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Overview of Validation and Basic Concepts of Process Validation

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Abstract: Quality is the primary goal of any industry and the items it produces. The pharmaceutical business is currently interested in several perspectives on achieving such quality. Validation is the process of planning and practising the actions that will be documented. Validation and quality assurance will work in tandem to ensure the items' overall quality. Process validation focuses on process design aspects and maintaining process control during commercialization, as well as communicating that process validation is a continuous programme and aligning process validation activities with the product lifecycle. Process validation also emphasises the role of objective metrics and statistical tools and analyses, as well as understanding, identification, and control of variability, and provides assurance on product quality/productivity consistency across the product's life cycle.

Keywords: Quality, Validation, Process Validation, Protocol, Prerequisites, Regulatory basis. throughout life cycle of product.

INTRODUCTION The primary goal of any pharmaceutical factory is to continuously produce products with the required attributes and quality at the lowest possible cost. Although validation studies have been undertaken in the pharmaceutical industry for a long time, there is a growing interest in validation due to their industry's increased emphasis on quality assurance programmes in recent years, which is essential to an effective production operation .

Validation is a term that first used in the United States in 1978.Validation has evolved over time to encompass a wide range of activities ranging from analytical methods used for quality control of drug substances and drug products to computerised systems for clinical trials, labelling, or process control. Validation is founded on, but not mandated by regulatory requirements, and is best viewed as an important and integral part of cGMP [2].

The term validation simply refers to the assessment of validity or the action of demonstrating effectiveness. Validation is a collaborative process including professionals from several plant disciplines.

This principle assumes that the following conditions exist: quality, safety, and efficacy are designed or built into the product. Quality cannot be sufficiently assured simply by inspecting or testing in-process and finished products. Each stage of a manufacturing process is managed to ensure that the all quality features, including specifications, are met by the finished product.

A drug product's development is a time-consuming process that includes drug discovery, laboratory testing, animal research, clinical trials, and regulatory approval. Process controls include raw material inspection, in-process controls, and end product objectives. The goal is to monitor and validate the manufacturing process's online and offline performance. Even when the manufacturing process has been validated, contemporary good manufacturing practise involves the establishment of a well-written protocol for process controls to monitor its performance [3].

FDA regulations outlining current good manufacturing practise (cGMP) for completed medicines are specified in 21 CFR parts 210 and 211 for validation. The cGMP rules demand that manufacturing processes be developed and controlled to ensure that in-process ingredients and finished products consistently and reliably fulfil preset quality requirements. The cGMP rules in sections 210 and 211 necessitate process validation in both general and specific terms.

VALIDATION HISTORY

In order to improve pharmaceutical quality, two FDA officials, Ted Byers and Bud Loftus, established the notion of validation in the mid 1970s (Agalloco 1995). It was proposed in direct reaction to many sterility issues large volume parenteral market. The first validation activities were focused on the processes involved in making these products, but quickly spread to associated process of pharmaceutical. 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 [5].

Definations

European commission

1991 -Validation-"Act of demonstrating, in conformity with GMPs, that Any..." method produces the required results." 2000 - "Documented evidence that the process, when operated within established parameters, can produce a Medicinal product that meets its predetermined specifications and quality attributes."

US FDA Definition

"Process validation" is defined as "the establishment of documented evidence that provides a high degree of assurance that a specified process will consistently produce a product that meets its pre-determined specifications and quality characteristics."

ICH Definition

"Process Validation is the process of ensuring and providing documentary evidence that processes within their specified design parameters are capable of repeatedly and reliably producing a finished product of the required quality."

WHO Definition

"The documented act of demonstrating that any procedure, process, equipment, material, activity, or system produces the desired result."

Pharmaceutical Validation is Required

Validation is an essential component of quality assurance; it entails conducting a systematic examination of systems, facilities, and processes to determine whether they fulfil their intended functions sufficiently and consistently as defined. A validated process is one that has been shown to provide a high degree of assurance that uniform batches that satisfy the relevant criteria will be generated and has thus been formally certified. Validation does not improve processes in and of itself; rather, it ensures that processes have been correctly developed and are under control.

Assurance of Quality

Without validation, even if a process is fully understood and in a confident state, quality control of the created product cannot be assured.

Cost Reduction

Because each phase of validation is constantly monitored, there are fewer rejects and reworks, resulting in significant cost savings.

