ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

To Study on the Process of Validation the FDA Guidelines.

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ABSTRACT

A dosage form is the physical shape of a chemical compound dose intended to produce a predictable therapeutic response to a treatment, and it is included in a formulation capable of large-scale manufacture while maintaining consistent product quality. Validation is a critical step in achieving and maintaining the final product's quality throughout the process, not just at the end. Process validation is a systematic approach to indenting, assessing, documenting, and reevaluating critical manufacturing processes in order to ensure consistent quality. This article gives a general overview of process validation in the pharmaceutical manufacturing process, as well as its significance.

Keywords: Validation, Documenting, Assessing, Predictable.

https://doi.org/10.33887/rjpbcs/2022.13.1.20

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ISSN: 0975-8585

INTRODUCTION

Drugs are an important part of any health-care regimen. The physical representation of a dose of a chemical molecule intended for therapeutic use as a medicine or therapy is known as a dosage form. The dosage form must be of the highest quality feasible. Dosage form design's major purpose is to generate a predictable therapeutic response to a pharmaceutical in a formulation that can be mass produced at a large scale while preserving consistent product quality. The steps involved in the development of a drug product into a dosage form include drug discovery, laboratory testing, animal research, clinical trials, and regulatory registration. Before a product is released into the market, it must meet a number of quality criteria, including identity, chemical, and physical stability, appropriate preservation against microbial contamination if necessary, strength, quality, purity, uniformity of drug dose, stability, acceptability to users, including prescribers and patients, as well as appropriate packing, labelling, and validation.

Process validation

Process validation is an important part of pharmaceutical companies' quality assurance systems since it is a key factor in determining the safety and quality of their products. Process validation is a systematic approach to indenting, measuring, evaluating, documenting, and revaluing critical manufacturing processes in order to ensure consistent quality. Process validation is a quality assurance function that aids in the verification of drug product quality by supplying recorded evidence that the manufacturing process is performing as planned on a regular basis. Process validation is used in the pharmaceutical, biotechnology, medical device, and herbal industries. Regulatory bodies are still on the lookout for companies that have certified manufacturing techniques for certain finished goods. The constant monitoring and evaluation of the process performance is known as manufacturing process validation. The complexities of modern manufacturing processes may need the adaptation or change of established parameters, while unexpected variables may have an impact on the manufacturing process and end product quality. The bioavailability of a medicine can be influenced by minor changes in an ingredient's physical properties or the order in which compounds are introduced. In this case, a sample of the finished product may meet compendial dissolving requirements yet have a dissolution pattern that differs dramatically from that created before to the changes. Following any change in process or product qualities or control processes, revalidation may be required as a result of these impacts. (1) To maintain the validated status of a process, actions must be taken to guarantee that any process changes are discovered and dealt with promptly. Equipment, standard operating procedures, manufacturing instructions, environmental conditions, or any other aspect of the process system that impacts its state of control and, as a result, its state of validation can all be subjected to change control methods. Validation, which includes the qualification of systems and equipment, is the recorded act of ensuring that any procedure, process, or product is fit for its intended purpose. Because safety and efficacy must be incorporated into the product rather than confirmed at the end, staff must be trained and the system monitored during production. Various elements maintain the product's quality, safety, and efficacy, including careful selection of quality materials/components, product and process design, process control, in-process control, and end-product testing. Due to the complexity of pharmaceutical products, routine end-product testing is insufficient for a variety of reasons. Furthermore, quality cannot be checked in the finished drug product; rather, it must be embedded into the manufacturing processes, which must be continuously monitored to guarantee that the final product fulfils all quality standards. Because of the careful design and validation of systems and process controls, a high level of confidence can be created that all lots or batches produced will meet their specifications.

Phases of Validation

The activities relating to validation studies are classified into three phases:

Phase 1

The Qualification Phase encompasses all activities related to product development, formulation, pilot batch studies, scale-up studies, technology transfer to commercial scale batches, establishing stability conditions, storage and handling of in Qualification, Master Formula Record, Operational Qualification, and Process Capability.

Phase 2

The Validation Phase (also known as the Process Qualification Phase) is used to confirm that all Critical Process Parameters' set limitations are valid and that satisfactory goods can be produced even in "worst case" scenarios.

Phase 3

Maintenance Phase involves reviewing all process-related documents, including validation audit reports, on a regular basis to ensure that no changes, deviations, failures, or modifications to the production process have occurred, and that all SOPs, including Change Control procedures, have been followed. The Validation Team checks for any changes or deviations that might warrant Requalification and Revalidation at this time. Written plan defining the validation process, including test parameters, product qualities, production and packaging equipment, and decision points on what constitutes acceptable test results. This document should outline the critical steps in the manufacturing process that should be assessed, as well as the allowable range of variability and how the system will be evaluated. The validation methodology outlines the tasks that must be done. The protocol should describe the procedure and control factors that were chosen, as well as the number of batches that will be included in the study and how the data will be analysed for relevance after it is assembled. The approval date of the validation team should also be given.

The rationale for changing or amending a procedure after it has been approved must be documented (4).

The validation procedure should be numbered, signed, and dated, and it should contain the following details:

1The validation study's objectives and extent of coverage.
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 (5-8)

Types of process validation (9-15):

- Prospective process validation
- Retrospective process validation
- Concurrent validation

Approaches in Process Validation

Validation as part of a carefully planned collection and review of data, from the process design stage to commercial production, is a more rational strategy that offers scientific evidence that a process is capable of consistently delivering excellent product. Process validation entails a series of activities that take place throughout the product and process lifecycle. The activities of process validation are divided into three levels.

