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PROCESS VALIDATION: AN OVERVIEW

Chandra Kant[1]*, Ujjwal Nautiyal[1], M. Senthil Kumar[1], Vikas Verma[1], Rupinder Singh[1]

[1]Department of Pharmacy, Himachal institute of Pharmacy, Paonta Sahib, (H.P), India.

ABSTRACT

Process Validation emphasizes on process design elements and maintaining process control during commercialization and communicate that process validation is an ongoing program and align process validation activities with product lifecycle. It has always been known that facilities and processes involved in pharmaceutical production impact significantly on the quality of the products. The processes include raw material and equipment inspections as well as in-process controls. Process controls are mandatory in good manufacturing practice (GMP).

Keywords: Validation, Master plan, Stages, Types

Introduction

Pharmaceutical Process Validation is the most important and recognized parameters of cGMPs. The concept of validation has expanded through the years to embrace a wide range of activities from analytical methods used for the quality control of drug substances and drug products to computerized systems for clinical trials, labelling or process control. Validation isfounded on, but not prescribed by regulatory requirements and is best viewed as an important and integral part of cGMP.[1] According to FDA, assurance of product quality is derived from careful and systemic attention to a number of importance factors, including: selection of quality process through in-process and end-product testing.[2] The concept of validation was first proposed by two Food and Drug Administration (FDA) officials, Ted Byers and Bud Loftus, in the mid 1970s in order to improve the quality of pharmaceuticals.[3]

Validation essentialisation

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.

**Correspondence*
Chandra Kant
Department of Pharmacy,
Himachal Institute of Pharmacy, Paonta Sahib (H.P), India.

Adequate validation is beneficial to the manufacturer in many ways

- It deepens the understanding of processes; decreases the risk of preventing problems and thus assures the smooth running of the process.
- It decreases the risk of defect costs.
- It decreases the risk of regulatory noncompliance.
- A fully validated process may require less in-process controls and end product testing.[4]

Validation should thus be considered in the following situations:

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

When any new manufacturing formula is adopted, steps should be taken to demonstrate its suitability for routine processing. [5]

Phases in process validation

Phase 1:This is the Pre-validation Qualification Phase which covers all activities relating to product research and development, formulation pilot batch studies, scale-up studies, transfer of technology to commercial scale batches, establishing stability conditions and

storage, and handling of in-process and finished dosage forms, equipment qualification, installation qualification, master product document, operational qualification and process capacity.

Phase 2: This is the Process Validation Phase. It is designed to verify that all established limits of the critical process parameter are valid and that satisfactory products can be produced even under the worst conditions.

Phase 3: This is known as the Validation Maintenance Phase, it requires frequent review of all process related documents, including validation of audit reports, to assure that there have been no changes, deviations, failures and modifications to the production process and that all standard operating procedures (SOPs), including change control procedures, have been followed. At this stage, the validation team comprising of individuals representing all major departments also assures that there have been no changes/deviations that should have resulted in requalification and revalidation. A careful design and validation of systems and process controls can establish a high degree of confidence that all lots or batches produced will meet their intended specifications. It is assumed that throughout manufacturing and control, operations are conducted in accordance with the principle of good manufacturing practice (GMP) both in general and in specific reference to sterile product manufacture[6].

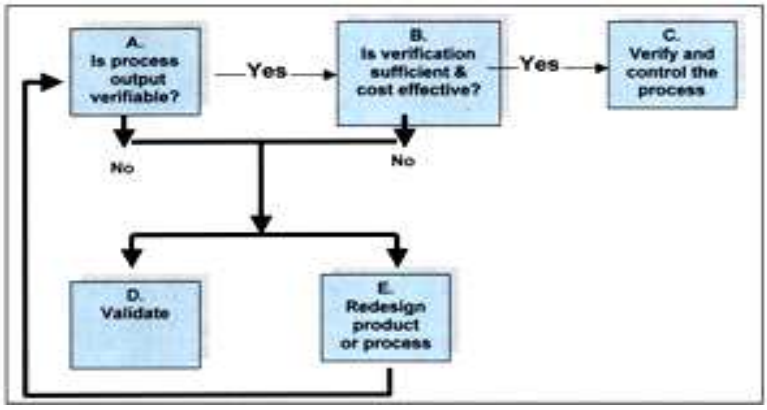

Fig 1: Shows decision tree for process validation

Types of process validation [7-9]

Prospective Validation

- Conducted prior to the distribution of either a new product or a product made under a modified production process, where the modifications are significant and may affect the products characteristics.
- It is a preplanned scientific approach and includes the initial stages of formulation development, process development, setting of process specifications, developing in-process tests sampling plans, designing of batch records, defining raw material specifications, completion of pilot runs, transfer of technology from scale-up batches to commercial size batches, listing major process is executed and environmental controls.
- Validation protocol is executed before the process is put into commercial use.

