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A Comprehensive Review on Process Validation

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ABSTRACT
Process validation refers to the documented evidence that any procedure, process, equipment, material, activity or system actually leads to the expected result. It is an integral component of quality assurance which includes the efficient investigation of systems, facilities, and procedures aimed toward deciding if they execute their planned capacities sufficiently and reliably determined Validation should in this way be considered in the following circumstance:. The objective of process validation is to demonstrate that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product that meets its predetermined quality attributes and quality attributes. Process validation, in this regard, sets a sharp focus on the control of critical quality attribute and Critical process parameters directly affecting the quality of the final drug product. This is accomplished through establishment of documented evidences accomplished by validation team lead by quality assurance, which collect, analyses and evaluation of data from the process design and manufacturing of a product so that an assurance of guarantee that process could deliver quality products meeting specifications.

KEYWORDS –Validation, Process validation, Protocol ,History andTypes of Process validation, Phases of validation

I. INTRODUCTION

Validation is the documented act of proving that anyprocedure, process, equipment, material, activity or system actually leads to expected result.[1]It is an essential component of quality assurance it includes the efficientinvestigation of systems, facilities, and procedures aimed towarddeciding if they execute their planned capacities sufficiently and reliablydeterminedValidation should in this way be considered in thein followingcircumstance

- Completely new procedure.
- Latest equipment.
- Procedure and equipment which have been adjusted to suit altered needs
- Procedure where the finished result test is a poor and undependable marker of product quality.[2]

The validation protocol is reviewed and approved by Head of Quality Assurance, Head of Quality engineering, Validation Manager, Production Manager and Speclist in validation Discipline which help to determination of written plan how to test a process and product quality with specific reference criteriafor ensuring product and process quality, safety and efficacy. The validation protocol implicatesthe following components for validation which may includes

1. Purpose and Scope of validationprocess.
2. Type of validation.
3. Total no of batches to be validated.
4. Validation team with qualifications and their responsibility.
5. Critical process attributes with their specifications.
6. Stastical tools used analysis of data.
7. Validated test methodfor raw materials and in process testing with specification.
8. Calibration and qualification criteria forequipment and process with specification.
9. Documentation of results, conclusion and approval of study results.[3,4]

Importance of validation

- Assurance of quality
- Process optimization
- Minimal batch failure andincreased productivity
- Reduction in rejection
- Easier maintenance of equipment
- Increased output and product consistently
- Fewer complaints about process related failure
- More rapid innovation
- Ensures compliance with Regulatory standards
- Improve product quality and safety

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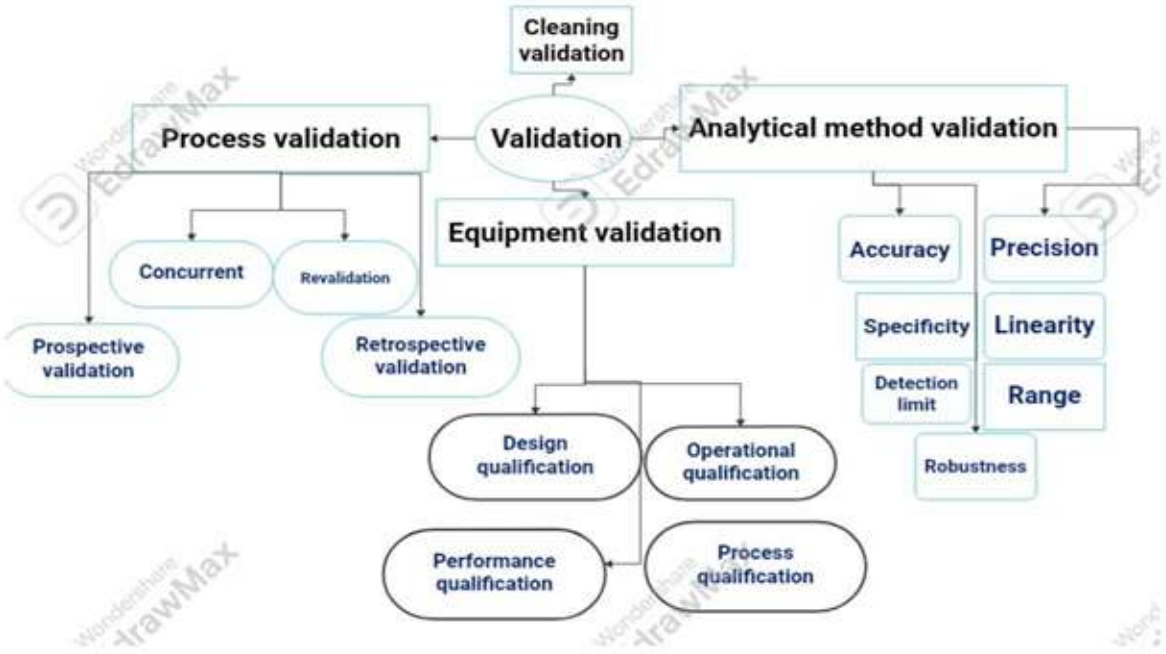
- Improves Operational Efficiency and Reduces Costs[5]

