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# Review Article on Process Validation and Its Types and Theoretical Approaches

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**ABSTRACT**

Quality assurance functions primarily to watch the very fact that the standard function is being performed. Its role in process validation is quickly associated with its main functions. It performs the tests that demonstrate the product's content uniformity. It's going to also perform the statistical evaluation of the test results to point out that the method is reproducible. Quality assurance initiates the action to eliminate nonconforming product. It implements the inspection criteria and sets the specification for the merchandise approval or rejection. It analyses the merchandise complaints to find out how effective its test program has preventing rejectable product from arrived the market places.

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## INTRODUCTION:

The quality system regulation defines process validation as 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. Process validation may be a key element in assuring that these principles and goals are met. The essential principles for validation could also be stated as follows:

1. Establish that the method equipment has the capability of operating within required parameters.

2. Demonstrate that controlling, monitoring, and measuring equipment and instrumentation are capable of operating within the parameters prescribed for the method equipment.

3. Monitor the validated process during routine operation. As needed, requalify and recertify the equipment. [1]

## IMPORTANCE OF VALIDATION

1. Assurance of quality.

2. Time bound.

3. Process optimization.

4. Reduction of quality cost.

5. Reduction in rejections.

6. Increased output.

7. Avoiding of capital expenditures

8. Fewer complaints about process related failures.

9. Reduced testing in process and in finished goods.

10. Improved employee awareness of processes.[2]

## NEED FOR VALIDATION

1. It might not be feasible to use equipment not knowing if it'll produce the merchandise we would like, 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 specification.

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

3. The efficient use of those resources is important for the continued success of the industry. the value of product failure rejects, reworks, recalls, complaints are sufficient a part of total production cost.

4. Detailed study and control of the manufacturing process batch validation is important if failure cost is to be reduced and productivity is improved. There are three reasons by pharmaceutical industry are concerned that their processes perform consistently expected that's, that are validated.

5. Assurance of quality, cost reduction. [3, 4, 5]

## BENEFITS OF VALIDATION

### 1. Reduction of quality cost

Through proper validation, the values of the subsequent process are often optimized.

a) Preventive costs are costs incurred so as 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 related to a non-conformance condition after the merchandise had left the company's ownership.

### 2. Process optimization

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

**3. Assurance of quality**

Validation and process control are the guts of GMPs. Without validated and controlled process it's impossible to realize quality products. Hence validation may be a key element in assuring the standard of the product.

**4. Safety**

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

**5. Better customer quality**

Through proper validation, market recall is avoided which results in better customer care and quality of the product. [6]

**ADVANTAGES OF VALIDATION:**

1. Extensive reporting capability.

2. Improved ability to set target parameters and relevant limits for regular production with validation results.

3. Advanced data and evaluation capabilities and increase confidence about the process fertility and product quality.

4. Enhanced ability to statistically evaluate the process performance and product variants e.g.

Individuals, averages, range, control limits. [7]

| **Department** | **Responsibility** |
|---|---|
| Manager Production | Responsible for manufacturing of batches and review of protocol and report. |
| Manager QC | Responsible for analysis of samples collected |
| Executive QC | Responsible for samples collection and submission to QC |
| Manager Maintenance | Providing utilities and engineering support |
| Executive Production | Responsible for preparation of protocol and manufacturing of validation batches |
| Manager QA | Responsible for protocol authorization and preparation of summary report. |

**ELEMENTS OF VALIDATION: -**

**1. Design Qualification (DQ)**

1. Design qualification outlines its main characteristics the system is designed to address the user requirements, regulatory compliance and the logic of choosing a particular supplier.

2. Care should be taken when keeping together design qualification, as it will be the main impact on installation, operation and performance qualification. More work that further, the design is specified in the qualification the task must be included in the installation, operational and performance qualification processes. [8]

Important DQ is included in the consideration.

1. GMP and regulatory requirements.

2. Criteria of operation.

3. Facilitate airflow, movement flow and pressure Rule.

4. Reliability and efficiency

5. Turning requirements

6. Ability and installation of equipment. [6]

**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 [6].

**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 [6]

**4. Performance Qualification (PQ)**

1. It is defined as the process of testing a system produces repetitive and consistent quality the process of displaying a product or in other words that the tool may meet the specified requirement design qualification. [8]

PQ consideration included

1. Actual product and process parameters and procedures installed in OQ.

2. Acceptance of the product

3. Assurance of processing capacity as per establishment OQ. Process repetition, long-term process stability. [6]

**TYPES OF VALIDATION: -**

**1. Prospective Validation**

a. Prospective validation is usually carried out when always need a new formula, process and/or feature accredited before regular Production begins. It is also usually functional when there is enough historical information unavailable or inadequate and in process and final product testing is insufficient to ensure high degree of confidence for product quality.

b. In prospective validation, validation is the protocol the process is run before it is placed commercial use. During product development phase, the manufacturing process should be classified in individual measures. Every step should be evaluation on the basis of experience or theory consideration to determine critical parameters which can affect the quality of the finished product.

c. Every experiment should have a plan and full documentation in the authorized protocol. All equipment, production environment and there should be analytical testing methods full recognition has been given.

d. Only master batch documents can be prepared after the critical parameters of the process identified and machine setting, component there is specification and environmental conditions has been determined.

e. Series of chess using this defined procedure should be produced. In theory, numbers processes are carried out and observations are made should be sufficient to allow a normal range of to establish to provide diversity and trends adequate data for evaluation.

f. Three that it is generally considered acceptable finally with continuous bash chess/run agreed parameters, giving the desired product quality forms the right belief process.

