PROCESS VALIDATION: ACTION OF PROVING EFFECTIVENESS

Kashyap Ankita*¹, Rana AC², Singh Gurpreet¹

¹Department of Pharmaceutics, Rayat Institute of Pharmacy, Rail Majra S.B.S Nagar, Punjab, India
²Department of Pharmacology, Rayat Institute of Pharmacy, Rail Majra S.B.S Nagar, Punjab, India

ABSTRACT

The most discussed and important subject of pharmaceutical industry is none other than validation. Validation is a tool of quality assurance which provides confirmation of the quality in equivalent systems, in process, software and testing methods. Validation of individual steps of the manufacturing process is called process validation. A properly designed system will provide a high degree of assurance that every step, process change has been properly evaluated before its implementation. Three consecutive batches are taken up for process validation.

Keywords: Process Validation, FDA, Validation Protocol, Qualification.

INTRODUCTION

Process Validation is defined as the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality products. Validation was earlier defined as a documented procedure for obtaining, recording and interpreting data required to show that a process will consistently comply with predetermined standards. The word validation simply means, ‘assessment of validity’ or action of proving effectiveness.¹ According to European community for medicinal products, validation is ‘action of proving’, in accordance with the principles of GMP that any procedures, process, requirement, material, activity or system actually leads to expected results. Ted Byers and Bud Loftus were the first FDA officials to propose the concept of validation in the mid 1970’s. FDA has the authority and responsibility to inspect and evaluate process validation performed by manufacturers.² The CGMP regulations for validating pharmaceutical (drug) manufacturing require that drug products be produced with a high degree of assurance of meeting all the attributes they are intended to possess (21 CFR 211.100(a) and 211.110(a)).³ USFDA defined process validation as ‘establishing documented evidence which provides high degree of assurance that a specific process will consistently produce a product meeting its pre determined specifications and quality characteristics.⁴
Thus validation is a scientific study of process:

1) To inspect that the process is consistently doing what it is supposed to do (i.e. that the process is under control).

2) To demonstrate the process variables acceptable limits for these variables and to set up appropriate in process controls.

**RESPONSIBILITIES OF VARIOUS PHARMACEUTICAL DEPARTMENTS WHEN CARRYING OUT PROCESS VALIDATION.**

**Quality Assurance**

a) Review of Equipment qualification, facility qualification and utility validations reports.

b) QA is responsible for: Review of Equipment qualification, facility qualification and utility validations reports.

c) cGMP compliance during manufacturing process, review and evaluation of the data/results generated during validation.

d) Preparation, training and approval of protocol, review of the data compiled, review of deviations (if any), monitoring the process as per the process parameters and for withdrawal of validation samples in co-ordination with Production.

e) Preparation of Process validation summary report, its review and approval.

**Production**

It is responsible for:

a) Training of personnel for unit operation.

b) Executing the batches as per the Batch production record and execution of Process Validation Protocol.

c) Compilation of data related to manufacturing area and furnishing the same for review. Review of protocol and summary report.

**Quality Control**

QC is responsible for:

a) Raw material and packing material analysis

b) In process and finished product samples analysis as per the sampling plan.

c) Collection and review of in process test data and Finished Product analysis data.

d) Submission of data/results to QA for review and evaluation
e) Analysis of in process samples and compilation of data.

**Engineering.**

It is responsible for:

a) Qualification and calibration of all the processing equipment/instrument before the start of Process validation batches.

b) To maintain the system to provide required environmental conditions and other utilities for manufacturing of the batches.

**TYPES OF PROCESS VALIDATION**

Depending on when it is performed in relation to production, validation can be prospective, concurrent, retrospective or revalidation (repeated validation).

**Prospective Validation**[^5,6]

Prospective validation is carried out during the development stage by means of a risk analysis of the production process, which is broken down into individual steps: these are then evaluated on the basis of past experience to determine whether they might lead to critical situations.