Concurrent Validation

- A process where current production batches are used to monitor processing parameters. It gives of the present batch being studied, and offers limited assurance regarding consistency of quality from batch to batch.
- Concurrent Validation may be the practical approach under certain circumstances. Examples of these may be when: A previous validated process is being transferred to a third party contract manufacturer or to another site. The product is a different strength of a previously validated product with the same ratio of active/inactive ingredients.
- The number of lots evaluated under the Retrospective Validation was not sufficient to obtain a high degree of assurance demonstrating that the process is fully under control.
- The numbers of batches produced are limited.
- Process with low production volume per batch and market demand.

- Process of manufacturing urgently needed drug due to shortage or absence of supply.

In all above cases concurrent validation is valid, provided following conditions are appropriately.

Retrospective Validation

- Conducted for a product already being marketed, and is based on extensive data accumulated over several lots and over time.
- Retrospective Validation may be used for older products which were not validated by the fabricator at the time that they were first marketed, and which is now to be validated to confirm to the requirements of division 2, Part C of the Regulation to be Food and Drugs Act.
- Retrospective Validation is only acceptable for well established detailed processes and will be Inappropriate where there have recent changes in the formulation of the products, operating procedures, equipment and facility
- Some of the essential elements for Retrospective Validation are: Batches manufactured for a defined period, Number of lots released per year,Batch size/strength/manufacturer/year/period, Master manufacturing/packaging documents, List of process deviations, corrective actions and changes to manufacturing documents, Data for stability testing for several batches, Trend analysis including those for quality related complaints.

Process Re-Validation

- Required when there is a change in any of the critical process parameters, formulation, primary packaging components, raw material fabricator, major equipment or premises.
- Failure to meet product and process specifications in batches would also require process re-validation.
- Re-Validation becomes necessary in certain situations: 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 a revalidation except that this new equipment, Must be qualified, Changes in the plant/facility, Variations revealed by trend analysis (e.g. process drifts).

Process validation protocol and master plan

Process validation protocols should include the following elements:

- Objectives, scope of coverage of the validation study.
- Validation team membership, their qualifications and responsibilities.
- Type of validation: prospective, concurrent,retrospective, re-validation.
- Number and selection of batches to be on the validation study.
- A list of all equipment to be used; their normal and worst case operating parameters.
- Outcome of IQ, OQ for critical equipment.
- Requirements for calibration of all measuring devices.
- Critical process parameters and their respective tolerances.
- Process variables and attributes with probable risk and prevention shall be captured.
- Description of the processing steps: copy of the master documents for the product.
- Sampling points, stages of sampling, methods of sampling, sampling plans.
- Statistical tools to be used in the analysis of data.
- Training requirements for the processing operators.
- Validated test methods to be used in inprocess testing and for the finished product.
- Specifications for raw and packaging materials and test methods.
- Forms and charts to be used for documenting results Format for presentation of results, documenting conclusions and for approval of study results.[10,11]

