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Review Article

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A Review on Validation and Basic Concepts of Process Validation with Emphasis on Prospective Validation

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Abstract The aim of present review article is to focus light on process validation and its basic concepts in pharmaceutical industry. Validation is a key aspect of Quality system. Prime requirement of quality is that everything should be validated (process, system, equipment etc.). "Process validation is establishing documented evidence which provides a high degree of assurance that a specified process will consistently produce a product meeting its pre- determined specifications and quality characteristics." Process Validation emphasize on process design elements and maintaining process under control during commercialization and communicate that process validation is an ongoing program and align process validation activities throughout product lifecycle. Process validation provides assurance that the drug product can meet standards for the identity, strength, quality, purity, and stability of the drug product.

Keywords Process validation, parameters, protocol, commercialization, inspection, cGMP, Food and Drug Administration (FDA)

Introduction

Pharmaceutical Validation is the most significant and accepted parameters of cGMPs. The major objective of pharmaceutical industry is to manufacture products of required attribute and quality consistently, at the lowest conceivable cost. Validation is a intellection that has been developed continuously since its first formal aspect in the United States in 1978. The need of the process validation is that appears of the quality system (QS) regulation. The Aim of a quality system is to always produce result that are suitable for their wilful use. The process validation is the certification of the validation documents that must be submitted with the submission file for marketing authorization. The process validation is deliberated to assist manufacturers in tolerant quality management system (QMS) necessities concerning process validation and have common applicability to manufacturing process. Validation has become one of the Pharmaceutical industry's most familiar and discussed subjects. Its critical success factor in product support and ongoing commercialization. Quality is always an authoritative requirement when we consider any product. Therefore, the drugs must be manufactured to the highest quality levels. Finished product testing by itself does not assurance the quality of the product. A process validation procedure is required as specified by the current good manufacturing practices Regulations for Finished pharmaceuticals and is therefore applicable to manufacturing of drugs.

Validation is one of the main and essential part of cGMP. Validation is based on, FDA regulations that narrate current good manufacturing practice(cGMP) for complete pharmaceuticals that are provided in 21 CFR parts 210 & 211. The cGMP regulations need that manufacturing processes are designed and controlled to assure that the in-process materials and the finished outcome meet fixed quality requirements and do so always and reliably.

Validation is therefore one the element of pharmaceutical quality assurance related with a particular process, the process vary widely, there is no universal approach to validation and regulatory bodies such as FDA and EC who have evolve general and non-mandatory guide lines. Then the word validation simply means, assessment of validity" or action of proving effectiveness. Process controls include raw materials in-process controls that targets for final products. The motive is to monitor the on-line and the off-line performance of the manufacturing process and then to validate it. After the manufacture, process is validated and current good manufacturing practice also need that their is well-written procedure for the process controls and is accepted to monitor its performance. This paper also provides an overview of the pharmaceutical validation and the process controls in drug development. The concept of validation can be applied to the new drugs, new dosage forms and generic drug development [1-3].

History of Validation

The concept of validation was first proposed by two FDA officials, Ted Byers and Bud Loftus, in the middle of 1970's in an order to improve its quality of the pharmaceuticals. It was proposed in direct response for several problems in the sterility of the large volume of parenteral market. The first validation task was focused on the action involved in the manufacturing of these products, but quickly spread to the associated process of pharmaceutical.

U.S.F.D.A. was the colonizer to advice the concept of the process validation, but till 29th September 1978 the definition of process validation did not appear in any part of the literature of U.S.F.D.A. no cGMP regulations talked anything related to process validation [4].

Definitions

US FDA Definition

"Process validation is establishing documented evidence which provides a high degree of assurance that a specified process will consistently produce a product meeting its pre- determined specifications and quality characteristics" [5, 6, 7, 8].

ICH Definition

"Process Validation is the means of ensuring and providing documentary evidence that processes within their specified design parameters are capable of repeatedly and reliably producing a finished product of the required quality."

European commission

Validation "Act of proving, in accordance of GMPs that Any" process actually leads to expected results. 2000- "Documented evidence that the process, operated within established Parameters, can perform effectively and reproducibly to produce a Medicinal product meeting its predetermined specifications and quality attributes".

Necessity 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 [9].