Types of validation Method



Introduction to process validation[6-9]

Process validation is establishing documented evidences accomplished by validation teamlead by quality assurance which collecting, analysing and evaluation of data from process design and manufacturing of a product for ensuring that process can reliably produce a product that meets predetermined quality specification. The purpose of process validation is every batch product be safe, effective and having good quality.[6]It is beneficial to manufacturer which deepens the understanding of process, maintaining consistency and reliability of product, decreases the risk of defect cost and regulatory Non-complianceit requires less in-process Controls and end- product testing.[7]

In the pharmaceutical industry, the purpose of process validation is to demonstrate that the manufacturing process consistently yields a product that meets its quality, safety, and efficacy standards. For this reason, the focus is primarily on controlling critical quality attributes (CQAs) and critical process parameters (CPPs)—those factors that directly influence the quality of the finished product. Process validation should confirm that the impurity profile for each API and finished product is within the limits specified.[8]

Process validation is widely practiced by pharmaceutical, biotechnological, medical device and herbal industries. The PV lifecycle concept links product and process development, the qualification of the commercialManufacturing processes, and maintenance of the commercial production process in a coordinated Effort.Regulatory bodies continue to find firms for some finished product to have validated manufacturing processes. Manufacturing process validation is a process in which the process performance is constantly monitored and evaluated. The state of validation refers to the condition in which a pharmaceutical process consistently operates within predefined parameters, producing results that meet all quality, safety, and efficacy standards. To maintaining validated status of a process, measures must be taken that will allow any significant processchanges to be recognized and resolved quickly. Such change control measures can apply to equipment, standard operating procedures,manufacturing instructions, environmental conditions or any other aspect of the process system that has an effect on its state of control and therefore on the state of validation.[9]

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Process validation andTypes.

❖ **Define According to WHO:**

Process validation isthe collection and evaluation of data, throughoutthe product life-cycle, which provides documented scientific evidence that processes capable of consistently delivering quality products.[10]

❖ **Definition according to USFDA:**[11]

1987 Definition

"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

2011 Definition

"The collection and evaluation of data, from the process design stage throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality products.

"Pharmaceutical CGMPs for the 21st Century – A Risk Based Method," particularly with regard to the use of Industrial advances in pharmaceutical manufacturing, as well as implementation of new risk controlling and Quality system tools and concepts.

❖ **EMA Definition**

Process validation is the documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes.[12]

❖ **ICH Definition**

"Process Validation" as per ICH is defined As "the technique of verifying and giving proof that Processes under their stated design specifications are well able to generate final products with the best possible quality.

History of process validation.[13-14]

The concept of validation was first proposed by two Food and Drug Administration (FDA) officials, Ted Byers and Bud Loftus, in 1979 in the USA, to improve the quality of pharmaceuticals. It was proposed in direct response to several problems in the sterility of the large volume parenteral market.

1978: GMP includes validation.
1987: First validation guidelines (Equipment IQ)
2000: New Approaches/Documentary presentation.
2008: New Process validation Draft guidelines.(Equipment and analytical validation)
2011: New Process validation guidelines issued
2012-2020:Continouousimprovement ICH guidelines Q8-Q10, Integration of RTRT, PAT
2021-2024:ICHQ12 guidelines, Digital transformation in manufacturing, AI and ML in manufacturing process, AI in process validation

Scope of process validation

- It helps in reducing variability between differentfor ensuring uniformity in batch products adheres to quality criteria of purity, identity and potency
- It ensures high degree of quality of products within acceptance limits
- It maintain product integrity
- To demonstrate the robustness of the manufacturing process
- Process validation will ensure a robust product that is highly reproducible over time.
- Major changes after the initial validation will result in the need for subsequent Revalidation.
- To reduce the risk of defect costs and regulatory noncompliance.[7, 15,16,17]

Advantages of process validation

- It expand real time monitoring that is checks process parameters like temperature,pressure,chemical concentration and adjustment is carried out if necessary for ensuring process stays within desired limits.
- It enhances data and evaluation capacities and increased confidence about process reproducibility and products.
- It enhanced reporting capability.
- It improve ability to set target parameter and control limits for routine production, correlating with validation results
- It is simple process and moisture sensitive,heat sensitive products can also be processed.
- Decreases the risk of preventing problems and thus ensure the smooth running of the process.
- Enhanced ability to statistically evaluate process Performance and product variables e.g. individuals; mean; Range; control limits.
- Process optimization:Optimization focuses on achieving the highest possible efficiency while maintaining quality standards. Optimize is "To Make as effective, perfect or useful as possible". The Optimization of the facility, equipment, systems, and Processes plays vital role ensuring product comply with quality attributesleads to a product that meets quality

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standards at the lowest cost, balancing both effectiveness and cost-efficiency.
- Reduction of quality costs Quality costs are divided in to four categories. They are:A)Preventive costs.B) Appraisal costs.

