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REVIEW ARTICLE PROCESS VALIDATION AS QUALITY ASSURANCE TOOL.

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ABSTRACT

Validation is the most recognized and important parameter of GMPs. This article provides an introduction about the process validation of the pharmaceutical manufacturing process and its importance according to The U.S. Food and Drug Administration (FDA). This work is to present an introduction and general overview on process validation of the pharmaceutical manufacturing process. Quality cannot be ensured by sampling, testing, release of materials and products. 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 of a process will ensure production of a drug of reproducible quality. In the pharmaceutical industry, Process Validation performs this task to build the quality into the product because according to ISO 9000:2000, it has proven to be an important tool for quality management of pharmaceuticals.

Keywords: Quality assurance, Process validation, GMP, pharmaceutical industry.

INTRODUCTION

The process validation is establishing documented evidence which provides a high degree of assurance that a specific process consistently produced a product meeting its predetermined specifications and quality characteristics.

- Pharmaceutical Process Validation is the most important and recognized parameter of cGMPs. 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 goals are met. The process validation is standardization of the validation documents.

- Process validation and process controls are two important key parameters which can ensure the various parameters in manufacturing of dosage forms.

- Validation is a tool of a quality assurance which provides confirmation of the quality in equipment systems, manufacturing process, software and testing methods.

HISTORY

The concept of validation was first proposed by two Food and Drug Administration (FDA) officials, Ted Byers and Bud Loftus, in 1979 in the USA, to improve the quality of pharmaceuticals. It was proposed in direct response to several problems in the sterility of the large volume parenteral market.

validation history

- 1978 - GMP include validation.
- 1987 - First validation guidelines (equipment IQ).
- 2000 - New Approaches/Documentry presentation.
- 2008 - New Process validation Draft guidelines.
  (Equipment & analytical validation)
- 2011 - New Process validation guidelines issued.

IMPORTANCE OF VALIDATION

1. Assurance of quality.
2. Time bound.
3. Process Optimization.
4. Reduction of Quality cost.
5. Reduction in rejections
6. Increased output.
7. Avoiding of capital expenditures
8. Fewer complaints about process related failures.

9. Reduced testing in process and in finished goods.

10. Improved employee awareness of processes.

11. Easier maintenance of equipment.

WHY IS VALIDATE A PROCESS

The main reasons for validation are:

1. **Quality assurance:**
   Quality cannot be assured by daily quality control testing because of the limitations of statistical samples and the limited facilities of finished product testing. Validation checks the accuracy and reliability of a system or a process to meet the predetermined criteria. A successful validation provides a high degree of assurance that a consistent level of quality is maintained in each unit of the finished product from one batch to another batch.

2. **Economics**:
   Due to successful validation, there is a decrease in the sampling and testing procedures and there are less number of product rejections and retesting. This leads to cost-saving benefits.

3. **Compliance**:
   For compliance to current good manufacturing practices CGMPs, validation is equipment.

PROCESS VALIDATION

- Process validation is a basic factor for drug product safety and quality and thus a fundamental component of the quality assurance system used by pharmaceutical manufacturers.
- Process validation is a systemic approach to indenting, measuring, evaluating, documenting and revaluation the critical steps in the manufacturing process to ensure reproducible quality products.
- Process validation is a quality assurance function that helps to ensure drug product quality by providing documented evidence that the manufacturing process consistently does what it is supposed to do.
- Process validation is widely practiced by pharmaceutical, biotechnological, medical device and herbal industries.
- Manufacturing process validation is a process in which the process performance is constantly monitored and evaluated.

OBJECTIVES OF PROCESS VALIDATION

- The manufacturing process, in addition to each equipment, must be validated.
- The goal is to create a strong manufacturing process that consistently produces a drug product with less variation that adheres to quality criteria of purity, identity, and potency.
- A validation plan for the manufacturing process should be formed and executed by engineers in order to satisfy guidelines. The validation plan usually involves just a PQ section.
- If major changes occur after the initial validation will result in the need for subsequent revalidation like equipment validation.
- In the end, process validation will ensure a robust product that is highly reproducible over time.

BENEFITS OF VALIDATION

1. **Reduction of quality cost**

a. Preventive costs are costs incurred in order to Prevent failure and reduce evaluation costs.
b. Appraisal costs of inspection, testing and quality Evaluation.
c. Internal failure costs.
d. External failure costs associated with a non-Conformance condition after the product had left The company's ownership.

2. **Process optimization**
   The optimization of the facility, equipment system and Closures etc. results in a product that meets quality Requirements at the lower costs. Trained, qualified People are the key elements in process optimization That results in improving efficiency and productivity.