Assurance of Quality

Without validation, a process that is well understood and in a state the confidence, control of quality of the product manufactured cannot be assured without validation

Cost Reduction

Since each and every step in validation is monitored constantly there lesser rejects and reworks which would lead to an effective cost reduction.

Government Regulation

Validation is considered to be an integral part of GMPs. Worldwide compliance with validation requirements is necessary for obtaining approval to manufacture and to introduce new products.

The FDAs cGMP refer to the concepts of the validation in 211.110 and 211.113 sections. Section 211.110 states that, such control procedures shall be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in process materials and drug product.

The accuracy, sensitivity, specificity and reproducibility of test methods employed by the firm shall be established and documented.

A general requirement for process validation is contained in the medical device cGMP, regulation, section 820.100(b) (1) which states that, "Where deviations from device specifications could occur as a result of the manufacturing process itself, there shall be written procedures describing any processing controls necessary to assure conformance to specifications" [10].

Objective of Process Validation

- To reduce variation between various batches.
- To provide a high degree of assurance of quality of the product.
- To decrease the risk of defect costs and regulatory noncompliance.
- To ensure the consistency of the manufacturing operation and reproducibility of the process.
- To demonstrate the robustness of the process.
- A fully validated process may require less in-process controls and end product testing.
- To ensure the existence of all necessary quality assurance system within organization [10,11]

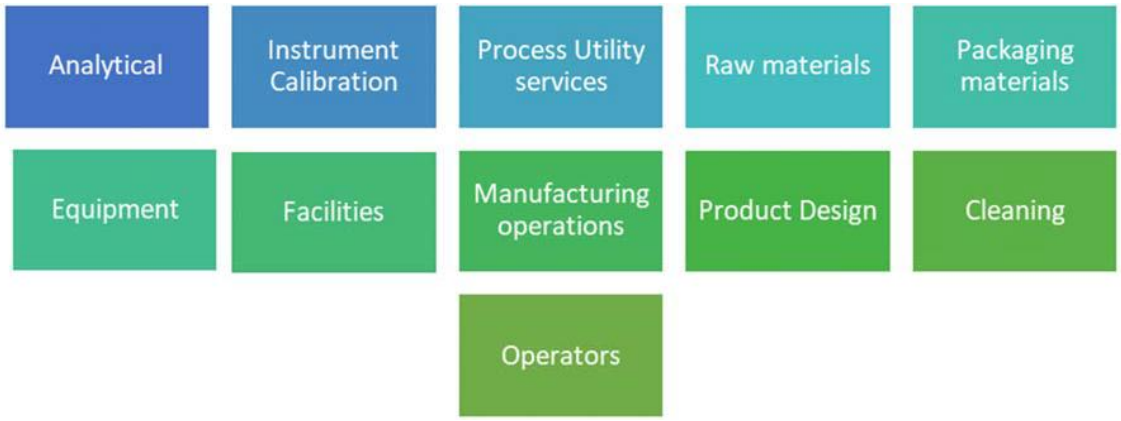
Reason for Process Validation

The possible reason of performing process validation may include:

- New product or existing products as per SUPAC changes.
- Change in site of manufacturing.
- Change in batch size.
- Change in equipment.
- Change in process existing products.
- Change in composition or components.
- Change in the critical control parameters.
- Change in vendor of API or critical excipient.
- Change in specification on input material.
- Abnormal trends in quality parameters of product through review during Annual Product Review (APR).
- Trend of Out of Specification (OOS) or Out of Trend (OOT) in consecutive batches [12].

Scope of Validation

Pharmaceutical Validation is a huge area of work and it is practically covers every aspect of the pharmaceutical processing activities, hence explaining the Scope of Validation becomes a really hard task. However, an organized look at the pharmaceutical operations will point out at least the following areas for the pharmaceutical validation [13]:-



Elements of Validation

Installation Qualification (IQ)

Establishing by objective evidence that all key aspects of the process equipment and ancillary system installation adhere to the manufacturer's approved specification and that the recommendation of the supplier of the equipment are suitably considered.

IQ considerations are:

- Equipment design features (i.e. material of construction clean ability, etc.)
- Installation conditions (wiring, utility, functionality, etc.)
- Calibration, preventative maintenance, cleaning schedules.
- Safety features.
- Supplier documentation, prints, drawings and manuals.
- Software documented.
- Spare parts list.
- Environmental conditions (such as clean room requirements, temperature, and humidity) [14, 15].