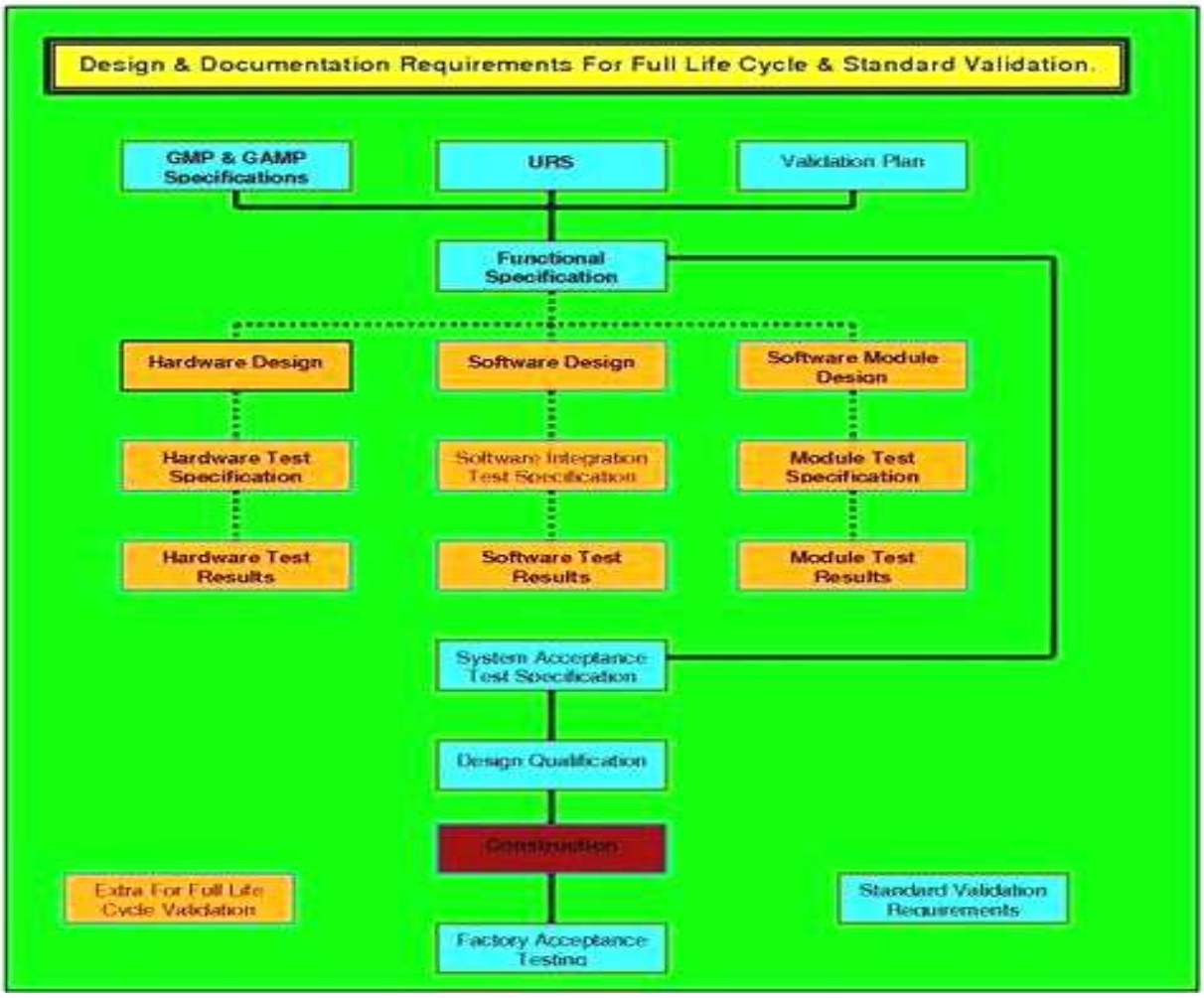

Fig 2: Shows process Validation Master Plan

The Validation Master Plan is a top layer document and should not go into specific detail; but present an overall picture of the company facility, organisation and capability. It must give a clear and concise overview, to a reviewer, of how the company has integrated all the applicable cGMP requirements into every aspect of its operations. It must define validation activities and allot responsibilities for authoring, reviewing, approving, and executing validation documentation and tasks. It must define the range of documentation spreading from the VMP to the VP, URS, DQ, IQ, OQ, P1Q, and P2Q. It must explain and detail the company's approach to risk based validation and the interaction of the VRA, VA, and 21 CFR Part 11. Facilities are portrayed with the use of layered drawings; where different layers show individual systems and equipment lists give equipment type and identity details. It is normal to include layered drawings to enable a clear and easily observed presentation of the following systems.

- Facility building overall location and access.
- Facility production/clerical/controlled areas, rooms or zones.
- Raw material ingress and finished product egress routes.
- Personnel ingress and egress routes, along with changing areas.
- Utility Layouts
- Electrical layouts
- Controlled atmospheric areas along with air flow directions and pressure regimes.
- Dressing codes for these controlled areas [12].

Pharmaceutical equipment process validation
Installation Qualification

- This ensures that all major processing and packaging equipment, and ancillary systems are in conformity with installation specification, equipment manuals schematics and engineering drawing.
- It verifies that the equipment has been installed in accordance with manufacturers recommendation in a proper manner and placed in an environment suitable for its intended purpose.

Operational Qualification

- This is done to provide a high degree of assurance that the equipment functions as intended.
- Operational qualification should be conducted in two stages:**Component Operational Qualification**,of which calibration can be considered a large part and **System Operational Qualification** to determine if the entire system operates as an integrated whole[13,14].

Process Performance Qualification

- This verifies that the system is repeatable and is consistently producing a quality product.
- These exercises assure, through appropriate performance lists and related documentation, that equipment, ancillary systems and sub-systems have been commissioned correctly. The end results are that all future operations will be reliable and within prescribed operational limits [15, 16].

Conclusion

Pharmaceutical Process Validation is the most important and recognized parameters of cGMP. It is necessary, before approval of a new drug, that an accurate and reliable assessment for its effectiveness and safety for the intended indication and target patient population is demonstrated. Generally, pharmaceutical validation and process control provide a certain assurance of batch uniformity and integrity of the product manufactured.

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