Stage 1 - Process Design

The goal of this stage is to build a process that can consistently deliver a product that meets its quality criteria, based on knowledge gathered via development and scale-up operations. - Establishing a Process Control Strategy - Building and Capturing Process Knowledge and Understanding.

Stage 2 - Process Qualification

During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing. Process qualification has two stages. They are:

1. Design of the facility and qualification of the equipment and utilities
2. Process performance qualification (PPQ), in this stage CGMP-compliant procedures must be followed.

a. Design of a Facility and Qualification of the equipment and utilities Following details are needs to be identified in stage 1. The details are as follows:

1. The studies or tests to use.
2. The criteria appropriate to assess outcomes.
3. The timing of qualification activities.
4. The responsibilities of relevant departments and the quality unit.
5. The procedures for documenting and approving the qualification.

b. Process Performance Qualification which includes PPQ Protocol and PPQ Protocol execution and its Report

Stage 3 - Continued Process Verification

The third validation stage's purpose is to provide continual confidence that the process remains in a controlled state (the validated state) during ordinary commercial manufacturing. Information and knowledge from product and process development are essential for a successful validation programme. The foundation for building a manufacturing process control method that results in products with the necessary quality attributes is knowledge and understanding. Process Validation Considerations in General (12, 15) Good project management is important at all phases of the product lifecycle. The process validation programme will be more effective and efficient with better administration and archiving that collect scientific knowledge. The methods listed below ensure that information about the process is collected and evaluated consistently, and that it is accessible later in the product lifetime. Process validation team members have backgrounds in process engineering, industrial pharmacy, analytical chemistry, microbiology, statistics, manufacturing, and quality assurance, among other areas. The process validation team includes professionals from numerous fields such as process engineering, industrial pharmacy, analytical chemistry, microbiology, statistics, manufacturing, and quality assurance. Project plans, as well as senior management's complete support, are critical components for success. Throughout the lifecycle of a product, Various studies can be started to learn more about the product and process by observing, correlating, or confirming facts. All investigations should be prepared and carried out using good scientific principles, well recorded, and authorised in accordance with the specified procedure for the lifecycle stage. The notion of criticality as a continuum rather than a binary state is more beneficial with a lifecycle approach to process validation that incorporates risk-based decision making across the lifetime. All parameters should be examined for their roles in the process and impact on the product or in-process material, and they should be reevaluated when new information becomes available. The degree of control over those factors should be proportional to the danger they pose to the operation and its outcome. In other words, for parameters that offer a larger risk, a higher degree of control is appropriate. Many products are one-of-a-kind or require lengthy manufacturing methods.

Documentation (12)

Documentation of the process validation lifecycle, from product conception to full-scale manufacturing, is critical for successful communication in complex, long, and multidisciplinary projects. Documentation is necessary to ensure that knowledge gained about a product or process is accessible and understandable to everyone participating in the lifecycle at each stage. Ideal documentation includes a detailed history of the ultimate product being made, as well as transparent information and scientific access to the manufacturing process.

Analytical Methodology (12)

The accuracy and precision of measuring techniques used to test and assess the quality of drug components, in-process materials, and final products are critical to process expertise. During product and process development, validated analytical procedures are not always necessary. Analytical methods, on the other hand, should be scientifically sound (e.g., specific, sensitive, and accurate) and produce dependable results. For laboratory experiments, appropriate equipment function should be ensured. Procedures for maintaining analytical methods and equipment, as well as documentation and calibration practises, should be documented or specified to support process development initiatives. Process parameters that could be critical for common Solid dosage form unit activities (16):

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 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

Benefits of process validation

- Reduction in rejections and reworks
- Increased throughput
- Reduction in utility costs
- Avoidance of capital expenditures
- Fewer complaints about process related failures
- Reduced testing in process and finished goods
- More rapid and accurate investigations into process deviations
- More rapid and reliable start-up of new equipment
- Easier scale-up from development work
- Easier maintenance of the equipment
- Improved employee awareness of processes
- More rapid automation

Process validation program can be made more effective and efficient through (15):

- Good project management
- Robust scientific knowledge collection, management and archiving
- collection and assessment of information methods
- Reducing the burden of redundant information gathering
- Use of an integrated team approach
- Appropriately documented Project Plans
- The support of senior management
- Statistical assessment of data

FDA Guidelines

Manufacture of the following product type are specifically excluded from the scope of the guidance. Where alternative guidance or regulation is used by the FDA, it has been specified:

Product Type	Relevant Guidance/Regulation
Type A medicated product (articales and feed) For animal use	NA
Medical devices	Global Harmonisation Task Force SG3/ N99-10: Quality Management System- Process Validation Guidance ed. 2 (2004)
Dietary supplement	NA
Human tissue	FDA Guidance for industry: Validation Of Procedures for Processing of Human Tissue intended for Transplantation March [March2002]

FDA Guidelines Key change in the new guidance

The revised guidance is essentially a reworking of the original document from 1987. Although the main idea of the papers is comparable, there is very little wording from the original that has been retained. There are various major differences, ranging from the formal definition of process validation to the emphasis on product life cycle and risk management ideas, to name a few. The significant distinctions are outlined below.

CONCLUSION

Process validation is critical in the pharmaceutical sector for achieving and maintaining final product quality. Validation should be an element of any pharmaceutical industry training programme. To guarantee that the product meets its quality, production, and regulatory standards, the process validation team should determine the relevant parameters of the process and product. The information gathered early in the process can offer the foundation for a successful validation programme. The parameters chosen must be critical to the process's control. Validation and its procedure will become more well known, allowing regulatory authorities around the world to ensure consistent quality products.

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