C) Internal failure costsD) External failure costs.
By understanding and managing these categories of quality costs, organizations can optimize their quality control processes, reduce waste, and improve customer satisfaction.[16,18]

Reason for Process validation
The reasons for performing process validation can be summarized as:
- New product or existing products as per SUPAC changes.
- Change in site of manufacturing.
- Change in batch size
- Change in equipment.
- Change in process existing products.
- Change in composition or components
- Change in the critical control parameters.
- Change in vendor of API or critical excipient.
- Change in specification on input material.
- Abnormal trends in quality parameters of Product through review during Annual Product Review (APR).
- Trend of Out of Specification (OOS) or Out of Trend (OOT) in consecutive batches.[19]

Process validation protocol
Process Validation protocols should define the critical process parameters (CPPs), the critical quality attributes (CQAs), and the related acceptance criteria. It should include:
- A description of the process and a reference to the master batch record.
- Functions and responsibilities.
- A summary of the CQAs to be considered and specification limits.
- A summary of the CPPs and their limits.
- A summary of other attributes and parameters to be investigated and monitored, as well as reasons for their inclusion.
- A list of equipment and facilities to be used along with their calibration status.
- A list of analytical methods and method validation.
- In-process controls with acceptance criteria.
- Additional testing to be carried out.
- A sampling plan.
- Methods for registration and evaluation of results.
- The process for batch release and certification.[20-21]

THE REGULATORY BASIS FOR PROCESS VALIDATION
The concept of process validation from its beginnings in the early 1970s through the regulatory aspects associated with current good manufacturing practice (cGMP) regulations and the application thereof to various analytical, quality assurance, pilot plant, production, and sterile product and solid dosage forms considerations.

FDA Regulations:
FR Part 211 addresses various aspects of validation
- Section 211.100(a):Written procedures to control production and processes.
- Section 211.110(a):Monitoring and validating manufacturing processes to manage variability , sampling and testing in process material and drug products.
- Section 211:110(b): Analyze process performance and control batch-to-batchvariability.Inprocess specificationshall be derived from previous acceptable process average and process variability estimates where possible and determined by the application of Sample statistical procedures where appropriate
- Section 211:160(b) :Samples CGMP regulations regarding sampling
- Section 211:165(d):specifications and statistical Quality control criteria as condition of Approval and release .
- Section 211:165(a):Batch must be meet it's predetermined specification
- Section 211:84(b):The number of containers to be Sampled, and the amount of material to be taken from each container, shall be based upon appropriate criteria such as statistical criteria for component variability, confidence levels, and degree of precision desired, the past quality history of the supplier.
- Section 211.180(e) :that information and Data about product quality and manufacturingExperience be periodically evaluated to Determine need for changes in Specifications or manufacturing of Control procedures.

