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A REVIEW ON PHARMACEUTICAL PROCESS VALIDATION AND ITS SIGNIFICANCE

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ABSTRACT

Quality assurance functions primarily to monitor the fact that the quality function is being performed. Its role in process validation is readily associated with its main functions. Validation has become one of the pharmaceutical industries most recognized subjects. Validation is the art of designing and practicing the designed steps alongside with the documentation. Validation and quality assurance will go hand in hand, ensuring the thorough quality for the products. It analyzes the product complaints to learn how effective its test program has been in preventing rejectable product from reaching the market place. According to GMP validation studies are essential part of GMP these are required to be done as per predefined protocols, the minimum that should be validated include process, testing and cleaning as a result such control procedure stablish to monitor the output and validation of manufacturing processes that may be responsible for variability of drug product. The validation study provide the accuracy, sensitivity, specificity and reproducibility of the test methods employed by the firms, shall be established and documented. Thus validation is an essential part of quality assurance.

KEYWORDS: Quality assurance, GMP, protocols, pharmaceutical validation, pharmaceutical process control.

INTRODUCTION

This principle incorporates the understanding that the following conditions exist: Quality, safety, and efficacy are designed or built into the product. Quality cannot be adequately assured merely by in-process and finished product inspection or testing. Each step of a manufacturing process is controlled to assure that the finished product meets all quality attributes including specifications.[1]

Validation is a process of establishing documented evidence which provide a high degree of assurance that specific process will consistently produce a product meeting its predetermined specification and quality attributes. It is a concept that has evolved in unite states in 1978. The concept of validation has expanded through the years to embrace a wide range of activities from analytical methods.

It is used for the quality control of drug substances and drug products to computerized systems for clinical trials, labelling or process control. It is best viewed as an important and integral part of cGMP.

The basic principles for validation may be stated as follows:

a. Establish that the process equipment has the capability of operating within required parameters.
b. Demonstrate that controlling, monitoring, and measuring equipment and instrumentation are capable of operating within the parameters prescribed for the process equipment.
c. Monitor the validated process during routine operation. As needed, re qualify and recertify the equipment.[2]

Why validation is required?

The pharmaceutical industry uses expensive material, sophisticated facilities and equipments and highly qualified personals.

- Detailed study and controlled of the manufacturing process batch validation is necessary if failure cost is to be reduced and productivity is improved.
- If would not be feasible to use equipment not knowing if it will produce the product we want, not to employ the people with no assurance that they can do or fail to implement process checks or examination to assure that product meet specifications.
- The efficient use of these resources is necessary for the continued success of the industry. The cost of product failure, rejects, reworks, recalls, complaints are the sufficient part of total production cost.
- Assurance of quality, cost reduction.

Importance of validation

a. Increased throughput.
b. More rapid and reliable start up of new equipment.
c. Easier scale- up from development work.
d. More rapid automation.
e. Reduction in utility cost.
f. Help timely corrective action.
g. Assure consistent production performance.
h. Allow parametric release.
i. Ensure achievement of quality goal.

Benefits of Validation[3]

1. Reduction of quality cost

Through proper validation, the cost of the following process can be optimized.

a. Preventive costs are costs incurred in order to prevent failure and reduce appraisal costs.
b. Appraisal costs of inspection, testing and quality evaluation.
c. Internal failure costs.
d. External failure costs that associated with a non conformance condition after the product had left the company's ownership.

2. Process optimization

The optimization of the facility, equipment system and closures etc. results in a product that meets quality requirements at the lower costs. Trained, qualified people are the key elements in process optimization that results in improving efficiency and productivity.

3. Assurance of quality

Validation and process control are the heart of GMPs. Without validated and controlled process it is impossible to achieve quality products. Hence validation is a key element in assuring the quality of the product.

4. Safety

Validation can also result in increased operator safety. Properly calibrated, validated instruments and gauges used to reduce accidents and results in safety.

5. Better customer quality

Through proper validation, market recall is avoided which results in better customer care and quality of the product.