Government Regulation

Validation is seen as an essential component of GMPs. Worldwide validation compliance is required for acquiring approval to produce and introduce new products. The FDA's cGMP refers to validation ideas in sections 211.110 and 211.113. According to Section 211.110, such control measures must be implemented in order to monitor the output and validate the performance of those manufacturing processes that may be responsible for creating variability in the characteristics of the process materials and medication product. The firm's test techniques' accuracy, sensitivity, specificity, and repeatability must be established and recorded. The medical device cGMP rule, section 820.100(b) (1), contains a general obligation for process validation, which states, "Where deviations from device specifications occur."

Scope of Validation

Pharmaceutical Validation is a broad field that encompasses almost every component of pharmaceutical manufacturing activities, making defining the Scope of Validation a tough assignment. However, a thorough examination of pharmaceutical activities will reveal at least the following areas for pharmaceutical validation:

Importance of Validation

Assurance of quality

• Time constraint

• Process optimization

• Raw materials

• Packaging materials

• Equipment

• Facilities

• Manufacturing operations

• Product Design

• Cleaning

• Operators

• Minimal batch failures, improved efficiency and productivity

• Reduction in rejections

• Increased output

• Avoidance of capital expenditures

• Fewer complaints about process-related failures

• Reduced testing in process and finished goods

• Easier scale-up from development work

• Easier equipment maintenance

• Improved employee awareness of processes

• More rapid automation

• Government regulation (Compliance with validation requirements is required for obtaining approval to manufacture and introduce new products)

Planning for Validation:

All validation activities should be prepared ahead of time. A validation master plan (VMP) or equivalent documents should clearly describe and document the major parts of a validation programme.

• The VMP should be a summary document that is brief, concise, and easy to understand. • The VMP should include at least the following information:

Validation policy. Organisational structure of validation activities. A list of the facilities, systems, equipment, and processes that will be validated.

Documentation format: This is the format for protocols and reports. Planning and scheduling are essential. Change the control. Make a reference to an existing document. In the case of major projects, different validation master plans may be required.

Validation Set Up

To establish the desired characteristics. These features include both physical and chemical properties. In the case of parenterals, ideal characteristics should include stability, the absence of pyrogens, and the absence of visible particles. Acceptance specifications for the product should be established in order to achieve uniformity and consistency in the desired product attributes, and the specifications should be derived from testing and challenging the system on a sound statistical basis during the initial development and production phases, and they should continue through subsequent routine production. To meet the product specifications, the method and equipment should be chosen. Design engineers, production personnel, and quality assurance personnel, for example, may all be involved. The process should be described precisely, and each stage of the process should be documented.

TYPES/METHODS OF VALIDATION

Validation Prospective It is described as the established written evidence that a system does what it claims to do in accordance with a predetermined protocol. This validation is typically performed prior to the distribution of a new product or a product created using an altered manufacturing process. At least three sequential production sizes were tested (Consecutive batches). The validation technique is carried out in Prospective Validation before the process is placed into commercial use. The manufacturing process should be divided into discrete steps throughout the product development phase. To establish the essential parameters that may affect the quality of the finished product, each phase should be analysed using experience or theoretical considerations. To determine the criticality of these, a series of experiments should be designed.

A succession of batches should be created using this stated method. In principle, the number of process runs and observations should be adequate to determine the usual extent of variation and trends and offer sufficient data for evaluation. Three successive batches/runs within the final agreed parameters, yielding product of the appropriate quality, are generally regarded as sufficient validation of the process. In practise, gathering this information may take some time. When deciding on a process validation technique, some factors should be taken into account. Among these should be the use of separate lots of active raw materials and main excipients, batches manufactured

on different shifts, and the employment of various equipment and facilities dedicated to pharmaceutical manufacturing.

During the validation batch procedure, significant sampling and testing on the product should be undertaken at various stages and thoroughly recorded. The final product in its packaging should also be thoroughly tested.

Following the completion of the study, recommendations on the level of monitoring and the inprocess controls required for routine production should be made. These should be documented in the Batch manufacturing and packaging record or in the relevant standard operating procedures. restrictions, frequencies, and actions to be performed if the restrictions are exceeded should all be defined. Prospective validation should include, but is not limited to: • A brief summary of the procedure.

• A summary of the important processing steps that need to be studied.

• A list of the equipment/facilities to be utilised (including measuring, monitoring, and recording equipment) as well as the status of its calibration.

• Release requirements for the finished product.

• As needed, a list of analytical procedures.

• In-process controls with acceptability criteria proposed.

• Additional testing will be performed, including acceptance criteria and analytical validation as needed.

• A sampling strategy.

• Techniques for recording and analysing data.

• Roles and responsibilities.

• A suggested timetable.