Where possible critical situations are identified, the risk is evaluated, the potential causes are investigated and assessed for probability and extent, the trial plans are drawn up, and the priorities set. The trials are then performed and evaluated, and an overall assessment is made. If, at the end, the results are acceptable, the process is satisfactory. Unsatisfactory processes must be modified and improved until a validation exercise proves them to be satisfactory. This form of validation is essential in order to limit the risk of errors occurring on the production scale, e.g. in the preparation of injectable products.

**Concurrent Validation**[^5,6]

Concurrent validation is carried out during normal production. This method is effective only if the development stage has resulted in a proper understanding of the fundamentals of the process. The first three production-scale batches must be monitored as comprehensively as possible. The nature and specifications of subsequent in-process and final tests are based on the evaluation of the results of such monitoring. [^1] This careful monitoring of the first three production batches is sometimes regarded as prospective validation.
validation. Concurrent validation together with a trend analysis including stability should be carried out to an appropriate extent throughout the life of the product.

**Retrospective Validation**[^5,^6]

Retrospective validation involves the examination of past experience of production on the assumption that composition, procedures, and equipment remain unchanged; such 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. Retrospective validation is obviously not a quality assurance measure in itself, and should never be applied to new processes or products. It may be considered in special circumstances only, e.g. when validation requirements are first introduced in a company. Retrospective validation may then be useful in establishing the priorities for the validation programme. If the results of a retrospective validation are positive, this indicates that the process is not in need of immediate attention and may be validated in accordance with the normal schedule. For tablets which have been compressed under individual pressure-sensitive cells, and with qualified equipment, retrospective validation is the most comprehensive test of the overall manufacturing process of this dosage form. On the other hand, it should not be applied in the manufacture of sterile products.

**Revalidation**[^5,^6]

Revalidation is needed to ensure that changes in the process and/or in the process environment, whether intentional or unintentional, do not adversely affect process characteristics and product quality. Revalidation may be divided into two broad categories:

- Revalidation after any change having a bearing on product quality.
- Periodic revalidation carried out at scheduled intervals.

**Facility Validation**[^7]

It should include planning, documentation, construction and testing to design specifications and cGMP requirements.

**Services Validation**[^7]

This involves qualification activities like
a) Environmental control system e.g. HVAC and AHU.
b) Water Storage and Distribution System.
c) Compressed Air System.
d) Steam Distribution System etc.

**Analytical Method Validation**[^7]

It involves evaluation of product quality attributes through testing to demonstrate reliability is being maintained throughout the life cycle and that the precision, accuracy, specificity, LOD, LOQ, linearity, selectivity have not been compromised.

**Cleaning Validation**[^7]

It involves high degree of cleaning procedure to give assurance that the cleaning process results in equipment/area having product contamination below the acceptable level.

**Computer Validation**[^7]

It involves validating the software used for automation or testing purposes.

**Equipment Validation**[^7]

It involves qualifying the design, installation, operation, instrumentation, control system and performance of the equipment.

**KEY ELEMENTS REQUIRED FOR A SUCCESSFUL VALIDATION**[^8]

The essential tools or elements required for conducting successful validations are as follows:

1) **Understanding**: The single and the most important of all is the requirement of good understanding of what validation is. This understanding goes beyond the basic definition of validation, beyond the concept of ‘requiring a minimum of three runs.’ This understanding must be anchored by sufficient years of practical experience and knowledge. It will permit sound and logical decisions even under most intense situations.

2) **Experience**: Solid validation experience along with resources are needed to attain success in validation program by a firm.

3) **Communication**: Communication is the best method of environment understanding. Communication is essential for any activity that requires more than one resource to complete. This point is understandable considering that conducting effective validation involves multiDepartments as mentioned earlier in the role of various departments.
4) **Co-operation and Focus**: Commendable co-operation and focused effort amongst departments like Quality control, Quality assurance, project engineering, process engineering, project management, facilities, accounting, regulatory etc is must.

5) **Resources**: Resources means personnel who will plan and execute equipment on which validations will be performed on materials with which to conduct validations. Laboratory that will perform necessary analysis should provide necessary funding for the validations allocate sufficient time to perform validations. Validation can often begin but cannot be completed if any one of these resources is missing.