Advantages of Validation

A) Improved ability to set target parameters and control limits for routine production, correlating with validation results.
B) Enhanced ability to statistically evaluate process performance and product variables e.g., individuals, mean, range, control limits.
C) Enhanced data and evaluation capabilities and increased confidence about process reproducibility and product quality.
D) Enhanced reporting capability.
E) Expanded real time monitoring and adjustment of process.[4]
F) Reduced testing in process and in finished goods.
G) More rapid and reliable start-up of new equipments.
H) Easier scale-up form development work.
I) Easier maintenance of equipment.
J) Improved employee awareness of processes.
K) Fewer complaints about process related failure.
L) More rapid and accurate investigations into process deviation.
M) More rapid and reliable start-up of new equipment.[5,6,7]

Elements

1. Design qualification (DQ)

A. The design qualification outline the key features of the system designed to address the user requirements, regulatory compliance and selection rationale of a particular supplier.

B. Caution should be taken when putting together a design qualification since it will have major impact on installation, operation and performance qualification. The more function that are specified in design qualification, the more work have to be included in the Installation, operational and performance qualification processes.[8]

Important DQ consideration include

1. GMP's and regulatory requirements.
2. Performance criteria.
3. Facility air flow, movement flow & pressure regimens.
4. Reliability & efficiency.
5. Commissioning requirements
6. Construct ability & installation of equipment.[3]

2. Installation qualification (IQ)

1. Documentary evidence to prove that the premises supporting utilities and the equipment have been built and installed in compliance with their design specifications.[8]

Important IQ consideration include

1. Installation conditions (wiring, utilities, and functionality)
2. Calibration, Preventive maintenance, cleaning schedules.
3. Safety features.
4. Supplier documentation, prints, drawings and manuals.
5. Software documentation
6. Spare parts list.[3]

3. Operational qualification (OQ)

1. Operational qualification is a series of tests that measures the performance capability of the equipment. Operational qualification focuses on the equipment, rather than demonstrating performance capabilities relating to producing a particular product.[8]

OQ considerations include

1. Process control limits (time, temperature, pressure, line speed, and setup conditions).
2. Software parameters.
3. Raw material specification.
4. Process operating procedures
5. Material handling requirements.
6. Process change control
7. Training
8. Short term stability and capability of the process.[3]

4. Performance qualification (PQ)

1. It is defined as the process to verify that the system is repeatable and consistently producing a quality product or in other words the process to demonstrate that the instrument can fulfill requirement outlined in the design qualification.[8]

PQ consideration include:

1. Actual product and process parameters and procedures established in OQ.
2. Acceptability of the product.
3. Assurance of process capability as established in OQ.
4. Process repeatability, long term process stability.[3]

Responsibilities[9]

Department	Responsibility
Manager production	Responsible for manufacturing of batches and review of protocol and report.
Manager QC	Responsible for analysis of samples collected.
Manager maintenance	Providing utilities and engineering support.
Executive QC	Responsible for samples collection and submission to QC.
Manager QA	Responsible for protocol authorisation and preparation of summary report.
Executive production	Responsible for preparation of protocol and manufacturing of validation batches.

Phases in Process Validation

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

Phase 1 Pre validation phase or the qualification phase

It covers all activities relating to product research and development, formulations, pilot batch studies, scale up studies, transfer of technology 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, process capability.[10]

Phase 2 Process validation phase

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.

1. That all systems subsystem or unit operations of a manufacturing process perform as intended.
2. That all critical parameters operate with in their assigned control limit.
3. That such studies and trials, which form the basis of process capability design and testing, are verifiable and certifiable through proper documentation.

Phase 3 Validation Maintenance phase

This phase requires frequent review of all process related documents, including validation audit report to assure that there have been no changes, deviations, failures, modifications to the production process and that all SOP have been followed, including change control procedure. At this stage the validation team also assures that there have been no changes, deviations that should have resulted in requalification and revalidation.[11]

A careful design and validation of systems and process controls can establish a high degree of confidence that all lots or batches produced will meet their intended specifications. It is assumed that throughout manufacturing and control, operations are conducted in accordance with the principle of good manufacturing practice (GMP) both in general and in specific reference to sterile product manufacture. The validation steps recommended in GMP guidelines can be summarized as follows:[12]

1. 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.
2. 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.
3. All data generated during the course of studies should be formally reviewed and certified as evaluated against pre-determined criteria.
4. Suitable testing facilities, equipment, instruments and methodology should be available.
5. 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 inprocess equipment should be properly installed, qualified and maintained.