Process validation batches should be the same size as the intended industrial scale batches. If validation batches are to be sold or supplied, the conditions under which they are manufactured must fully conform with the standards of Good Manufacturing Practise, including the successful outcome of the validation exercise and the marketing permission.

Concurrent Validation

It is similar to prospective validation, except that the operational firm will sell the product to the public at its market price throughout the qualification runs, and it is also similar to retrospective validation.

• This validation entails monitoring important processing steps in-process as well as product testing. This aids in the generation and documentation of evidence demonstrating that the manufacturing process is under control.

• In rare situations, it may be permissible not to finish a validation programme before routine production begins. Authorised employees must justify, document, and approve the decision to do concurrent validation. Concurrent validation documentation requirements are the same as those for prospective validation.

Retrospective Validation

On the basis of a review and analysis of historical data, it is described as established documented evidence that a system performs what it claims to do. This is accomplished by reviewing previous manufacturing testing data to demonstrate that the process has always been under control. This type of validation of a procedure for a product

that is already in use. Retrospective validation is only applicable for well-established processes and is not appropriate when the product's composition, operating procedures, or equipment have recently changed. Such techniques should be validated using previous data. The stages involved necessitate the creation of a specific methodology as well as the reporting of the outcomes of the data review, which leads to a conclusion and a recommendation.

Some of the necessary components for Retrospective Validation Manufacturing batches over a set period of time (minimum of 10 last consecutive batches). The number of lots released each year.

• Batch size, strength, manufacturer, year, and period.

• Manufacturing/packaging master documentation.

• Current active materials/finished product requirements.

• A list of process deviations, remedial measures, and manufacturing document revisions.

• Data for multiple batches of stability testing.

Revalidation

Re-validation provides evidence that modifications made to a process and/or the process environment have no negative impact on process characteristics or product quality. The documentation requirements will be the same as for the initial process validation.

Facilities, systems, equipment, and procedures, including cleaning, should be assessed on a regular basis to ensure their continued viability. If no significant modifications to the validated status have occurred, a review with evidence that the facilities, systems, equipment, and procedures meet the stipulated requirements eliminates the need for revalidation.

The following are some of the changes that must be validated:

• Raw material changes (physical qualities such as density, viscosity, particle size distribution, and moisture, among others, which may affect the process or outcome).

• Changes in the active raw ingredient manufacturer's source.

• Packaging material changes (main container/closure system)

• Process changes (e.g., mixing time, drying temperatures, and batch size)

• Equipment modifications (for example, the addition of an automatic detecting system). Changes in equipment that entail the replacement of equipment on a "like for like" basis do not generally necessitate revalidation, unless the new equipment is certified.

• Modifications to the plant/facility. The choice to forego revalidation studies must be thoroughly justified and recorded.

Basic Concept of Process Validation

Pharmaceutical Process Validation is one of the most significant and well-known cGMP criterion. Process validation is a requirement of the quality system (QS) regulation. A quality system's goal is to continuously deliver products that are fit for their intended purpose [19]. Process validation is an important part of ensuring that these principles and goals are followed. The process validation is the standardisation of the validation documents that must be presented with the marketing permission submission file.

Installation Qualification (IQ)

Providing objective evidence that all essential parts of the process equipment and ancillary system installation correspond to the manufacturer's approved specification and that the equipment supplier's recommendations are appropriately considered**.**

• Equipment design aspects (i.e. material of construction, clean ability, etc.) are IQ factors.

• Installation requirements (wiring, utility, functionality, and so on).

• Cleaning schedules, calibration, and preventative maintenance.

• Security features.

• Prints, drawings, and manuals from suppliers.

• The software is documented.

• A list of spare parts.

• Environmental factors (such as clean room specifications, temperature, and humidity).

Operational Qualification (OQ) is the process of establishing process control limits and action levels based on objective evidence that results in a product that meets all established requirements.

• Process control constraints (time, temperature, pressure, line speed, setup conditions, and so on) are among the OQ issues.

• Software settings.

• Specifications for raw materials

• Operating procedures for the process.

• Material handling specifications.

• Process transformation management.

• Education.

• The process's short-term stability and capabilities (latitude studies or control charts).

• Failure modes, action levels, and worst-case scenarios.

• During this step, statistically valid techniques such as screening trials can be employed to optimise the process.

Performance Qualification (PQ)

Providing objective evidence that the process regularly generates a product that meets all predetermined parameters under anticipated situations.

PQ considerations include:

• In OQ, actual product and process specifications and procedures are established.

• The product's acceptability.

• Assurance of process capability as defined in the OQ.

• Process reproducibility and long-term stability.

