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Review

A Review on Process Validation

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ABSTRACT

Validation is one of the important steps in achieving and maintaining the quality of the final product. If each step of production process is validated, we can assure that the final product is of the best quality. Process validation is the process for improving the safety and quality of the dosage from which is manufactured in the pharmaceutical industry. Basically process validation emphasize the role of objective measure and statistical tools and control of validation and give assurance on consistent of quality/ productive throughout life cycle of product result from process validation method can be used to judge the quality and consistency of analytical result. The validation study provides the accuracy, sensitivity, specificity and reproducibility of the test methods employed by the firms, shall be established and documented. Thus the validation is an essential part of the quality assurance.

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Introduction

Validation is an act of proving that procedure, process, equipment, material, activity or system perform as expected under given set of condition and also give the required accuracy, precision, sensitivity, ruggedness, etc. Method for process validation is the process used to confirm that the analytical procedure employed for a specific test is suitable for its intended use. Result from method validation can be used to judge the quality and consistency of analytical result it is an integral part of good analytical practice. The process is developed in such a way that the required parameters are achieved and it ensures that the output of the process wills consistency meet required parameter during the routine production.

History

The concept of validation was first proposed by two FDA officials, Ted byears and Bud Loftus,

in the mid1970'sin order to improve the quality of pharmaceuticals (Agalloco 1995). It was proposed in direct response to several problem in the sterility of large volume parenteral market. The first validation activities were focused on the processes involved in making the products but quickly A spread to associated process pharmaceutical (Chpman, KG., 1998). U.S.F.D.A. was the pioneer in advocating the concept of process validation. But till 29th September 1978 the definition of process validation did not appear in any part of literature of U.S.F.D.A. no cGMP regulations talked anything about process validation (Khushboo, DS., 2014).

Validation

The process of providing documented evidences, that provides high degree of assurance a result with pre determine acceptance criteria.

Importance of Validation

– Assurance of quality,
– Time bound,
– Process Optimization,
– Reduction of quality cost,
– Increased throughput,
– Easier scale-up form development work,
– Easier maintenance of equipment,
– More rapid and reliable startup of new equipment,
– More rapid automation,
– Reduction in utility cost.

Validation Protocol

Detailed protocol for performing validations is essential to ensure that the process is adequately validated.

Process validation protocols should include the following elements;

– Scope of coverage of the validation study.
– Objectives 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.
– Format for presentation of results, documenting conclusions and for approval of study result.

Process Validation

'Process Validation is establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics." It is beneficial to the manufacturer in many ways (Nash, RA.,1966);

– It deepens the understanding of processes, decreases the risk, preventing problems and thus assures the smooth running of the process.
– It decreases the risk of defect costs.
– It decreases the risk of regulatory non-compliance.
– A fully validated process may require less in-process controls and end- product testing.
– 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.

Objectives of Process Validation

– The manufacturing process, in addition to the individual equipment, must be validated.

– The goal is to create a robust manufacturing process that consistently produces a drug product with minimal variation that adheres to quality criteria of purity, identity, and potency.4(Kaur.H., Singh. G., *etal.*,2013)

– A validation plan for the manufacturing process should be drafted and executed by engineers in order to satisfy guidelines. The validation plan usually involves just a PQ section.

– Just as equipment validation, major changes after the initial validation will result in the need for subsequent revalidation.

– In the end, process validation will ensure a robust product that is highly reproducible over time.

Advantages of process validation

– Expanded real time monitoring and adjustment of process.

– Enhanced ability to statistically evaluate process performance and product variables. e.g., individuals; mean; range; control limits.

– Enhanced data and evaluation capabilities and increased confidence about process reproducibility and product quality.

– Improved ability to set target parameters and control limits for routine production, correlating with validation results

– Enhanced reporting capability.

Phases of Process Validation

Pre-validation Phase or Qualification Phase

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

Process Validation Phase (Process Qualification 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 case" conditions. (patel VB., *et al*., 2011)

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. (Sharma PP., 2008)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

Type of Process Validation

There are four types viz; Prospective Validation, Concurrent Validation, Retrospective Validation and Process Re-Validation (Potdar, MA., 2007).

Prospective Validation

This validation usually carried out prior to distribution either of a new product or a product made under a revised manufacturing process. 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. In Prospective Validation, the validation protocol is executed before the process is put into commercial use. 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

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

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 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.

• Process with low production volume per batch and market demand.

Retrospective Validation

Conducted fir 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 times that they were first marketed, and which are now to be validated to confirm to the requirements of division of the Regulation to be Food and Drugs Act.

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

Some of the essential elements for Retrospective Validation are;

• 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 already in distribution.

Process–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.

The following are examples of some of the planned or unplanned changes that may require re-validation:

• Changes in raw materials (physical properties such as density, viscosity, particle 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

• Changes in the plant/facility.

• Re-Validation becomes necessary in certain situations.

Basic Principle for Process 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 (Anonymous, 2011).

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).

Operational Qualification (OQ)

Establishing by objective evidence process control limits and action levels which result in product that all predetermined requirements (Kathiresan, K., *et al.,* 2010).

OQ considerations includes;

●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. (Anonymous, 2004)

Performance Qualification (PQ): establishing by objective evidence that the process, under anticipated conditions, consistently produces a product which meets all predetermined requirements.(Health Canada/ pharmaceutical dosage form., 2009).

