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Minireview: Process Validation as Essential Tool in Pharmaceutical Industry

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ABSTRACT

Process validation is an important tool in modern pharmaceutical industry. Validation gives a quality proof to the product which was manufactured under specified condition and quality parameter defined by GMP. The process validation is established documented evidence which provides high degree on assurance that a specific process consistently produced a product meeting its predetermined specifications and quality characteristic. If each step of manufacturing process is validated, we can assure that the final product is of desire quality. Validation of the individual steps of the processes is called the process validation. The validation study provides the accuracy, sensitivity, specificity and reproducibility of the test. This article covers Introduction, type of validation, Phases of Process Validation, Documentation, SOP, Validation Master Plan and Validation Protocol. Validation is an integral part of quality assurance, during the formulation of any product quality has always been an important factor and therefore training is required before moving on at every step such as manufacturing material, equipment, process and procedures so that the quality of the product may be regulated.

Keywords: Process Validation, Process Validation Stages, Validation master plan, protocol, quality control.

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INTRODUCTION

Process validation is a defined in the *Federal Register* supplementary information section as "QA function providing documented evidence that helps ensure drug product quality." It has also been defined as the act of "establishing evidence that provides a high degree of assurance that provides a high degree of assurance that a specific process a will consistently produce a product meeting its predetermined specification and quality attributes.

It is required in license submission for all product regulated by CBER or CDER. Basic goal of validation is to ensure that At every step quality is built in to the system and training is required before moving on at every step such as manufacturing material, equipment, process and procedure so that the quality of the product may not be affected. The purpose of setting validation parameters is to monitor the on-line and off-line performance of the manufacturing process, and hence, validate it. So main concept of validation mainly revolves around and procedure involved during manufacturing of the product. For future enhancement of effectiveness and safety of the drug product after approval regulatory agencies such as USFDA also required that the drug product be tested for it's identity, safety, purity, quality and stability before it can be launched. Method validation is the process by which it is established that performance characteristics of the method meet the requirement for the intended analytical application.

Validation mainly based on, FDA regulations describing current good manufacturing practice (CGMP) for finished pharmaceuticals are provided in 21 CFR parts 210 and 211. The CGMP regulations require that manufacturing processes be designed and controlled to assure that in-process materials and the finished product meet predetermined quality requirements.[1]

Validation lifecycle: [2,3,4,5]

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. This particular definition did not appear in any of the yearly revision of that particular compliance programmed but until March 29, 1983 it was the only official definition of process validation on March 29, 1983 draft on guidelines entitled "Guidelines on General Principles of Process Validation" was made available and the same was finalized in May, 1987.

The term process validation was first used is debatable, as the concepts underlying the term are quite old and the use of synonyms such as verification and confirmation appears to predict the use of validation. Process validation involves a series of activities taking place over the lifecycle of the product and validation process as shown in **Figure 1**. The activities relating to validation studies may be classified into three stages:

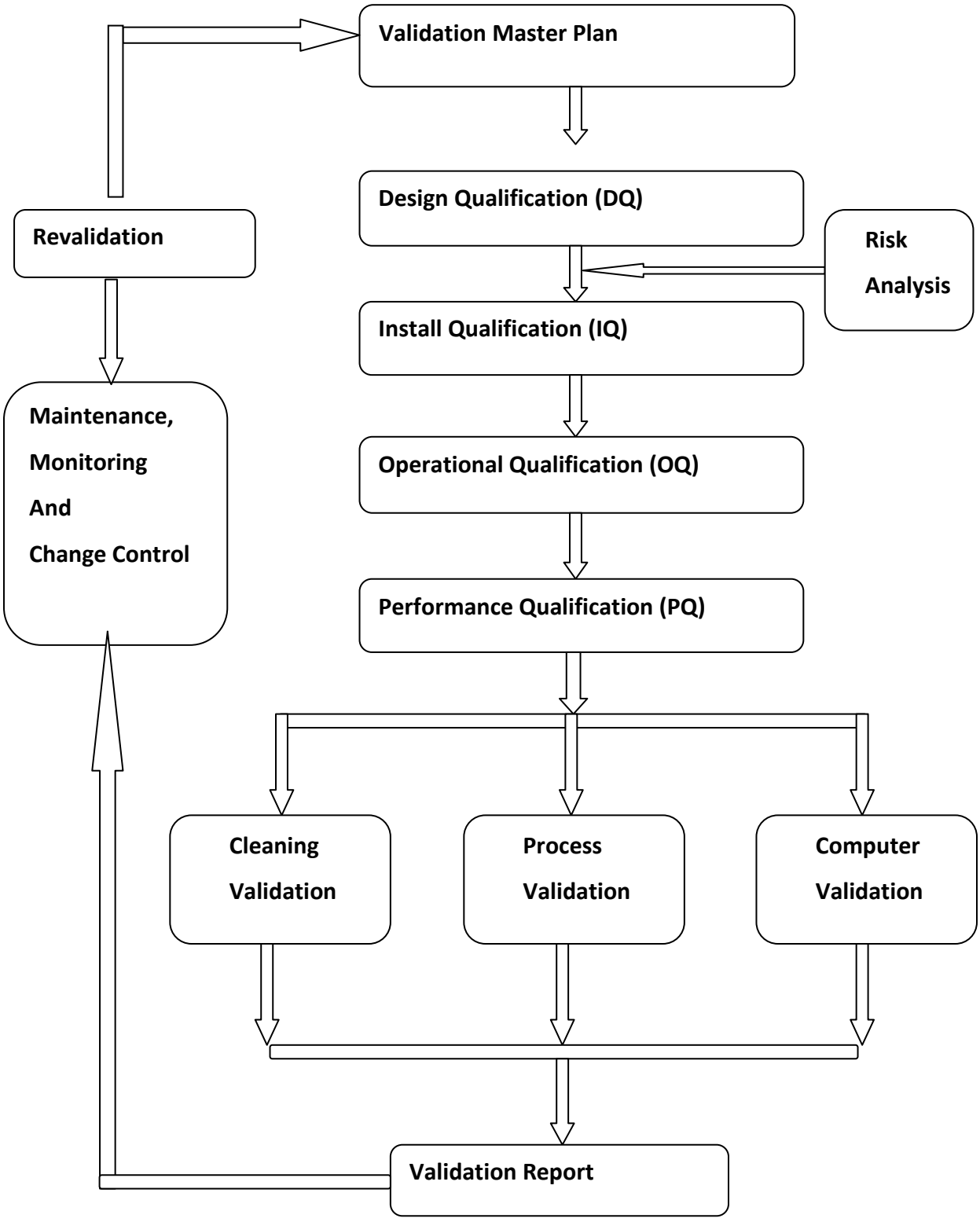

Figure.1: Validation Life Cycle

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 confirm 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". "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

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. 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.

TYPES OF PROCESS VALIDATION

- Prospective validation
- Retrospective validation
- Concurrent validation
- Revalidation

Prospective validation: [6,7,8,9]

Prospective validations defined as the establishment of documented evidence that a system does what it purports to do based on pre-planned protocol. This validation is usually carried out prior to the introduction of new drugs and their manufacturing process. This approach to validation is normally undertaken whenever a new formula, process or facility must be validated before routine pharmaceutical formulation commences.

It is a preplanned scientific approach and includes the initial stages of formulation development, process development, setting of process 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.

Retrospective validation [8,9]

Conducted for a product already being marked, 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 are now to be validated to confirm to the requirements of division 2, Part Cove 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.

Concurrent validation [10,11,12]

In-process monitoring of critical processing steps and end-product testing of current production can provide documented evidence to show that the manufacturing process is in a state of control. Is similar to 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.

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 were not sufficient to obtain a high degree of assurance demonstrating that the process is fully under control. The number of batches produced are limited.

Revalidation [9,13]

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. Almost all GMP texts recommend that whenever there are significant changes in the facility, equipment or process, revalidation should be carried out. Revalidation provides the evidence that changes in a process-introduced intentionally/unintentionally; 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.

Phases in process validation: [5,14,15,16,17]

The activities relating to validation studies may be classified into three phases.

Pre-Validation Phase:

Developing an understanding regarding the functional relationships between parameters (material and process) and quality attributes. 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.

Process validation is required, in both general and specific terms, by the CGMP regulations in parts 210 and 211. The foundation for process validation is provided in § 211.100(a), which states that there shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity.

Process Validation Phase

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.

Validation Maintenance Phase

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. This phase is for monitoring and improving control and reducing product and process variation.

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.

Documentation:

Types of documentation:

- Validation master plan
- Validation protocol
- Validation report
- Standard Operating Procedure

Validation master plan: [8,14,18,19,20]

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.

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 revalidation.

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.

The VMP should be a summary document, which is brief, concise and clear. The VMP should contain data on at least the following:

- Validation policy.
- Organizational structure of validation activities.

- Summary of facilities, systems, equipment and processes to be validated.
- Documentation format: The format to be used for protocols and reports.
- Planning and scheduling.
- Change control.
- Reference to existing document.
- In case of large projects, it may be necessary to create separate validation master plans.

Validation protocol [8,20,21,22]

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 cross-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.

Detailed protocol for performing validations is essential to ensure that the process is adequately validated. 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 process testing and for the finished product.

- Specifications for raw and packaging materials and test methods.
- Forms and charts to be used for documenting results.

Validation report: [1,18,23]

A written report should be available after completion of the validation. If found acceptable, it should be approved and authorized (signed and dated).

The validation report should contain the approved validation protocol, tabulated or graphical results, process monitoring (forms), and all analytical results of the validation batches. The validation report should have a conclusion that explains the manufacturing statement and opinion stability testing on all validation batches must be performed according to the protocol.

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

SOP (Standard Operating Procedure) [18,24,25,26,27,28]

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 e.g., the laboratory operations involving the receipt of reagents, standards, preparation of reagents, labeling 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.

The general format of the SOPs involves:

- Title
- Code
- Objective

- Scope
- Definitions
- Description
- Safety
- Documentation
- Effective date, review date, version
- Number.
- Footer: Prepared By, Reviewed By,
- Approved By, Authorized By.
- References

Benefits of process validation [8,29]

- Consistent through output.
- Reduction in rejections and reworks.
- Reduction in utility cost.
- Avoidance of capital expenditures.
- Fewer complaints about process related failure.
- Reduced testing I process and finished goods.
- 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.

CONCLUSION

From the study it can be stated that pharmaceutical Process Validation is the most important and recognized parameters of cGMP. The cGMP regulation require that manufacturing processes be designed and controlled to assure that in-process materials and finished product meet predetermined quality requirements and do so consistently and reliably. Process validation is an integral part of among all validation like equipment validation, cleaning validation, vender validation etc. Validation is art step of assure to identity, strength, purity, safety, and efficacy of pharmaceutical product. Validation is the commonest word in the areas of drug development, manufacturing and specification of finished products. It also renders reduction in the cost linked

with process monitoring, sampling and testing. Apart from all the consistency and reliability of a validated process to produce a quality product is the very important for an industry. From the review study it is concluded that pharmaceutical validation and process controls are important to assure that the drug product can meet standards for the identity, strength, quality, purity and stability.

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