Operational Qualification (OQ)

Establishing by objective evidence process control limits and action levels which result in product that all predetermined requirements.

OQ considerations include:

- Process control limits (time, temperature, pressure, line speed, setup conditions, etc.)
- Software parameters.
- Raw material specifications
- Process operating procedures.
- Material handling requirements.
- Process change control.
- Training.
- Short term stability and capability of the process, (latitude studies or control charts).
- Potential failure modes, action levels and worst-case conditions.
- The use of statistically valid techniques such as screening experiments to optimize the process can be used during this phase.

Performance Qualification (PQ)

Establishing by objective evidence that the process, under anticipated conditions, consistently produces a product which meets all predetermined requirements.

PQ considerations include:

- Actual product and process parameters and procedures established in OQ.
- Acceptability of the product.
- Assurance of process capability as established in OQ.
- Process repeatability, long term process stability.

Re – Qualification

Modification to, or relocation of equipment should follow satisfactory review and authorization of the documented change proposal through the change control procedure. This formal review should include consideration of re qualification of the equipment. Minor changes or changes having no direct impact on final or in-process product quality should be handled through the documentation system of the preventive maintenance program [14-15].

Types/Methods of Validation

Prospective Validation

It is defined as the established documented evidence that a system does what it purports to do based on a preplanned 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).

In 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 categorized 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 experiment should be designed to determine the criticality of these factors. Each experiment should be planned and documented fully in an authorized protocol.

All equipment, production environment and the analytical testing methods to be used should have been fully validated. Master batch documents can be prepared only after the critical parameters of the process have been identified and machine settings, component specifications and environmental conditions have been determined.

Using this defined process a series of batches should be produced. In theory, the number of process runs carried out and observations made should be sufficient to allow the normal extent of variation and trends to be established to provide sufficient data for evaluation. It is generally considered acceptable that three consecutive batches/runs within the finally agreed parameters, giving product of the desired quality would constitute a proper validation of the process. In practice, it may take some considerable time to accumulate these data. Some considerations should be exercised when selecting the process validation strategy. Amongst these should be the use of different lots of active raw materials and major excipients, batches produced on different shifts, the use of different equipment and facilities dedicated for commercial production, operating range of the critical processes, and a thorough analysis of the process data in case of Requalification and Revalidation.

During the processing of the validation batches, extensive sampling and testing should be performed on the product at various stages, and should be documented comprehensively. Detailed testing should also be done on the final product in its package.

Upon completion of the review, recommendations should be made on the extent of monitoring and the inprocess controls necessary for routine production. 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.

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, and also similar to retrospective validation.

- 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.

Retrospective Validation

It is defined as the established documented evidence that a system does what it purports to do on the review and analysis of historical information. This is achieved by the review of the historical manufacturing testing data to prove that the process has always remained in control. This type of validation of a process for a product already in distribution.

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.

Validation of such processes should be based on historical data. 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 access 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.

Revalidation

Re-validation 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.

Facilities, systems, equipment and processes, including cleaning, should be periodically evaluated to confirm that they remain valid. 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 [16, 17].

Stages of Process Validation

Process Validation is defined as the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product. Process Validation involves a series of activities taking place over the lifecycle of the product and process. The activities relating to validation studies may be classified into three stages:

Stage 1 – Process Design

"Focusing exclusively on qualification efforts without also understanding the manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities. 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. Also this is the stage in which the establishment of a strategy for process control is taking place using accumulation knowledge and understanding of the process. "

Stage 2 – Process Qualification

During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing. It confirms that all established limits of the Critical Process Parameters are valid and that satisfactory products can be produced even under "worst case" conditions. GMP compliant procedures must be followed in this stage and successful completion of this stage is necessary before commercial distribution of a product.

There are two aspect of Process Qualification:

- Design of Facilities and Qualification of Equipment and Utilities
  - Proper design of manufacturing facility is desired under 21 CFR part 211, subpart C, of the cGMP regulation on Buildings and Facilities.
  - Activities performed to assure proper facility design and that the equipment and utilities are suitable for their intended use and perform properly.

- Process Performance Qualification

"Criteria and process performance indicators that allow for a science and risk-based decision about the ability of the process to consistently produce quality products".

