Process Validation

Process Validation

Definition

USFDA Guidelines on Process Validation - A Review

"The collection and assessment of data, from the process design stage all the way through production, which establishes logical indication that a process is capable of consistently delivering quality products"[1]

Process Validation

Why Validate?

- Regulatory Requirement
- Demonstrates that quality is built into the process and that the process is under control.
- End user Safety

  Goals of Quality Assurance are : Safety, Effectiveness, Quality and Purity.

- Profit : Decrease of costs of bad quality (COBQ)
- Reputation : Satisfaction of customers, Branding

Why Validate?

- Annual product reviews
- Complaint reviews
- Discrepancy and failure investigations
- Change control
- Reprocess/rework evaluation
- Return/salvage investigations
- Reject investigations
- Stability failure investigations

What to Validate?

- Processes
  - Aseptic
  - Sterilization
  - Manufacturing
- Test Methods
- Lab Instrumentation
- Equipment and Utilities
- Computerized Systems
- Cleaning Procedures

MFT

PV

AMV

DIOPQ

CSV

CV

Process Validation

Validation GMP

- The documented act of demonstrating that any procedure, process and activity will consistently lead to the expected results. It includes qualification of systems and equipment.
- Manufacturing processes are clearly defined and controlled.
- All critical processes are validated to ensure consistency and compliance with specifications.

Validation GMP

- Validation studies are conducted in accordance with pre-defined protocols. Written reports summarizing recorded results and conclusions are prepared, evaluated, approved and maintained.
- Changes to production processes, operating parameters, equipment or materials that may affect product quality and/or the reproducibility of the process are also to be re-validated prior to implementation.

Prospective Validation

- 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 broken down 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 experiments should be designed to determine the criticality of these factors. Each experiment should be planned and documented fully in an authorized protocol.

Prospective Validation

- 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 (CPP) and machine settings, component specifications and environmental conditions have been determined.

Prospective Validation

- 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.

Concurrent Validation

- Concurrent validation may be the practical approach under certain circumstances. Examples of these may be:
- when a previously validated process is being transferred to a third party contract manufacturer or to another manufacturing site
- where the product is a different strength of a previously validated product with the same ratio of active / inactive ingredients
- when the number of lots evaluated under the Retrospective Validation were not sufficient to obtain a high degree of assurance demonstrating that the process is fully under control
- when the number of batches produced are limited (eg. Orphan drugs).

The term "orphan drug" refers to a product that treats a rare disease affecting fewer than 200,000 Americans.

Retrospective Validation

- 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.
- The steps involved in this type of validation still require the preparation of a protocol, the reporting of the results of the data review, leading to a conclusion and recommendation.

Retrospective Validation

- Retrospective validation is only acceptable for well established detailed processes that include operational limits for each critical step of the process and will be inappropriate where there have been recent changes in the formulation of the product, operating procedures, equipment and facility.
- The source of data for retrospective validation should include amongst others, batch documents, process control charts, maintenance log books, process capability studies, finished product test results, including trend analyses, and stability results.

Process Validation

Essential elements of 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
- Trend analyses including those for quality related complaints

Process Re-Validation

- 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.
- Periodic review and trend analysis should be carried out at scheduled intervals.

Change Control

- Written procedures should be in place to describe the actions to be taken if a change is proposed to a product component, process equipment, process environment, processing site, method of production or testing or any other change that may affect product quality or support system operations.

Process Validation

Planned / unplanned changes

- 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
- Changes in the plant/facility.
- Variations detected by trend analysis

Process Validation

Validation Phases

Process Validation

Approach to Process Validation:

Stage 1: Process Design: The marketable manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities[2]

Stage 2: Process Qualification: Throughout this stage, the method design is estimated to determine if the process is capable of reproducible marketable business.[3]

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

Process Validation

Stage1: Process Design:-

Constructing and Apprehending Process Knowledge and Understanding:

- The functionality and limits of commercial manufacturing equipment should be considered in the process design.
- Design of experiments (DOE) studies can help to develop process knowledge by revealing relationships, including multivariate interactions, between the variable inputs and the resulting outputs.
- Risk analysis tools can be used to display possible variables for DOE studies .

Creating an Approach for Process Control:

- Controls and consist of material analysis and equipment monitoring at significant.
- These controlled records are established in the Master formula records and control processing points.
- The calculated commercial production and control records should be carried forward to the next stage for confirmation.

Process Validation

Phase 1

- Pre-Validation Phase or the 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, storage and handling of in-process and finished dosage forms, Equipment Qualification, Installation Qualification, master production documents, Operational Qualification, Process Capability.

Developmental Validation

- Development validation is the establishment of acceptable process parameters during the development phase. This must be confirmed upon scale-up to the production batch size.
- Prospective validation follows, in several batches or runs are made on the production scale to test consistent and reliable results.