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Global Standards

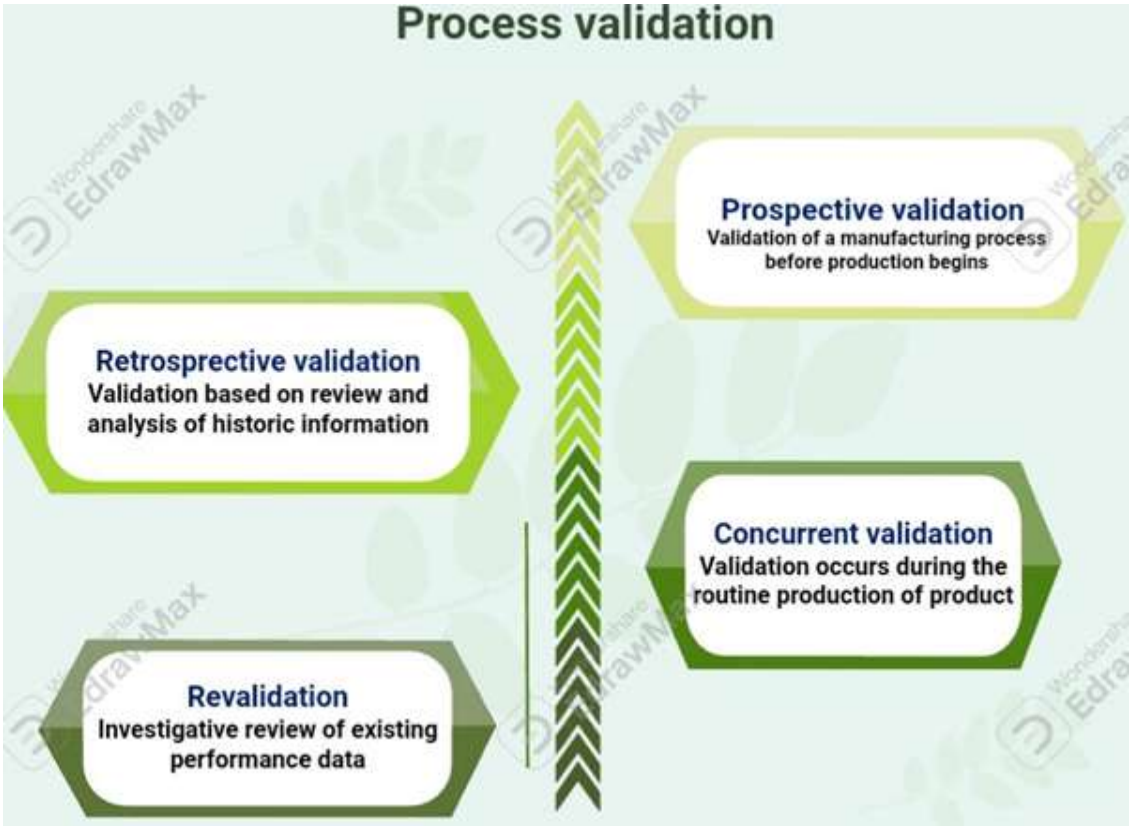
Validation is not limited to FDA requirements but extends to international bodies like the World Health Organization (WHO), Pharmaceutical Inspection Co-operation Scheme (PIC/S), and the European Union (EU). Each organization emphasizes documented evidence proving consistent process performance. Regulators are focusing on reducing the cost of validation while integrating it early in product design and development. Innovations like 100% drug product analysis may streamline future validation processes and align international standards.[22-26]

Prerequisite of process validation

Prerequisite" refers to all the necessary conditions, activities, and preparations that must be completed before initiating the process validation itself. Qualification of Manufacturing and control systems, along with the composition of the drug products carried out beforethe processvalidation. ThisInstallationqualification, Operationalqualification,performance qualification of equipment and system ensures that all systems ,equipment,and components are performing as expected and meet predefined specifications. During the development stage detailed study must be performed like studying of compatibility between API and excipient, Assessing interactions between the final drug product and packaging materials is carried out before submitting marketing authorization application the drug product details must be thoroughlyevaluated and approved. It is essential to validate critical services equipment cleaning and sanitization to prevent cross contamination for ensuring the product quality and safety. Different parts of manufacture must be validated including basic administrations (water, air, nitrogen, control supply, and so forth.)Proper training and motivation of personnel are fundamental prerequisites for successful validationby following Good Manufacturing Practices.[27, 28,29]

Types of process validation

1. Prospective validation
2. Retrospective validation
3. Concurrent validation
4. Revalidation [30]



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1.**Prospective validation**[31-40,57, 67]

It is defined as the established documented evidence that a system does what it purports to do based on a pre-planned protocol.[32]This approach to validation is normally undertaken whenever the process for a new Formula (or within a new facility) must be Validated before routine pharmaceutical Production commences. It is used for facilities, processes, and process controls in operation use that have not undergone a formally documented validation process.[31]These experimental plan called the validation protocol is executed (following completion of the qualification trials) before the process is put to commercial use. Most validation efforts require some degree of prospective experimentation in order to generate validation support data. This phase is crucial before the process is officially put into commercial use.[39]This validation usually carried out prior to distribution either of a new product or a product made under a revised manufacturing process performed on at least three successive production sizes. The validation procedure involves running at least three consecutive production batches (full production scale) to demonstrate that the process consistently yields a product meeting quality, safety, and efficacy standards. Prospective process validation is executed After the completion of the R and D trial in Order to produce the product for the Commercial purpose.[34]Three batches are considered sufficient to demonstrate reproducibility and to confirm that the process performs as expected. Sampling data is consistent within each batch And across all three batches which demonstrates that The process performs in a robust and reproducible Manner capable of producing the drug substance.[33, 38]

Key elements to consider in a prospective validation study

- 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/recordingEquipment) 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.[32]