6. When appropriate attention has been paid to the above, the process, if aseptic, may be validated by means of "process simulation" studies.
7. The process should be revalidated at intervals and Comprehensive documentation should be available to define support and record the overall validation process.

Types of Validation

1. Prospective Validation

a. Prospective validation is usually undertaken when ever a new formula, process and/or facility need to be validated before routine pharmaceutical production starts. It is also usually employed when sufficient historical data is either unavailable or insufficient and in process and final product testing is inadequate to ensure high degree of confidence for product quality characteristics and reproducibility.[11]
b. In prospective validation, the validation protocol is executed before the process is put into commercial use. During the product development phase, production process should be categorized into individual steps. Each step should be evaluated on the basis of experience or theoretical consideration to determine the critical parameters that may affect the quality of the finished product.
c. Each experiment should be planned and documented fully in an authorized protocol. All equipments, production environment and the analytical testing methods to be used should have been fully validated.
d. Master batch documents can be prepared only after the critical parameters of the process have been identified and machine setting, component . specification and environmental condition have been determined.
e. Using this defined process a series of batches should be produced. In theory, the number of process runs carried out and observations made should be sufficient to allow the normal extent of variation and trends to be established to provide sufficient data for evaluation.
f. It is generally considered acceptable that three consecutive batches/runs with in the finally agreed parameters, giving product of the desired quality would constitute a proper validation of the Process.
g. During the processing of the validation batches extensive sampling and testing should be prepared on the product at various stages and should be documented comprehensively. Detailed testing should also be done on the final product in its package.
h. Upon completion of the review, recommendations should be made on the extent of monitoring and the in- process controls necessary for routine production. These should be incorporated into the batch manufacturing and packaging record or into appropriate SOP. Limits frequencies and actions to be taken in the event of the limits being Exceeded should be specified.

2. Concurrent Validation

It is similar to the prospective, except the operating firm will sell the product during the qualification runs to the public at its market price. This validation involves in process monitoring of critical processing steps and product testing. This helps to generate and documented evidence to show that the production process is in state of control.[13] Current validation is appropriate when.

a. It is not possible to complete a validation program before routine manufacturing starts and it is known in advance that finished product will be for sale. E.g. During transference of process to contract manufacturer.
b. It is more appropriate to validate process during routine production due to well understanding of process. E.g. On change in tablet shape or strength.
c. Extensive testing and monitoring ensures the desired quality characteristics of product with high degree of confidence.[11]

3. Retrospective Validation

Retrospective validation is the validation of a process based on accumulated historical production, testing, control and other information for a product already in production and distribution. This type of validation make use of historical data and information which may be found in batch record, production log books, lot records, controls charts, test and inspection results, customer complaints or lack of complaints field, failure report, service report and audit report.[14]

Further, large historical data set available may provide higher confidence and better picture than data generated from few trials runs in prospective validation. This type of validation is acceptable only for well established processes in which critical quality attributes and critical process parameters are identified and documented. Besides that appropriate in process specification and control should be identified and documented and there should not be excessive process/product failure other than operator error or equipment failure unrelated to equipment suitability. The number of batches to review will depend on the process, but in general, data from 10 to 30 consecutive batches should be examined to assess process consistency. The review should include any batches that failed to meet specification. However, any discrepancies or failure in the historical data may be excluded provided there is sufficient evidence that the failure was caused by isolated occurrences.

E.g. employee error, and were not result of process variations.

4. Revalidation

1. Revalidation is the repetition of the validation process or a specific part of it. It is either performed periodically to ascertain the process or to incorporate changes in the procedure.[14]

2. Documentation requirements will be the same as for the initial validation of the process. Revalidation becomes necessary in certain situations.

a. Changes in raw materials (Physical properties such as density, viscosity, particle size distribution and moisture etc. that may affect the process or product).
b. Changes in the source of active raw material manufacturer.
c. Changes in packaging material (Primary container/ closure system).
d. Changes in the process (e.g. mixing time, drying and temperature batch size).
e. Changes in the plant/ facility.