6) **Budget**: Successful validation should not be limited by a budget assembled by personnel who have no appreciation for what is required to successful complete validation. Further, it is important to understand that validations costly.

7) **Plan**: The various departments involved need a perfect plan in order to get good team synergy.

8) **Training**: It is essential that lead validation resource for a given validation project initiate, facilitate, co-ordinate and/or communication the need for resource training as required by validation event.

9) **Standard Operating Procedures (SOPs)**: SOPs capture activities that routinely occur within a firm. Departments charged with abiding by or following these SOPs must first be trained against SOPs.

10) **QC Laboratory Support**: The testing is handled by the QC group. QC is expected to produce results in timely manner. So often the wait for the receipt of analytical results cases the entire validation project to come to halt. Thus validations are based on results obtained.

**PPQ OR VALIDATION PROTOCOL** [8,9]

A written protocol is the one that specifies the manufacturing conditions, controls, testing, and expected outcomes is essential for process validation. Apart from this, the protocol should give details of critical steps of the manufacturing process that should be measured, the allowable range of variability and the manner in which the system will be tested. [8]

A validation protocol provides a synopsis of what is hoped to be accomplished listing the selected process and control parameters, number of batches to be included in the study.
specifying how the data once assembled should be treated for relevance. The date of approval by the validation team should also be noted.\textsuperscript{[9]}

The following points would give an insight to the basic elements of a protocol: \textsuperscript{[9]}

- The manufacturing conditions, including operating parameters, processing limits, and component (raw material) inputs.
- The data to be collected and when and how it will be evaluated.
- Tests to be performed (in-process, release, characterization) and acceptance criteria for each significant processing step.
- The sampling plan, including sampling points, number of samples, and the frequency of sampling for each unit operation and attribute. The number of samples should be adequate to provide sufficient statistical confidence of quality both within a batch and between batches. The confidence level selected can be based on risk analysis as it relates to the particular attribute under examination. Sampling during this stage should be more extensive than is typical during routine production.
- Criteria and process performance indicators that allow for a science- and risk-based decision about the ability of the process to consistently produce quality products. The criteria should include:
  - A description of the statistical methods to be used in analysing all collected data (e.g., statistical metrics defining both intra-batch and inter-batch variability).
  - Provision for addressing deviations from expected conditions and handling of nonconforming data. Data should not be excluded from further consideration in terms of PPQ without a documented, science-based justification.
- Design of facilities and the qualification of utilities and equipment, personnel training and qualification, and verification of material sources (components and container/closures), if not previously accomplished.
- Status of the validation of analytical methods used in measuring the process, in-process materials, and the product.
- Review and approval of the protocol by appropriate departments and the quality unit.

**KEY FEATURES\textsuperscript{[10]}**

1) **Equipment and Process**
a) Equipment and Process: Installation Qualification (Document qualification, Installation Qualification, Operational Qualification, Process Qualification)

b) Process: Process Qualification

c) Product: Product Qualification

2) System to ensure timely revalidation

3) Documentation

1) Equipment and Process: Equipment and Process should be designed and/or selected so that product specification are consistently achieved. This should be done with participation of all appropriate groups that are concerned with assuring a quality product. Example: Engineering design, Production operations and Quality personnel.

a) Equipment:

   Design Qualification: User requirements should be considered when deciding on the specific design of a system or equipment. A suitable supplier should be selected for the appropriate system or equipment (approved vendor).

   Installation Qualification: The study establishes confidence that the process equipment and ancillary systems are capable of consistently operating with in the established limits and tolerances. The phase of validation includes:
   1) Examination of equipment design
   2) Determinations of calibrations
   3) Adjustment requirements
   4) Maintenance
   5) Identifying critical equipment features that could affect the process and product.