The objective of the prospective validation is to prove or demonstrate that the process will work in accordance with validation protocol prepared for the pilot production trials. During the product development phase the production process should be broken down into individual steps. Each step should be evaluated on the basis of experience or theoretical considerations to determine the critical parameters that may affect the quality of the finished product. A series of experiments should be designed to determine the criticality of these factors. Each experiment should be planned and documented fully in an authorized protocol.[35]The purpose of validation batches is to demonstrate that the manufacturing process can consistently produce products of the required quality at the intended scale.It is preferred that the validation batches made should be of the same size as the intended production scale batches, However when it is not practical to produce a batch of the full-scale size, regulatory guidelines generally allow for smaller batch sizes. The reduced batch size should typically be at least 10% of the intended production scale. This helps ensure that the validation process still reflects real production conditions and allows for a meaningful assessment of the process's ability to meet specifications.[36]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. 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.Amongst these should be the use of different lots of active raw materials and major excipients, batches produced on different shifts, the use of different equipment and facilities dedicated for commercial production, Operating range of the critical processes, and a thorough analysis of the process data in caseof requalification and Revalidation. During the processing of the validation batches, Extensive sampling and testing should be performed on the product at various stages, and should be documented comprehensively. Detailed testing should also be done on the final product in its package. Upon completion of the review, recommendations should be made on the extent of monitoring and the in-process controls necessary for routine production.

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These should be incorporated into the Batch manufacturing and packaging record or into appropriate standard operating procedures. Limits, frequencies and action to be taken in the event of the limits being exceeded should be specified.[37]The process should include identification and evaluation of individual steps, identification of critical situations, design of trial plans and set of priorities, performance of trials, recording of results, assessment and evaluation of observed results. If the results are unsatisfactory then the processes are modified and improved until acceptable results are obtained. This is essential to limit the risk and errors that may occur on production scale.[40]If it is intended that validation batches be sold or supplied, the conditions under which they are produced should comply fully with the requirements of Good Manufacturing Practice, including the satisfactory outcome of the validation exercise and the marketing authorization.

Benefits of prospective process validation

- It deepens the understanding of processes and decreases the risk of problems and thus assures the Quality of the product.
- The smooth running of the process.
- It decreases the risk of defect costs .
- It decreases the risk of regulatory noncompliance.
- A fully validated process may require less in-process controls and end product testing.[57]

Prospective validation should be done in accordance with a validation protocol the protocol should include:

- A description of the process.
- A description of the experiment.
- Details of the equipment and/or facilities to be used including measuring or recording equipment) together with its calibration status the variables to be monitored.
- The samples to be taken — where, when, how, how many and how much (sample size) the product performance characteristics/attributes to be monitored, together with the test methods.
- The acceptable limits.
- Time schedules.
- Personnel responsibilities.
- Details of methods for recording and evaluating results, including statistical analysis. [67]

2. Concurrent validation[19, 35,37,41-48]

Concurrent validation is used to ensure that establishing documented evidence that process do what they purport to do, based on the information generated during processthat is,A process where current production batches are used to monitor processing parameter.[41]The concurrent validation process is similar to that of prospective validation. This method of validation can only be successful if the development stage has resulted in a proper understanding of thefundamentals of the process.[42,44] It is similar to prospective, except the operating firm will sell the product during the qualification runs, to the public at its market price, and also similar to retrospective validation.[37]Concurrent validation is used for establishing documented evidence that a facility and processes do what they purport to do, based on information generated during actual imputation of the process.[47]In special situations, where getting the medicine to patients quickly is very important and the benefits are greater than the risks, it may be allowed to start regular production without completing the usual validation checks first. This is known as concurrent validation.However:

The decision to do this must be well-justified, clearly written in the Validation Master Plan (VMP), and approved by authorized personnel.

When using concurrent validation, there must be enough data to prove that each batch produced is consistent and meets the quality standards.

All results must be properly documented and reviewed by an authorized person before the batch is approved for sale.[43]Concurrent Validation may be the practical approach under certain circumstances. Examples of these may be

- 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 sufficientto 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 demanddrug due to shortage or absence of supply.

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- In all above cases concurrent validation is valid, provided following conditions are appropriately.
- Pre-approved protocol for concurrent validation with rational.
- A deviation shall be raised with justification and shall be approved by plant head /head process owner/Head-QMS.
- Product behaviour and history shall be reviewed based on developmental/scale up /test batches.
- A detailed procedure shall be planned for handling of the marketed product if any adverse reactions observed in concurrent validation process.
- Concurrent validation batches shall be compiled in interim report and shall be approved all key disciplines.[19]