- Part of the planning for stage 2 involves defining performance criteria and deciding what data to collect when, how much data, and appropriate analysis of the data.
- Likely consist of planned comparisons and evaluations of some combination of process measures as well as in-process and trial product attributes.
- Manufacturer must scientifically determine suitable criteria and justify it.
- Objective measures, where possible.
- May be possible to leverage earlier study data if relevant to the commercial scale.

Stage 3 – Continued Process Verification

Ongoing assurance is gained during routine production that the process remains in a state of control. The validation maintenance stage requires 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.

A successful validation program depends on the knowledge and understanding and the approach to control manufacturing processes. These include the source of variation, the limitation of the detection of the variation, and the attributes susceptible of the variation [18, 19].

Types of Documentation in Validation Process

- Validation master plan (VMP)
- Validation protocol (VP)
- Validation reports (VR)
- Standard operating procedure (SOP) [20-22]

Validation master plan:- An approved written plan of objectives and actions stating how and when a company will achieve compliance with the GMP requirements regarding validation. VMP is a summary intention document stating the scope of the validation and outlining the methods to be used to establish the performance adequacy. The validation master plan should provide an overview of the entire validation operation, its organizational structure, its content and planning. The main elements of its being the list/ inventory of the items to, relevant to product and process controls within a firm should be included in the validation master plan. It even holds the calibration and qualification of equipments, summary and conditions of Validation Protocol.

- Protocol approval sheet
- Table of content
- Objective and scope
- Validation team and responsibility
- Steps for validation and acceptance criteria
- Process validation plan
- Evaluation of formulation ingredients
- Evaluation of active raw material
- Evaluation of equipment
- Responsibility
- Manufacturing process flow chart
- Product details
- Equipment detail
- Critical process parameters
- In-process specification

- Sampling procedure and testing plan
- Revalidation criteria
- Change controls
- Deviations
- Stability
- Conclusion
- Report and conclusion

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).
- Recommendations on the limit and criteria to be applied on future basis.

SOP (Standard Operating Procedure)

Standard Operating Procedures (SOPs) are issued to specifically instruct employees in areas of responsibility, work instructions, appropriate specifications and required records. These outline procedures, must be followed to claim compliance with GMP principles or other statutory rules and regulations. The general aspects covered under the SOPs are the Preparation and maintenance of work area like washing and sterilization, decontamination and testing area. Even the work done in the laboratory were documented, for example, the laboratory operations involving the receipt of reagents, standards, preparation of reagents, labelling and storage, test procedures, reference material, identification, handling, storage and use deviations, errors. Even the details of the equipments and their maintenance were also involved.

Critical Process Parameters

Processing Stage	Critical Process Parameter	Evaluation Test
Sifting	Sieve Size	Before and After Use Sieve Integrity
	Sieve Integrity	
Dry Mixing	Mixing Time	Content Uniformity
	Mixing Speed	
Granulation	Binding Time	Content Uniformity
	Mixing Speed	Check the Mixing Time
	Load Size	Ampere (End Point)
	Amount of Granulating Agent	
Drying	Total Drying Time	LOD
	Inlet and Outlet Temperature	
	Load Size	
Sifting and Milling	Sieve Size	Sieve integrity
	Screen Type	
	speed	

	Knieves direction	
	Feed rate	Sieve analysis
Lubrication	Mixing Time	Description
	Blender Speed	Assay for Blend Uniformity
		LOD
		Bulk and Tapped Density
		Sieve Analysis
Compression	Compression Speed	Appearance
		Average Weight. and Uniformity of Weight
		Thickness and Diameter
	Compression Force	Hardness and Friability
		Disintegration Time
	Granule Feed Rate	Assay
Coating	Spray Rate	Coating Weigh
	Inlet and Outlet Temperature	
	Air Pressure	
	Speed of Rotation of Coating Pan	
Packaging	Forming and Sealing Temperature	Appearance of Tablet
		Sealing Quality (Knurling)
		Overprinting Quality
		Label Quality
		Leak Test [23-24]

Abbreviations

cGMP Current Good Manufacturing Practices
ICH International conference on Harmonization
FDA Food and Drug Administration
WHO World Health Organisation
IQ Installation Qualification
OQ Operational Qualification
PQ Performance Qualification
VMP Validation Master Plan
PVP Process Validation Protocol
PVR Process Validation Report
SOP Standard Operating Procedure

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