Qualification Review :

Equipment modification or relocation should occur after a satisfactory evaluation and authorization of the documented change proposal via the change control procedure. This formal evaluation should include a discussion of requalifying the equipment. Minor adjustments or changes that have no direct impact on final or in-process product quality should be managed through the preventive maintenance program's documentation system.

The Regulatory Basis for Process Validation :

From its inception in the early 1970s to the regulatory aspects associated with current good manufacturing practise (cGMP) regulations and their application to various analytical, quality assurance, pilot plant, production, and sterile product and solid dosage form considerations. The concept of preapproval inspection (PAI) was born in the early 1990s, with one of its fundamental tenets being the assurance that approved validation protocols and schedules were being generated, and that comprehensive development, scale-up, bio batch, and commercial batch validation data were required in order to achieve a successful regulatory PAI audit.

There are various compelling reasons to validate a product or process. To begin, producers are obligated by law to follow cGMP rules. Second, excellent business practise requires

Prerequisite of Process Validation

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Strategy for Industrial Process Validation of Solid Dosage Forms

The process validation approach chosen should be basic and straightforward. The five items below provide a strategy for process validation.

• The use of various batches of raw materials should be considered. Specifically, the active medication component and main excipients.

• Batches should be performed sequentially and on various days and shifts (the latter criterion being optional).

• Batches should be produced using the equipment and facilities intended for commercial production.

• During process operation, critical process variables should be set within their operating ranges and should not exceed their upper and lower control limits. The output replies should be well within the parameters of the finished product.

• Failure to achieve the Validation protocol standards for process input and output control should result in process requalification.

Process Validation within the Quality Management System

A quality management system's integrated needs include process validation. It is carried out within the context of a system that includes control over design and development, quality assurance, process control, and corrective and preventive action. The product should be designed to tolerate fluctuations in the manufacturing process, and the manufacturing process should be capable and stable enough to ensure continuing safe and acceptable performance. Corrective efforts frequently reveal insufficient processes/process validations. Each remedial action taken in a manufacturing process should take process validation/revalidation into account.

Reason for Process Validation

Process validation may be performed for a variety of reasons, including:

• new products or existing products as a result of SUPAC revisions.

• Manufacturing location shift.

• Alteration in batch size.

• Equipment replacement.

• Process modification for existing goods.

• Modifications to the composition or components.

• Modifications to important control parameters.

• Change in API or important excipient vendor.

• Modifications to the input material specification.

• Abnormal trends in product quality metrics discovered during the Annual Product Review (APR).

• A pattern of out-of-specification (OOS) or out-of-trend (OOT) in successive batches.

Benefits of Process Validation

• Consistent in output.

• A decrease in rejections and reworks.

• Utility cost savings. • Capital expenditures are avoided.

• Less complains regarding process failure.

• Less testing in the process and finished goods.

• More accurate and timely inquiries into process deviance.

• Faster and more reliable startup of new equipment.

• Development work can be scaled up more easily.

• Easier equipment maintenance.

• Increase staff understanding of processes.

• Faster automation.

Stages of Process Validation

Process validation is defined as the gathering and evaluation of data from the process design stage through commercial production to establish scientific evidence that a process is capable of consistently delivering high-quality products. Process validation entails a series of activities that take place throughout the product and process's lifecycle. The activities associated with validation studies can be divided into three stages:

Stage 1 - Process Design "During this stage, knowledge gained through development and scale-up activities is defined by focusing solely on qualification efforts without also understanding the manufacturing process." It encompasses all activities associated with product research and development, formulation, pilot batch studies, scale-up studies, technology transfer 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, and process capability. This is also the stage at which a process control strategy is being developed based on accumulated knowledge and understanding of the process.

Process Qualification (Stage 2) - The process design is examined at this stage to determine whether the process is capable of reproducible commercial manufacture. It ensures that the defined limitations of the Critical Process Parameters are valid and that suitable products may be generated even under “worst case” situations. GMP compliance methods must be followed in this step, and satisfactory completion of this stage is required before a product can be commercially distributed. Process Qualification has two components:

• Facility design and qualification of equipment and utilities Under 21 CFR part 211, subpart C of the cGMP rule on Buildings and Facilities, proper manufacturing facility design is sought. Activities conducted to ensure correct facility design and that the equipment and utilities are acceptable for

Stage 3 –

Process Verification Continued During routine production, continuous assurance that the process is under control is obtained. The validation maintenance stage necessitates a regular review of all process-related documents, including validation audit reports, to ensure that there have been no changes, deviations, failures, or modifications to the manufacturing process, and that all SOPs, including change control procedures, have been followed. A good validation programme is dependent on information and understanding, as well as the method used to control production processes. These include the source of variation, the limits of variation detection, and the traits vulnerable to variation.