It should involve close and intensive monitoring of the steps and critical points for at least first three production scale batches.Critical process parameters such as temperature, pressure, time, and flow rate are controlled and documented to ensure the desired outcome. If any deviation occurs, corrective actions can be taken promptly. Validation in the production unit mainly comprises of the determination and evaluation of the process parameters of the facilities applied for the scale-up to Final batch size. The control of all critical process parameters, the results of the in-process controls, finalControls and stability tests should prove the suitability of the important individual steps of a procedure.[30]Critical quality attributes CQAs are defined as "a Physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. concurrent process validation, CQAs are assessed during the process development and routine production phases to ensure consistent quality throughout the product lifecycle.[46]This is especially important in industries like pharmaceutical manufacturing, where process control and product quality are critical. In process supervising of critical processing phases and product testing lies under this validation which aids to produce the documented evidence showing the manufacturing procedure is proceed under a suitable state of control with quality characteristics.[48]This evidence ensures that the process consistently produces products that meet predefined quality standards.The data collected including the process parameters, in-process testing, and final product testing, can be used later for retrospective validation. This helps verify that the process remains consistent over time and allows the manufacturer to adjust processes as necessary based on the long-term performance of the process.[34]

3. Retrospective Validation[7,32,49-62]

Retrospective Validation is defined as the establishment of documented evidence that a system does what it purports to do on review and analysis of historical information. The sources of such data are production,QA and QC records. The issues to be addressed here are changes to equipment, process, specification and other relevant changes in the past.[32]Retrospective validation involves validating a process using historical data rather than performing a new set of experiments. It's commonly applied to processes that have been reliably used over time but may lack documented validation records. The main objective is to document evidence that a process consistently produces the desired outcome, even though it wasn't formally validated when initially implemented.[49]Data from batch documents, process control charts, annual product quality review reports, maintenance log books, process capability studies, finished product test results, including trend analyses, and stability results acts as a source for retrospective validation. Data from a minimum of ten consecutive batches produced will acceptable for retrospective validation. In case if there are less than ten batches, which is not sufficient to demonstrate retrospectively then the retrospective validation should be supplemented with data generated with concurrent or prospective validation.[56]

Essential elements for Retrospective Validation

- 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.
- Trend analysis including those for quality related complaints.[7,50, 51]

It is establishing document conducted for a product already marketed based on extensive data

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accumulated over several batches and over time.[52]Retrospective validation involves the examination of past experience of production on the assumption that composition, procedures, and equipment remain unchangedsuch experience and the results of in-process and final control tests are then evaluated. Recorded difficulties and failures in production are analysed to determine the limits of process parameters. A trend analysis may be conducted to determine the extent to which the process parameters are within the permissible range.[53]It may be utilized to provide necessary documentary evidence that the process is validated considering

- Critical Quality Attributes (CQA) & Critical Process Parameters have been identified.
- Appropriate in-process acceptance criteria & controls have been established
- These have not been significant process or product failure attributes to causes other than Operator error or equipment failure unrelated to equipment suitability
- Impurity profile have been established for existing process(Normally 10 to 30 batches)[54]

Before retrospective validation can be conducted, the equipment, facilities, and subsystems involved in the production process must be qualified according to cGMP standards. This qualification ensures that the manufacturing environment and equipment used are capable of consistently producing quality products, thereby supporting the validity of the historical data being analyzed. The Code of Federal Regulations (CFR) 21, Part 211.110(b) specifies the requirement for establishing valid in-process specifications. Valid in-process specifications for such characteristics shall be consistent with drug product final specifications and shall be derived from previous acceptable process average and process variability estimates where possible and determined by the application of suitable statistical procedures where appropriate. Statistical analysis of historical batch data is critical to confirm that the process is stable and reliable. This approach is often used for processes that have been in place for an extended period and have already demonstrated consistent quality, thus reducing the need for revalidation through prospective studies.[55]Retrospective validation is a validation approach used primarily for processes that have been operating stably over a period of time but were not subjected to formal validation during their initial implementation.[59] that is, one in which the method of manufacture has remained essentially unchanged for a period of time.[57]All difficulties and failures recorded are analyzed to determine limits of process parameters and product-related problems. As Retrospective validation is not considered to be a quality assurance measure it should not be applied to new processes or products. [58,60]However, it is generally less preferred in the modern regulatory environment, where prospective and concurrent validations are emphasized to ensure product quality and compliance.[61]In developing design spaces for existing products, multivariate models can be usedfor retrospective evaluation of historical production data. The variability present in historical data can impact the reliability and robustness of the resulting design space. If historical data shows significant variability, additional experiments or studies may be necessary to accurately define and validate the design space.[62]

4.Revalidation[6,63-69]

It's the repetition of validation process or part of it. This is carried out when there is any change or replacement in formulation , a equipment plan orsite, location, batch size [63]andin cases where sequential batches fail to meet product specifications, revalidation is carried out to identify and resolve potential issues in the process, raw materials, or equipment. This is crucial for maintaining consistent product quality.[69]Even in the absence of any changes, periodic revalidation is carried out at specific intervals to confirm that the manufacturing process remains in control. This helps ensure continued compliance with regulatory standards over time.[64]Revalidation is may be categorized into two types.