Controlled Parameters

- Time
- Temperature
- Pressure
- Mixing Speed
- Rates of Change

Proven Acceptable Range (PAR)

- Those values of the control parameters that fall; between the proven upper and lower worst-case conditions.
- PAR values are derived from developmental validation studies whose intent is primarily to establish the operational ranges to be used in the production environment.

Process Validation

Worst Case

- The highest or lowest value of a control parameter that has been studied in either development or validation.
- The worst case is often initially determined during development validation studies.

Process Validation

Developmental Process

- Optimization
- Understanding of process
- Process control
- Process reliability/flexibility

Process Validation

Development Validation

- Materials
- Identify sensitivity of process to raw material purity.
- Qualify raw material suppliers
- Processes
- Identify critical process variables
- Establish PAR's.
- Determine interaction of process variables

Process Validation

Phase 2

- Process Validation Phase (Process Qualification phase) 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” conditions.

Process Validation

Stage 2: Process Qualification:-

Element (1): Design of a facility and qualification of utilities and equipment

- Ensure qualification of facility, utilities and equipment is completed & documented prior to initiate process qualification.

Element (2): Process Performance Qualification (PPQ)

- The PPQ combines the actual facility, utilities, equipment's and the trained personnel with the commercial manufacturing controls.
- A company must successfully complete PPQ before commencing commercial distribution of the drug product.
- To understand the marketing process adequately, the manufacturer will need to consider the effects of scale.
- Strongly recommend firms employ objective measure (e.g. Statistical Metrics) wherever feasible and meaningful to achieve adequate assurance.
- The increased level of inspection, testing, and sampling should continue through the process verification stage as correct, to establish levels and occurrence of routine sampling and checking for the particular product and process.

Process Validation

- Considerations for the duration of the intensified sampling & checking period could include (not limited to):
  - ✓ Volume of production
  - ✓ Process Complexity
  - ✓ Level of process understanding
  - ✓ Experience with similar products and process

PPQ Report:

- To state a clear conclusion as to whether the data indicates the process meets the conditions established in the protocol. If not the report should state what should be accomplished before such a conclusion can be reached.
- This conclusion should be based on entire compilation of knowledge and information gained from the design stage through the PPQ stage.

Process Validation

Some of key elements to be captured in validation protocol as detailed below;

Key Elements	
➢ Manufacturing conditions, including operating parameters, processing limits, and raw material inputs	➢ Compression RPM (low, medium, target) is not recommended in protocol. ➢ Batch records docs not provide any detail about the RPM which are not worked
➢ Test to be performed and acceptance criteria for each significant processing step	➢ Currently followed
➢ Sampling plan (sampling points, number of samples, frequency of sampling)	➢ Sampling points not pictorially depicted (however SOP reference is mentioned)
➢ No. of samples should be adequate to provide sufficient statistical confidence of quality both within a batch and between batches	➢ Between the batches?
➢ Status of the validation of analytical methods used is measuring the product	➢ Currently not followed
➢ Provision for addressing deviations	➢ Currently followed
➢ Approval of the protocol by appropriate department	➢ Currently followed

- Validation shall be executed as per validation protocol duly approved by Quality unit.

Process Validation

Phase 3

- Validation Maintenance Phase requiring 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.
- At this stage the Validation Team also assures that there have been no changes/ deviations that should have resulted in Requalification and Revalidation.

Process Validation

Stage 3: Continued Process Verification:-[4]

- To confirm that "the process remains in a state of control during commercial manufacture."
- An ongoing process to collect and analyze product and process data that relate to product quality must be established.
- The results obtained should be statistically trended and reviewed by trained personnel.
- Recommend that a person with suitable training in statistical process control techniques develop the data collection plan and statistical methods.
- Good process design and development should anticipate significant sources of variability and establish appropriate detection, control and or qualification schemes, as well as suitable alert and action limits.
- Study of intra-batch as well as inter-batch variation is part of a comprehensive continued process verification program.
- Deviation can be detected by the timely assessment of
  - Defect complaints
  - OOS findings
  - Process deviation report
  - Process yield variations
  - Batch record & reports

Process Validation

- Manufacture line operatives and quality unit staff should be encouraged to provide feedback on process performance.
- Quality unit meet periodically with production staff to evaluate data, discuss possible trends and coordinate any correction or follow-up actions by product.
- Data collected during this stage might recommend ways to improve and/or optimize the process by altering some aspect of the process or product, such as the operating conditions, process controls, etc.
- Well justified rationale for the change, implementation plan, quality unit approval before implementation.

Concurrent Release of PPQ batches:

- FDA expects that simultaneous release will be used rarely.
- Circumstances and reasoning for simultaneous release should be fully described in the PPQ protocol0
- System of careful oversight of the distributed batch to facilitate rapid customer feedback.