3. **Assurance of quality**
   Validation and process control are the heart of GMPs. Without a validated and controlled process it is Impossible to achieve quality products. Hence Validation is a key element in assuring the quality of The product.

4. **Safety**
   Validation can also result in increased operator safety. Properly calibrated, validated instruments and gauges Used to reduce accidents and results in safety.

5. **Better customer quality**
   Through proper validation, market recall is avoided Which results in better customer care and quality of the product.

ADVANTAGES OF VALIDATION

1. Enhanced reporting capability.
2. Improved ability to set target parameters and Control limits for routine production, correlating With validation results.
3. Enhanced data and evaluation capabilities and Increased confidence about process Reproducibility and product quality.
4. Enhanced ability to statistically evaluate process Performance and product variables e.g. Individuals, mean, range, control limits.

RESPONSIBILITIES

Department	Responsibility
Manager production	Responsible for manufacturing of batches and review of protocol and report
Manager QC	Responsible for analysis of samples collected
Executive QC	Responsible for sample 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.

Table 1 : Responsibilities

ELEMENT OF VALIDATION

Qualification is a prerequisite of validation. The qualification includes the following:

1. **Design Qualification (DQ):-**

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):-

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):-

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):-

After IQ and OQ have been completed, the next qualification that should be completed is PQ. PQ should include the following:

- Tests using production materials, substitutes or simulated products.
- These can be developed from the knowledge of the process and facilities, systems or equipment.
- Tests to include conditions with upper and lower limits

TYPE OF VALIDATION

- Prospective process validation
- Retrospective process validation
- Concurrent validation

1.Prospective Validation: It is the establishment of documented evidence of what a system does or what it purports to do based upon a plan. This validation is conducted prior to the distribution of new products.

2. Retrospective Validation: It is the establishment of documented evidence of what a system does or what it purports to do based upon the review and analysis of the existing information. This is conducted in a product already distributed based on accumulated data of production, testing and control.

3. Concurrent Validation: It is the establishment of documented evidence of what a system does or what it purports to do with information generated during implementation of the system.

4. Revalidation: Whenever there are changes in packaging, formulation, equipment or processes which could have an impact on product effectiveness of product characteristics, there should be revalidation of the validated process.

Conditions that require revalidation studies are:

- Changes in critical component
- Change in facility or plant
- Increase or decrease in batch size
- Sequential batches that fail to conform product and process specifications

Change Control:-

Change control is defined as **"A formal system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect a validated status. The intent is to determine the need for action that would ensure and document that the system is maintained in a validated state.**

APPROACHES TO PROCESS VALIDATION

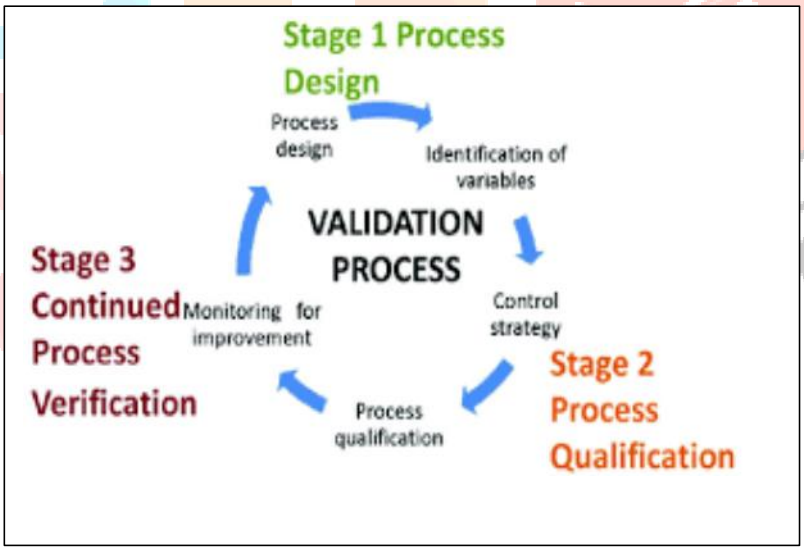

Fig: process validation

Process validation involves a series of activities taking place over the life cycle of the product and process.

Stage 1: process design

Process design is the activity of defining the commercial manufacturing process that will be reflected in planning master production and control records.

The goal of this stage is to design a process suitable for routine commercial that can consistently deliver a product that meets its quality attributes.

a. Building and capturing process knowledge and understanding.

General yearly process design experiments do not need to be performed under the cGMP conditions required for drugs intended for commercial distribution that are manufactured using stage 2(process qualification) and stage 3 (continued process verification).