Phases in Process Validation

alidation study activities can be divided into three categories:

Phase 1: Qualification for Pre-Validation

This phase encompasses all activities associated with product research and development, formulation pilot batch studies, scale-up studies, technology transfer 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.

Phase 2: Validation of the Process Its purpose is to ensure that all set critical process parameter limitations are valid and satisfactory. Even in the most adverse situations, products can be manufactured.

Phase 3: Validation Upkeep Phase To ensure that there have been no changes, deviations, failures, or modifications to the production process, and that all standard operating procedures (SOPs), including change control procedures, have been followed, all process related documents must be reviewed on a regular basis, including audit reports. At this point, the validation team, which includes representatives from all major departments, ensures that there have been no changes or deviations that should have resulted in requalification and revalidation. A thorough design and validation of systems and process controls can provide a high level of assurance that all lots or batches produced will fulfil the required standards. It is expected that activities are carried out in accordance with the principle of good manufacturing throughout manufacture and control.

Validation Protocol

To guarantee that the process is adequately validated, detailed protocols for completing validations are required. The following aspects should be included in process validation protocols:

• The validation study's objectives and extent of coverage.

• The membership of the validation team, as well as their credentials and responsibilities.

• Validation method: prospective, contemporaneous, retrospective, or re-validation.

• The number and composition of batches included in the validation study.

• A list of all the equipment that will be used, as well as their usual and worst-case operating conditions.

• IQ and OQ results for essential equipment.

• Calibration requirements for all measurement devices.

• The critical process parameters and their tolerances.

• Process factors and attributes associated with potential risk and prevention must be documented.

• Description of the processing steps: a copy of the product's master documentation.

• Sampling points, sampling stages, sampling methods

Validation Master Plan

The validation master plan should provide a high-level overview of the validation operation, including its organisational structure, content, and planning. Its key components are the list/inventory of objects to be validated and the planned timetable. The validation master plan should cover all validation activities linked to important technical operations, pertinent to product and process controls inside a company. All prospective, contemporaneous, and retrospective validations, as well as revalidation, should be included. Because the Validation Master Plan is a summary document, it should be brief, concise, and unambiguous. It should not repeat material that has already been documented elsewhere, but rather relate to existing papers such as policy documents, SOPs, validation processes, and reports. Khushboo DS et al. should be included in the format and content.

Process Validation and Quality Assurance

The link between quality assurance and process validation extends far beyond the purview of any quality assurance (QA) department. Nonetheless, process validation is a QA technique since it defines a quality standard for the specific process. The effort to ensure that goods have the strength, purity, safety, and efficacy represented in the company's new drug application (NDA) filings is embodied in quality assurance in pharmaceutical firms. Although quality assurance is typically defined as a departmental role, it must also be an inherent element of the activities of an organisation. When process validation becomes a general goal of an organization's technical and operational groups, it becomes the driving force behind quality standards in development work, engineering activities, quality assurance, and production.

Validation Report [36, 37]

Following the completion of the validation, a written report should be provided. If it is deemed satisfactory, it should be approved and authorised (signed and dated). The following information should be included in the report:

• The study's title and goal.

• Protocol citation.

• Material specifics.

• Resources.

• The programmes and cycles that are used.

• Procedures and test methodologies in detail.

• Outcomes (as compared to admission criteria).

• Recommendations on the limit and criteria to be used in the future.

Documentation

A formal protocol describing how qualification and validation will be carried out should be prepared. The protocol should be authorised and evaluated. Critical steps and acceptance criteria should be specified in the protocol. A report should be written that includes cross-references to the qualifying and/or validation protocols, summarising the data obtained, commenting on any deviations seen, and drawing the required conclusions, including recommending improvements to remedy inadequacies. Any changes to the plan as described in the protocol should be documented and justified. A format release for the next step in qualification and validation should be made as a written authorization after completion of an acceptable qualification.

cGMP requires the most paperwork during process qualification and ongoing process verification. Studies conducted during these

CONCLUSION

Validation is the most commonly used term in the fields of medication research, manufacturing, and completed product specification. A validated process's consistency and reliability in producing a quality product is critical for an industry. Pharmaceutical Process Validation is one of the most significant and well-known cGMP criterion. The process validation is meant to help manufacturers understand the quality management system (QMS) criteria for process validation and has broad applicability to the manufacturing process.

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