A decision not to perform revalidation studies must be fully justified and documented.[15]

5. Change control

Process validation of a solid dosage form should include an SOP to reassess a process whenever ther are significant changes in the process, equipment, facilities, reactants, process materials, systems and so on that may affect the critical quality attributes and specification of the solid dosage forms. All changes must be formally requested, documented and proposed changes were scientifically assessed and, depending on the changes, the need of revalidation will be determined.[16]

Validation Protocol[17,18]

Detailed protocol for performing validations are essential to ensure that the process is adequately validated. Process validation protocols should include the following elements:

- Objectives, scope of coverage of the validation study.
- Validation team membership, their qualifications and responsibilities.
- Type of validation: prospective, concurrent, retrospective, re-validation.
- Number and selection of batches to be on the validation study.
- A list of all equipment to be used; their normal and worst case operating parameters.
- Outcome of IQ, OQ for critical equipment.
- Requirements for calibration of all measuring devices.
- Critical process parameters and their respective tolerances.
- Process variables and attributes with probable risk and prevention shall be captured.
- Description of the processing steps: copy of the master documents for the product.
- Sampling points, stages of sampling, methods of sampling, sampling plans.
- Statistical tools to be used in the analysis of data.
- Training requirements for the processing operators.
- Validated test methods to be used in in process testing and for the finished product.
- Specifications for raw and packaging materials and test methods.
- Forms and charts to be used for documenting results.
- Format for presentation of results, documenting conclusions and for approval of study results.

Validation Life Cycle

Validation is a continuing and evolving process. The validation process which extends from very basic to very broad theoretical and methodical investigation of how the system and processes perform. Its scope encompasses documentation revision control, training and maintenance of the system and process. Evidence of validation should be seen at the corporate level and be reflected in the management structure.

Validation Master Plan

A validation master plan is a document that summarizes the company's overall philosophy, intentions and approaches to be used for establishing performance adequacy. The Validation Master Plan should be agreed upon by management. Validation in general requires meticulous preparation and careful planning of the various steps in the process. In addition, all work should be carried out in a structured way according to formally authorized standard operating procedures. All observations must be documented and where possible must be recorded as actual numerical results. The validation master plan should provide an overview of the entire validation operation, its organizational structure, its content and planning. The main elements of it being the list inventory of the items to be validated and the planning schedule. All validation activities relating to critical technical operations, relevant to product and process controls within a firm should be included in the validation master plan. It should comprise all prospective, concurrent and retrospective validations as well as re-validation. The Validation Master Plan should be a summary document and should therefore be brief, concise and clear. It should not repeat information documented elsewhere but should refer to existing documents such as policy documents, SOP's and Validation protocols and reports.

Approaches to Process Validation

Process validation involves a series of activities taking place over the life cycle of the product and process.

Stage 1: Process design

Process design is the activity of defining the commercial manufacturing process that will be reflected in planned master production and control records. The goal of this stage is to design a process suitable for routine commercial that can consistently deliver a product that meets its quality attributes.

a. Building and Capturing Process Knowledge and Under standing

Generally, early process design experiments do not need to be performed under the cGMP conditions required for

drugs intended for commercial distribution that are manufactured during stage 2 (Process qualification) and Stage 3 (Continued process verification). They should however, be documented in accordance with sound scientific methods and principles, including good documentation practices .Decision and justification of the controls should be identified and documented and internally reviewed to verify and preserve their value for appropriate use or adaptation later in the lifecycle of the process and product. Product development activities provide key inputs to the process design stage, such as the intended dosage forms, the quality attributes, and a general manufacturing pathways. And the process information available from product development activities can be leveraged in the process design stage. And the functionality and limitations of commercial manufacturing equipment should be considered in the process design, as well as predicted contributions to variability posed by different components lots, production operators, environmental conditions, and measurement systems in the production setting. And however the full spectrum of input variability which is mandatory for commercial production is not generally known at this stage. Design of experiment studies can provides an appropriate means to develop process knowledge by revealing relationship, including multivariate interactions, between the variables inputs (e.g. component characteristics or process parameters) and the resulting outputs (e.g. in-process material, intermediates, or the final product). Risk analysis tools are also used to screen potential variables for design of experiment studies to minimize the total number of experiments conducted while maximizing knowledge gained.

b. Establishing a strategy for process control

Process knowledge and understanding is the basis for establishing an approach to process control for each unit operation and the process overall. Strategies for process control can be designed to reduce input variation, adjust for input variation during manufacturing (and so reduce its impact on the output), or combine both approaches.

Stage 2 Process Qualification

During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.