They should however, be documented in accordance with sound scientific method and principle including good documentation practices.

Decisions of the controls should be identified and documented and internally reviewed to verify and preserve their value for appropriate use in the life cycle of the process and product.

Product development activities provide key input to the process design stage such as the intended dosage form,the quality attribute, and a general manufacturing pathway.

Limitations of commercial manufacturing equipment should be considered in the process design as well as the predicted contribution to variability posed by different component lots, production operators, environmental condition and measurement system in the production setting.

Risk analysis tools are also used to screen potential variables for design of experiments to minimize the total number of experiments conducted while maximum knowledge gained.

b. Establishing a strategy for process control

Process knowledge and understanding is the basis for establishing an approach to process control for each unit operation and the process overall.

strategies for process control can be designed to reduce input variation, adjust for input variation, during manufacturing (and so reduce its impact on the output) or combine both approaches.

Stage 2:process qualification

During this stage the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.

During the process qualification stage of process validation, the process design is evaluated to determine if it is capable of reproducible commercial manufacturing.

a. Design of a facility and qualification of utilities and equipment

Qualification of utilities and equipment generally include the following activities:

1. Selecting utilities and equipment construction Materials, operating principles, and performance Characteristics based on their appropriate uses.

2 .Verifying that utility systems and equipment are Built and installed in

compliance with the design Specification

3 . Verifying that the utility system and equipment operate in accordance with the process requirement in all anticipated operating ranges.

Qualification of utilities and equipment should be covered under individual plants or as part of an overall project plan and the plan should consider the requirement of use and it should incorporate risk management .

The plan should identify the following items;

a. The studies are tests to use,
b. The criteria appropriate to access outcome
c. The timing of qualifications activities
d. The responsibilities of the relevant department and the quality unit.
e. The procedure for documenting and approving the qualification.

b. Process performance qualification

The closest performance qualification is the second element of stage 2, process qualification. The PPQ combines the actual facility , equipment and the trained personnel with respect to the commercial manufacturing process, control procedure, and component to produce commercial batches.

A manufacturer must Successfully complete PPQ before
commencing Commercial distribution of the drug product.

In most cases, PPQ will have a higher level of sampling, additional Testing, and greater scrutiny of process performance When compared to routine commercial production.
The level of monitoring and testing should be sufficient To confirm uniform product quality throughout the Batch.

c. PPQ Protocol

A written protocol that specifies the manufacturing Conditions, controls, testing, and expected outcomes is Essential for this stage of process validation.

1. The manufacturing conditions, including operating Parameters, processing limits, and component (raw material) inputs.
2. The data to be collected and when and how it will Be evaluated.
3. Tests to be performed and acceptance criteria for Each significant processing step.
4. The sampling plan, including sampling points, Number of samples, and the frequency of Sampling for each unit operation and attributes. The number of samples should be adequate to Provide sufficient statistical confidence of quality Both within a batch and between batches. Sampling during this stage should be more Extensive than is typical during routine Production.
5. Design of facilities and the qualification of utilities And equipment, personnel training and Qualification, and verification of material sources.
6. Status of the validation of analytical methods used In measuring the process, in-process materials, And the product.

d.PPQ protocol execution and report

Execution of the PPQ protocol should not begin until it Is reviewed and approved by all departments, Including the quality unit.

Any departures from the Protocol must be made according to established Procedure or provisions in the protocol.

Such Departures must be justified and approved by all Departments including quality units before Implementation.

This report should include:

1. Discuss and cross-reference all aspects of the Protocol.
2. Summarize data collected and analyze the data, as Specified by the protocol.
3. Evaluate any unexpected observations and Additional data not specified in the protocol.
4. Summarize and discuss all manufacturing Nonconformances such as deviations, aberrant Test results, or other information that has bearing On the validity of the process.

Stage 3: Continued Process Verification

The goal of the third validation stage is continual Assurance that the process remains in a state of control (the validation state) during commercial manufacture.

A system or systems for detecting unplanned Departures from the process as designed is essential to Accomplish this goal. Data gathered during this stage Might suggest ways to improve and/or optimize the Process by altering some aspect of the process or Product, such as the operating conditions (ranges and Set points), process controls, component, or in-process Materials characteristics.

PHASES IN PROCESS VALIDATION

The activities relating to validation studies may be

Classified into three phases ;

Phase 1 Pre validation phase or the Qualification phase

It covers all activities relating to product research and Development, formulations, pilot batch studies, scale Up studies, transfer of technology to commercial scale Batches, stability conditions, storage and Handling of in- process and finished dosage forms, Equipment qualification, Installation qualification , Master production documents, operational Qualification, process capability.