- Revalidation in case of changes: After any change bearing on the product quality.
- Periodic revalidation:At scheduled intervals.[66, 68]

Revalidation in case of changes Revalidation becomes necessary in the following situations when there are significant changes that could impact the product quality, safety, or regulatory compliance:

- Changes in raw materials:changes in physical properties such as density, viscosity, Particle size distribution and moisture Etc., that may affect the process or product.
- Changes in the source of active raw material manufacturer.
- Changes in packaging material :primary container/closure system ,Exchange of packing

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material such as plastic is replaced with glass .Packaging procedure affecting product stability.

- Changes in the process :mixing Time, drying temperatures and batch Size it may affect subsequent processsteps and product quality.
- Changes in the equipment :Exchange of equipment which may affects process or product quality ,Exchange of major part of 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 re-validation exceptthat this new equipment must be Qualified.
- Changes in the plant/facility.
- Production area support area changes: Rearrangement of manufacturing area and support system may result in the changes, Repair and maintenance of support system, Changes in environmental conditions

Unexpected changes and deviation.Such changes are observed during self inspection or in audit, During the continuous process data trend analysis.[6,65,66,32]

Periodic revalidation

It is a well-known fact that changes in process may occur gradually even if experienced operators work correctly according to established methods. Similarly, equipment wearing may cause gradual changes. Consequently, it is advisable to perform revalidation on a scheduled basis even if no intentional changes have been introduced. The decision for periodic revalidation should primarily be made through review of historical data (data generated during in-process testing and finished product testing after the latest validation) in order to verify that the process is under control. During review of historical data, any trend in the data collected should be evaluated. Some processes, such as sterilization, need additional process testing as a complement to the historical data. The degree of testing required is apparent from the original validation.[66,68]Additionally, the following points should be checked at the time of a scheduled revalidation:

- The occurrence of any changes in master formula and methods, batch size etc. If changes have occurred, have they been assessed for impact on the product?
- Have calibrations been made according to established programme and time schedule?
- Was preventive maintenance been performed according to programme and time schedule?
- Are the Standard Operating Procedures (SOP's) properly updated?
- Are the SOP's followed?
- Have cleaning and hygiene programmes been followed?
- Have any changes been made in the analytical control methods?[66]

Documentation requirements for this type of validation shall be the same as for the initial validation of the process. A decision not to perform the revalidation studies must be fully justified and documented.[6]

Phases of validation[48,58,70-72]

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

- **Phase 1 Pre validation phase or the Qualification phase**
- **Phase 2 Process validation phase**
- **Phase 3 Validation Maintenance phase** [51]

Fig : Phases of validation

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STAGE 1: Pre validation phase or the Qualification phase

The commercial manufacturing process is defined during this stage based on Knowledge gained through development and scale-up activities.[72]It covers all activities relating to product research and Development, formulations, pilot Batch studies, scale up studies, transfer of technology to commercial scale Batches, stability Conditions, storage and Handling of in- process and finished dosage forms, Equipment Qualification, Installation qualificationmaster production documents, operational Qualification, Process capability.[70]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 here 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(emphasis added). This regulation requires Manufacturers to design a process, including Operations and controls, which results in a Product meeting these attributes.[71]

STAGE 2 :Process validation phases

During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial Manufacturing.This phase is 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 condition. It represents the actual studies or trials conducted to show.

- That all systems subsystem or unit operations of a manufacturing process perform as intended.
- That all critical parameters operate within their assigned control limit.
- That such studies and trials, which form the basis of process capability design and testing, are Verifiable and certifiable through proper documentation.[70]GMP acquiesce procedures must be followed in the particular stage and successful