During the process qualification stage of process validation, the process design is evaluated to determine if it is capable of reproducible commercial manufacture.

a. Design of a facility and qualification of utilities and equipment

Qualification of utilities and equipment generally includes the following activities:

1. Selecting utilities and equipment construction materials, operating principles, and performance characteristics based on their appropriate uses.
2. Verifying that utility systems and equipment are built and installed in compliance with the design specification.
3. Verifying that utility systems and equipment operate in accordance with the process requirements in all anticipated operating ranges. This should include challenging the equipment or system functions while under load comparable to that expected during routine production. It should also include the performance of interventions, stoppage, and start-up as is expected during routine production.

Qualification of utilities and equipment should be covered under individual plans or as part of an overall project plan. And the plan should consider the requirement of use and it should incorporate risk management and prioritize certain activities and to identify a level of effort in both the performance and documentation of qualification activities. The plan should identify the following items:

a. The studies or tests to use.
b. The criteria appropriate to assess outcomes.
c. The timing of qualification activities.
d. The responsibilities of relevant departments and the quality unit.
e. The procedures for documenting and approving the qualification.
f. The project plan should also include the firm's requirements for the evaluation of changes.

b. Process Performance Qualification

The process performance qualification is the second element of stage 2, process qualification. The PPQ combines the actual facility, utilities, equipment (each now qualified), and the trained personnel with respect to commercial manufacturing process, control procedures, and components to produce commercial batches. A successful PPQ will confirm the process design and demonstrate that the commercial manufacturing process performs as expected.

Success at this stage triggers an important milestone in the product life cycle. A manufacturer must successfully complete PPQ before commencing commercial distribution of the drug product. The decision to begin commercial distribution should be supported by data from commercial scale batches. The cumulative data from all relevant studies (e.g.designed experiments; laboratory, pilot, and commercial batches) should be used to establish the manufacturing conditions in the PPQ. To understand the commercial process sufficiently, the manufacturer will need to consider the effects of scale. In most cases, PPQ will have a higher level of sampling, additional testing, and greater scrutiny of process performance when compared to routine commercial production.

The level of monitoring and testing should be sufficient to confirm uniform product quality throughout the batch.

The increased level of scrutiny, testing, and sampling should be continued throughout the process verification stage as appropriate, to establish levels and frequency of routine sampling and monitoring for the particular product and process.

c. PPQ Protocol

A written protocol that specifies the manufacturing conditions, controls, testing, and expected outcomes is essential for this stage of process validation.

1. The manufacturing conditions, including operaating parameters, processing limits, and component (raw material) inputs.
2. The data to be collected and when and how it will be evaluated.
3. Tests to be performed and acceptance criteria for each significant processing steps.
4. The sampling plan, including sampling points, number of samples, and the frequency of sampling for each unit operation and attributes. The number of samples should be adequate to provide sufficient statistical confidence of quality both within a batch and between batches. Sampling during this stage should be more extensive than is typical during routine production
5. Design of facilities and the qualification of utilities and equipment, personnel training and qualification, and verification of material sources.
6. Status of the validation of analytical methods used in measuring the process, in-process materials, and the product.

d. PPQ Protocol Execution and Report

Execution of the PPQ protocol should not begin until it is reviewed and approved by all departments, including the quality unit. Any departures from the protocol must be made according to established procedure or provisions in the protocol. Such departures must be justified and approved by all departments including quality unit before implementation.

This report should include

1. Discuss and cross-reference all aspects of the protocol.
2. Summarize data collected and analyze the data, as specified by the protocol.
3. Evaluate any unexpected observations and additional data not specified in the protocol.
4. Summarize and discuss all manufacturing non conformances such as deviations, aberrant test results, or other information that has bearing on the validity of the process.

Stage 3: Continued Process Verification

The goal of the third validation stage is continual assurance that the process remains in a state of control (the validation state) during commercial manufacture. 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/or 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 source.[20]

CONCLUSION

From the study it can be stated that pharmaceutical Process validation is the most important and recognized parameters of cGMP. The cGMP regulation require that manufacturing processes be designed and controlled to assure that in-process materials and finished product meet predetermined quality requirements and do so consistently and reliably. The product should be designed robustly enough to withstand variations in the manufacturing process and the manufacturing process should be capable and stable to assure continued safe products that perform adequately. Process validation involves a series of activities taking place over the lifecycle of the product and process.

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