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.(Validation master plan ., 2004)

Validation of Analytical Method

Method validation confirms that the analytical procedure employed for a specific test is suitable for its intended use. The validation of an analytical method is the process by which it is established by laboratory studies that the performance characteristics of the method meet the requirement for the intended application. This implies that validity of a method can be demonstrated only though laboratory studies. Methods should be validated or revalidated (Green, JM., 1996)

● Before their introduction and routine use;
● Whenever the conditions change for which the method has been validated, e.g., instrument with different characteristics; and
● wherever the method is changed and the change is outside the original scope of the method.

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 (Kathiresan K.,*et al.*,2010).

The following stages were performed in Process Validation-

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 0000000dosage 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;

(a) 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

(b) 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. (Md. Shaib., 2012)
• 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.

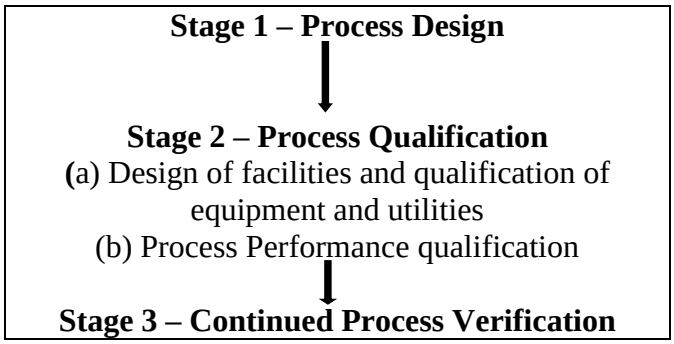

Fig.1: Stages of Process Validation

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.

Validation Life Cycle

Validation is a continuing and evolving process. The validation process which extends from very basic to very broad theoretical and methodical investigation of how the system and processes perform. Its scope encompasses documentation revision control, training and maintenance of the system and process. Evidence of validation should be seen at the corporate level and be reflected in the management structure. Validation is a method for building and maintaining quality (Paruchuri R., *et al.*,2012).

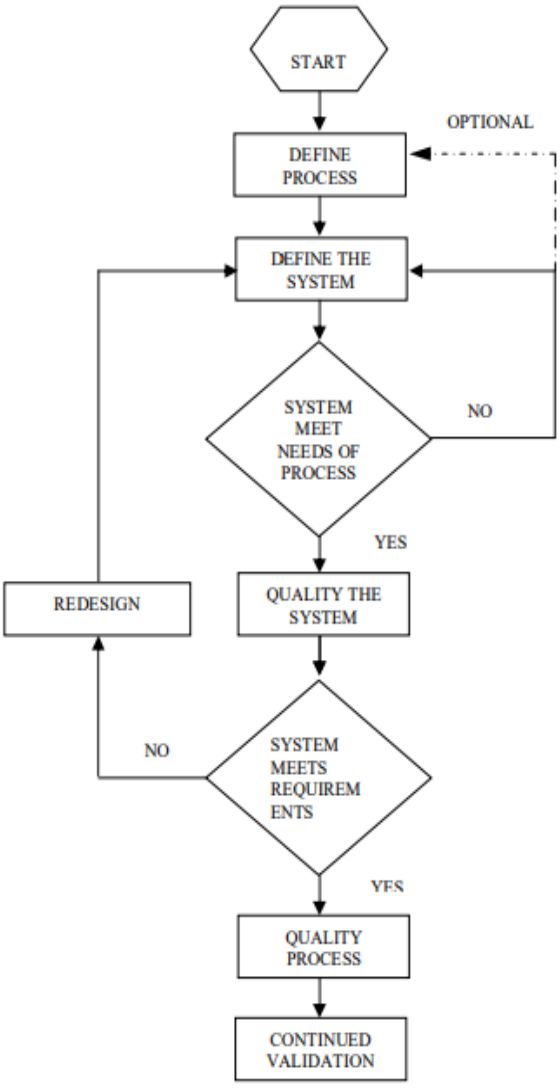

Fig: Validation Life Cycle

The Regulatory Basis for Process Validation

Once the concept of being able to predict process performance to meet user requirements evolved, FDA regulatory officials established that there was a legal basis for requiring process validation. The ultimate legal authority is Section 501(a)(2)(B) of the FD&C Act, which states that a drug is deemed to be adulterated if the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or were not operated or administrated in conformity with CGMP (Murthy DN., *et al*., 2012). Assurance must be given that the drug would meet the requirements of the act as to safety and would have the identity and strength and meet the quality and purity characteristics that it purported or was represented to possess. That section of the act sets the premise for process validation requirements for both finished pharmaceuticals

and active pharmaceutical ingredients, because active pharmaceutical ingredients are also deemed to be drugs under the act. The CGMP regulations for finished pharmaceuticals, 21 CFR 210 and 211, were promulgated to enforce the requirements of the act.17 Although these regulations do not include a definition for process validation, the requirement is implicit in the language of 21 CFR 211.100, which states: "There shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess."

Documentation

Documentation at each phase of the process validation lifecycle is essential for effective communication in complex, lengthy, and multidisciplinary projects. Documentation is important so that knowledge gained about a product and process is accessible and comprehensible to others involved in each phase of the lifecycle. Information transparency and accessibility are fundamental tenets of the scientific method. They are also essential to enable organizational units responsible and accountable for the process to make informed, science-based decisions that ultimately support the release of a product to commerce

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 contain 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.(CGMP Revision-1.,2011) 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.

Conclusion

Validation is the most widely used word in the areas of drug development, manufacturing and specification of finished products. The consistency and reliability of a validated process to produce a quality product is the very important for an industry. From the study it can be stated that Pharmaceutical Process Validation is the most important and recognized parameters of cGMP. 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 involves a series of activities taking place over the lifecycle of the product and process.

Conflict of Interest

The authors declare no conflict of interest.

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