   Operational Qualification: Systems and equipment should operate correctly and their operation should be verified in accordance with an operational qualification protocol. Crucial operating parameters should be identified. It should include verification of all operation of all system elements, parts, services, controls and other components.

b) Process

   Performance Qualification: The purpose of Performance Qualification is to provide rigorous testing to demonstrate the effectiveness and reproducibility of the process. understand what is required. Parts of the process which may vary so as to affect important product quality should be challenged.
c) **Product**

**Performance Qualification:** Product Process Qualification activities apply only to medical devices.

2) **System to ensure timely revalidation**

There should be a QA System in place which requires re-validation whenever there are challenges in packing, formulation, equipment or process which could impact on product effective characteristics and whenever there are changes in product characteristics.

The QA procedures should establish the circumstances under which re-validation is required. The extent of re-validation will depend upon the nature of changes and how they impact upon different aspects of production that had been previously validated.

c) **Documentation**

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

The degree and type of documentation required by CGMP vary during the validation lifecycle. Documentation requirements are greatest during Stage 2, process qualification, and Stage 3, continued process verification. Studies during these stages must conform to CGMPs and must be approved by the quality unit in accordance with the regulations.

Viral and impurity clearance studies, even when performed at small scale, also require quality unit oversight.

CGMP documents for commercial manufacturing (i.e., the initial commercial master batch production and control record and supporting procedures are key outputs of Stage 1, process design. We recommend that firms diagram the process flow for the full-scale process. Process flow diagrams should describe each unit operation, its placement in the overall process, monitoring and control points, and the component, as well as other processing material inputs (e.g., processing aids) and expected outputs (i.e., in-process
materials and finished product). It is also useful to generate and preserve process flow diagrams of the various scales as the process design progresses to facilitate comparison and decision making about their comparability.

**VALIDATION: THE STRATIGEM**

1) The first and foremost requirement is preparing a validation protocol. This would include the procedure for operating validation.

2) The next comes the purpose of application and scope of the method, defining the specified requirements and objectives.

3) This step contains the performance parameters along with the acceptance criteria. It should be noted that each stage should begin when the previous is over.

4) The validation experiments should be defined.

5) The equipment to be used for the purpose should possess the desired performance characteristics because the drug has to be manufactured in the equipment itself.

6) The raw materials to be used should meet the required standards that is the active drug substance and excipients should be of good quality.

7) Pre-validation programs should be performed.

8) This step is critical as the critical process variables should be set within their upper and lower critical limits during process operation. This would help in giving good outputs. The underlying meaning is that adjusting method parameters (acceptance criteria) is necessary.

9) SOPs or Standard operating procedures are must for executing the method in routine.

10) The basis for re-validation are meant to be explained.

11) The type and frequency of system suitability tests and/or analytical quality control (AQC) should be routinely checked. If the requirements of the validation protocol are not met with respect to process input and output, the process should be subjected to re-validation following an insight or analysis of data. This should further be followed by a co-ordinated formal discussion by the validation team.

12) Lastly the results are to be tabulated in the validation report.

**VALIDATION SUMMARY REPORTS**

**Validation Summary Reports** provide an overview of the entire validation project. Once the summary report is signed, the validation project is considered to be complete.
When regulatory auditors review validation projects, they typically begin by reviewing the summary report. The document should also contain a formal release statement to allow the system to be used for regulated work. The validation summary report should include:

- A description of the validation project
- All test cases performed, including if those test cases passed without issue
- All deviations reported, including how those deviations were resolved
- Reference to protocol
- The details of material and equipment used
- Evaluation, including comparison with the acceptance criteria and recommendations (including frequency of revalidation/requalification)
- Certification (approval)
- If applicable, preparation of an abbreviated version of the validation report for external use, for example by the regulatory authority
- The validation protocol and report may also include copies of the product stability report or a summary of it, validation documentation on cleaning, and analytical methods.\textsuperscript{[11,12]}

CONCLUSION

The validation summary report brings together all of the documentation collected throughout the whole of the life cycle. It gives a recommendation for management approval when the system is validated. The validation report should document detailed results of the validation effort, including test results. Whenever possible, test results should be expressed in quantified terms rather than stated as “pass/fail.” The report should be reviewed and approved by designated management.\textsuperscript{13}

REFERENCES


For Correspondence:
Kashyap Ankita
Email: ankidiva@gmail.com