Phase 2 Process validation phase

This phase is designed to verify that all established Limits of the critical process parameters are valid and That satisfactory products can be produced even under The worst case condition.

It represents the actual studies or trials conducted to show.

1. That all systems subsystem or unit operations of a Manufacturing process perform as intended.
2. That all critical parameters operate within their Assigned control limit.
3. That such studies and trials, which form the basis Of process capability design and testing, are Verifiable and certifiable through proper Documentation.

Phase 3 Validation Maintenance phase

1. This phase requires frequent review of all process Related documents, including validation audit report to Assure that there have been no changes, deviations ,Failures, modifications to the production process and That all SOP have been followed, including change Control procedure.
2. At this stage the validation team Also assures that there have been no changes.
3. Deviations that should have resulted in requalification And revalidation.

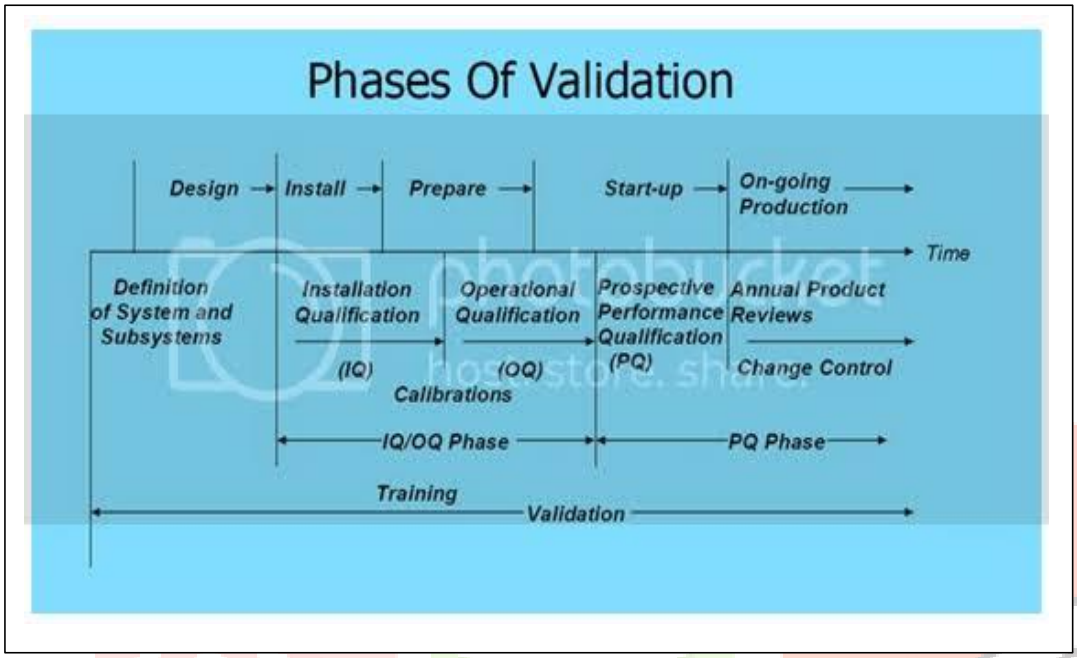

Fig: Phase of validation

VALIDATION MASTER PLAN

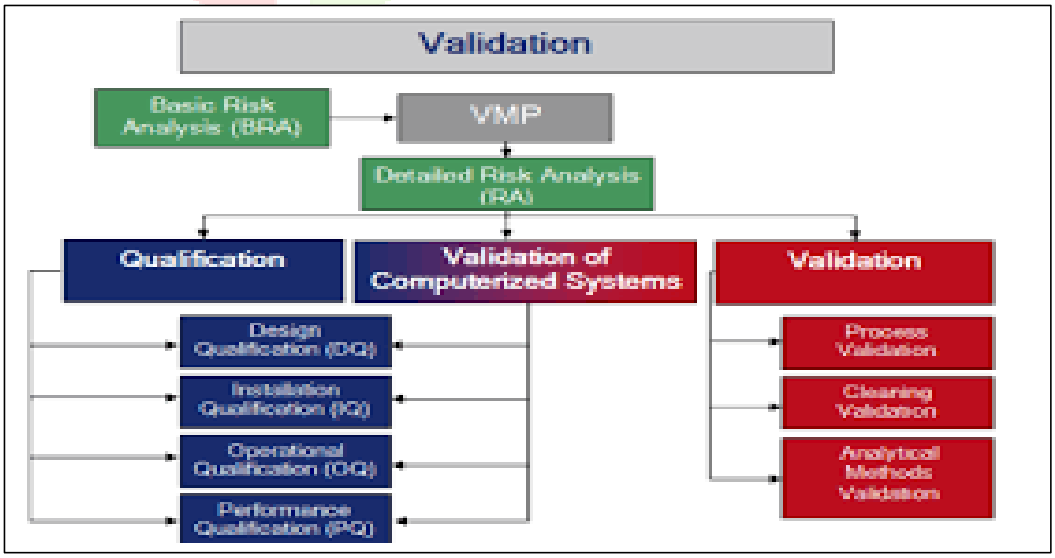

Fig: validation master plan

1. Validation master plan is a document that Summarizes the company's overall philosophy, Intentions and approaches to be used for establishing Performance adequacy.
2. 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.
3. In Addition, all work should be carried out in a structured Way according to formally authorized standard Operating procedures.
4. All observations must be Documented and where possible must be recorded as Actual numerical results.
5. The validation master plan Should provide an overview of the all validation Operation, its organizational structure, its content and Planning. The validation master plan should be a Summary document and should therefore be brief, summary and clear.
6. It should not repeat information Document other but should refer to existing Documents such as policy documents, SOP's and Validation protocols and reports.

ANALYTICAL METHODOLOGY

Validated analytical methods Are not necessarily required during product and process development Activities. Though, analytical methods should be scientifically Sound (e.g., specific, sensitive, and accurate) and provide results that Are reliable. There should be assurance of proper equipment function for Laboratory experiments. Procedures for analytical method and equipment Maintenance, documentation practices and calibration practices supporting Process-development efforts should be documented or described.

Potential critical process parameters for common Solid dosage form unit Operations :

1. Blending time for the powder.
2. Particle size distribution of the active.
3. Granulating time and speed.
4. Amount of granulating fluid-binder concentration.
5. Drying time – final moisture content.
6. Granule particle size distribution.
7. Granule API content and homogeneity.
8. Blending time of external phase.
9. Tablet hardness with respect to water content, friability, disintegration And dissolution.
10. Lubrication level with respect to tablet hardness,disintegration,Dissolution and die-ejection force.
11. Tablet mass and thickness, and control of uniformity of content.

