a method for building and maintaining quality. [24]

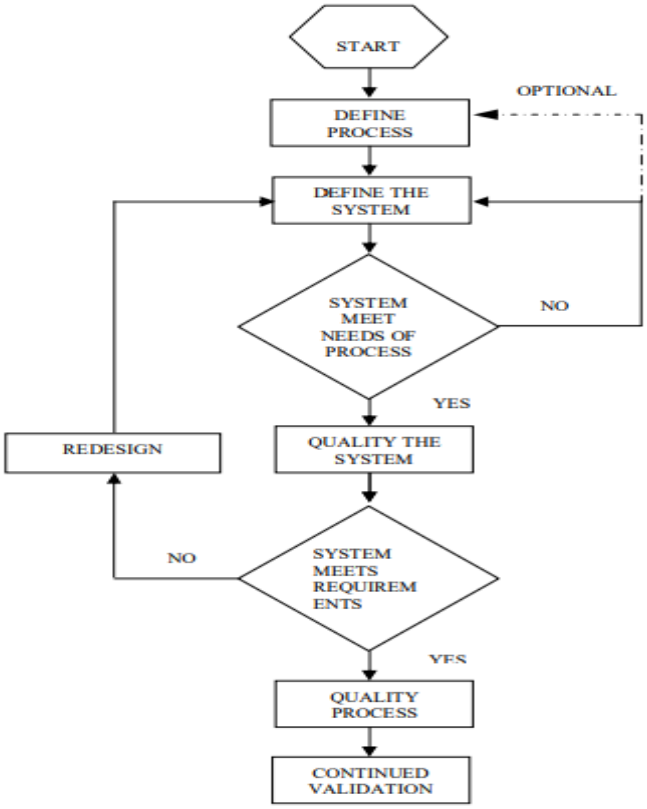

Figure 1. VALIDATION LIFE CYCLE

VALIDATION MASTER PLAN:

A validation master plan is a document that summarizes the company's overall philosophy, intentions and approaches to be used for establishing performance adequacy. The Validation Master Plan should be agreed upon by management.

Validation in general requires meticulous preparation and careful planning of the various steps in the process. In addition, all work should be carried out in a structured way according to formally authorized standard operating procedures. All observations must be documented and where possible must be recorded as actual numerical results. The validation master plan should provide an overview of the entire validation operation, its organizational structure, its content and planning. The main elements of it being the list inventory of the items to be validated and the planning schedule. All validation activities relating to critical technical operations, relevant to product and process controls within a firm should be included in the validation master plan. It should comprise all prospective, concurrent and retrospective validations as well as re-validation. The Validation Master Plan should be a summary document and should therefore be brief, concise and clear. It should not repeat information documented elsewhere but should refer to existing documents such as policy documents, SOP's and validation protocols and reports

The format and content should include:

- Introduction: validation policy, scope, location and schedule
- Organizational structure: personnel responsibilities plant/process/product description: rational for inclusions or exclusions and extent of validation
- Specific process considerations that are critical and those requiring extra attention
- List of products/ processes/ systems to be validated, summarized in a matrix format, validation approach
- Re-validation activities, actual status and future planning
- Key acceptance criteria
- Documentation format
- Reference to the required SOP's
- Time plans of each validation project and sub-project. [25]

ADVANTAGES [26,27,23]

- Consistent through output.
- Reduction in rejections and reworks.
- Avoidance of capital expenditures.
- Fewer complaints about process related failure.
- More rapid and accurate investigations into process deviation.
- More rapid and reliable start-up of new equipment.
- Easier scale-up from development work.
- Easier maintenance of equipment.
- Improve employee awareness of processes.
- More rapid automation.
- Assurance of quality
- Process optimization.
- Reduction of quality cost.
- Reduced testing in process and in finished goods.
- More rapid and reliable start-up of new equipments.
- Easier scale-up form development work.
- Easier maintenance of equipment.
- Improved employee awareness of processes.
- Expanded real time monitoring and adjustment of process.
- Enhanced ability to statistically evaluate process performance and product variables. e.g., individuals; mean; range; control limits.
- Enhanced data and evaluation capabilities and increased confidence about process reproducibility and product quality.
- Improved ability to set target parameters and control limits for routine production, correlating with validation results.
- Enhanced reporting capability.

THE REGULATORY BASIS FOR PROCESS VALIDATION [28,29]

Once the concept of being able to predict process performance to meet user requirements evolved, FDA regulatory officials established that there was a legal basis for requiring process validation. The ultimate legal authority is Section 501(a)(2)(B) of the FD&C Act, which states that a drug is deemed to be adulterated if the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or were not operated or administrated in conformity with CGMP. Assurance must be given that the drug would meet the requirements of the act as to safety and would have the identity and strength and meet the quality and purity characteristics that it purported or was represented to possess. That section of the act sets the premise for process validation requirements for both finished pharmaceuticals and active pharmaceutical ingredients, because active pharmaceutical ingredients are also deemed to be drugs under the act. The CGMP regulations for finished pharmaceuticals, 21 CFR 210 and 211, were promulgated to enforce the requirements of the act. Although these regulations do not include a definition for process validation, the requirement is implicit in the language of 21 CFR 211.100 , which 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.”

APPROACH TO PROCESS VALIDATION [30]

Stage 1: Process Design: The marketable manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities.

Stage 2: Process Qualification: Throughout this stage, the method design is estimated to determine if the process is capable of reproducible marketable business.

Stage 3: Continued Process Verification: Constant assertion is gained during routine production that the process remains in a state of control. [6]

CONCLUSION

Validation is the most widely used word in the areas of drug development, manufacturing and specification of finished products. The consistency and reliability of a validated process to produce a quality product is the very important for an industry. From the study it can be stated that Pharmaceutical Process Validation is the most important and recognized parameters of cGMP. Quality assurance techniques must be used to build the quality into the product at every step and not just tested for at the end. Process validation involves a series of activities taking place over the lifecycle of the product and process.

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