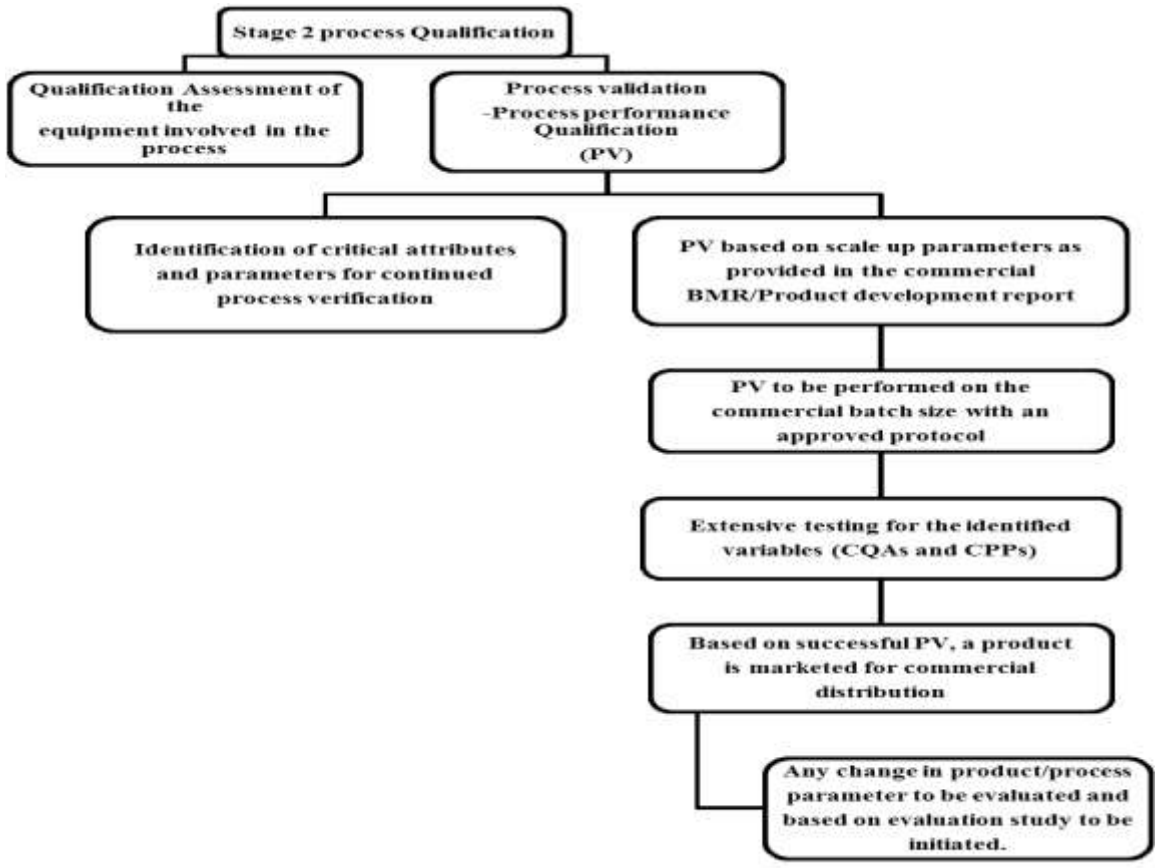

Fig :Stage 2 Process qualification

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STAGE 3: Continued Process Verification

Ongoing Assurance is gained during routine production that the Process remains in a state of control 72The validation of periodic repair stage needs frequent appraisal of all process related documents, as well as validation audit reports to assure that where have been no changes, deviations, failures, modifications to the production process, and that all SOPs Have been superseded, including change in control procedures. A fruitful validation program rest on the knowledge, understanding and the approach to control industrial processes. These include the source of variation, the limitation of the finding of the variation, and the qualities liable of the variation.[71]A system or systems for detecting unplanned departures from the process as designed is essential to accomplish this goal. Data gathered during this stage might suggest ways to improve and optimize the process by altering some aspect of the process or product, such as the operating conditions (ranges and Set points), process controls, component, or in-process materials characteristics.[70] 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.[73]

- As a pre-requisite, all studies should be conducted in accordance with a detailed, pre-established protocol or Series of protocols, which in turn is subject to formal – change control Procedures.
- Both the personnel conducting the studies and those running the process being studied should be appropriately trained and qualified and be suitable and competent to perform the task assigned to them.
- All data generated during the course of studies should be formally reviewed and certified as evaluated against Pre-determined criteria.
- Suitable testing facilities, equipment, instruments and methodology should be available.
- Suitable clean room facilities should be available in both the 'local' and background environment.
- There should be assurance that the clean room environment as specified is secured through initial commissioning (qualification) and subsequently through the implementation of a programme of re-testing – in-process equipment should be properly installed, qualified and maintained.
- When appropriate attention has been Paid to the above, the process, if Aseptic, may be validated by means of "process simulation" studies.
- The process should be revalidated at intervals.
- Comprehensive documentation should be available to define support And record the overall validation process.[73,74,75]

II. CONCLUSION

The essence of validation is to prove that the processes, procedures, and equipment function appropriately, with the result coming out to be consistent and reliable. In this context, process validation is at the forefront in confirming that the production process is properly designed, qualified, and maintained to assure products of quality. This is achieved through efficient validation protocols, thereby enhancing product quality, minimizing failures and rejections, meeting regulatory standards, and optimizing operational efficiency. Therefore, the result will always be to enhance productivity and improve safety, which eventually saves costs since it forms the very basis of quality assurance and continuous improvement.

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