If the tablet is film-coated, the following additional parameters may require Validation:

1. Spray rate of coating solution.
2. Inlet and outlet air temperatures.

3. Coating mass of polymer with respect to table appearance, friability, Disintegration and dissolution

VALIDATION PROTOCOL

After preparing the validation master plan, the next step Is to prepare the validation protocol**.**

The validation protocol provides a synopsis of what is hoped to be Accomplished. The protocol should list the selected process and control Parameters, state the number of batches to be included in the study and Specify how the data, once assembled, will be treated for relevance. The Date of approval by the validation team should also be noted.

There are at Least the following contents in a validation protocol:

1. Objectives, scope of coverage of the validation study.

2. Validation team membership, their qualifications and responsibilities.

3. Type of validation: prospective, concurrent, retrospective, re-validation .

4. Number and selection of batches to be on the validation study.

5. A list of all equipment to be used; their normal and worst case operating parameters.

6. Outcome of IQ, OQ for critical equipment.

7. Requirements for calibration of all measuring devices.

8. Critical process parameters and their respective tolerances.

9. Description of the processing steps: copy of the master documents for the product.

10. Sampling points, stages of sampling, methods of sampling and sampling plans.

11. Statistical tools to be used in the analysis of data.

12. Training requirements for the processing operators.

13. Validated test methods to be used in in-process testing and for the finished product.

14. Specifications for raw and packaging materials and test methods.

15. Forms and charts to be used for documenting results.

16. Format for presentation of results, documenting conclusions and for approval of study results.

VALIDATION REPORT

A written report should be available after completion Of the validation. If found acceptable, it should be Approved and signed and dated.

The Report should include at least the following.

1. Title and Objective of study.
2. Reference to Protocol. Details of material.
3. Equipment.
4. Programme and cycles used.
5. Details of Procedures and test methods.
6. Results (compared with acceptance criteria).
7. Recommendations on the limit and criteria to be applied on future basis.

CONCLUSION

This article generally outlines the principles and Approaches that considers appropriate elements of Process validation for the manufacture of drugs, Including active pharmaceutical ingredients (APIs or Drug substances), collectively referred to as drugs or Products. And it incorporates principles and Approaches that all manufacturers can use to validate Manufacturing process. From this study, it can be stated that Process validation is a major requirement of cGMP regulation for finished pharmaceutical products and it helps in setting specification limits as a basis for releasing or rejecting product. It will carry out programs to determine whether or not the new information indicates the changes in product or process has occurred. Finally it performs the analytical tests that are used to generate the validation data required by the protocol.

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