g. Recognition during the process of chess there should be extensive sampling and testing prepared and on production, at different stages extensive documentation should. In detail should also be tested on the final product in its package.

h. Following the conclusion of the review, recommendations should be done on the extent of monitoring and restrictions required for regularity in the process product. This should be included in batch production and packaging records or in proper S.O.P. limits frequency and actions will be taken in case of limitation exceeded should be specified. [9]

**2. Concurrent Validation.**

It is the same as the future, except for active parenting the firm will sell the product during the qualification run people at its market price. This belief the process of critical processing involves observation measures and product testing. This helps generate and documentation to show evidence that the product the process is under control. [7]

When concurrent validation is appropriate:

a. It is not possible to complete the validation program and that's before regular production starts it is known in advance that the finished product will be sale. E.g., During the transfer of the process contract manufacturer;

b. It is more appropriate to recognize during the process regular production due to better understanding process. E.g., On a change in the shape of the tablet or strength.

c. Ensures extensive testing and monitoring product with desired quality characteristics high degree of confidence. [8]

**3. Retrospective Validation**

Retrospective validation is the validity of the process accumulated historical production, testing, control and other information for the product already production and distribution. This kind of belief can use historical data and information batch records, product log book, lots found records, control charts, test and inspection results, lack of customer complaints or grievances, failure report, service report and audit report. [1] Next, available large historical data may provide more confidence and a better picture than information probably out of a few tests recognition. This kind of belief is only acceptable well established processes of critical quality there are features and complex process parameters identify and documentation. Plus it's worth it the specificity and control of the process should be identified and documentation; and should not be excessive process/product failure except for / partner error equipment failure is not related to equipment suitability. The number of investigations to be reviewed will depend data on the process, but in general, 10 to 30 should be checked to evaluate the continuous batch process compatibility. The review should include anyone bash chess which failed to meet the specification. However, any there may be discrepancies or failures in disk or historical data exclude if there is sufficient evidence that the failure was caused by different events.

E.g., Employee error, and not the result of the process variations.

**4. Revalidation**

1. Revalidation is that the repetition of the validation process or a selected a part of it. It's either performed periodically to determine the method or to incorporate changes within the procedure. [8] Documentation requirements are going to be equivalent as for the initial validation of the method. Revalidation becomes necessary in certain situations.

a. Changes in raw materials (Physical properties such as density, viscosity, particle size distribution and moisture etc., which will affect the process or product).

b. Changes within the source of active staple manufacturer.

c. Changes in packaging material (Primarycontainer/ closure system).

d. Changes within the process (e.g. mixing time, drying temperature and batch size).

e. Changes within the plant/ facility.

A decision to not perform revalidation studies must befully justified and documented. [2]

**REGULATORY BASIS FOR PROCESS VALIDATION**

Once the concept of having the ability to predict process performance to satisfy user requirements evolved, FDA regulatory officials established that there was a legal basis for requiring process validation. The last word legal authority is Section 501 (a)(2)(B) of FD&C Act, which states that a drug is deemed to be adulterated if the methods utilized in, or the facilities or controls used for, its manufacture, processing, packing, or holding donot conform to or weren't operated or administered in conformity with cGMP. Assurance must tend that the drug would meet the wants of the act as to safety and would have the identity and strength and meet the standard and purity characteristics that it purported or was represented to possess. That section of the act sets the premise for process validation requirements for both finished pharmaceuticals and active pharmaceutical ingredients because active pharmaceutical ingredients also are deemed to be drug under the act. The cGMP regulations for finished pharmaceuticals, 21CFR 210 and 211, were promulgated to enforce the requirements of the act. Although these regulations do not include a definition for process validation, the requirement is inherent the language of 21 CFR211.100[5], which states: “There shall be written procedures for production and process control designed to assure that

the drug products have the identity, strength, quality, and purity they purports or are represented to possess."[11, 12, 13]

**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**

↓

***a. Building and Capturing Process Knowledge***

***and Under standing***

***b. Establishing a strategy for process control***

**Stage 2: Process Qualification**

↓

***a. Design of a facility and qualification of***

***utilities and equipment***

***b. Process Performance Qualification***

***c. PPQ Protocol***

***d. PPQ Protocol Execution and Report***

**Stage 3: Continued Process Verification**

**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, scaleup 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. [14]

**Phase 2: Process validation phase**

This phase is meant to verify that each one established limits of the critical process parameters are valid and that satisfactory products are often produced even under the worst-case condition. It represents the particular studies or trials conducted to show.

1. That each one system subsystem or unit operations of a manufacturing process perform as intended.

2. That each one critical parameter operates with in their assigned control limit.

3. That such studies and trials, which form the idea 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 back to assure that there are no changes, deviations, failures, modifications to the assembly process and that all SOP are followed, including change control procedure. At this stage the validation team also assures that there are no changes, deviations that ought to have resulted in requalification and revalidation. [8]

**VALIDATION MASTER PLAN: -**

A validation plan may be a document that summarizes the company's overall philosophy, intentions and approaches to be used for establishing performance adequacy. The validation plan should be prescribed by management. Validation ingeneral requires meticulous preparation and careful planning of the varied steps within the process. In addition, all work should be administered during a structured way consistent with formally authorized standard operating procedures. All observations must be documented and where possible must be recorded as actual numerical results. The validation plan should provide a summary of the whole validation operation, its organizational structure, its content and planning. The validation plan should be a summary document and will therefore be brief, concise and clear. It shouldn't repeat information document elsewhere but should ask existing documents like policy documents, SOP's and validation protocols and reports. [9]

**PROCESS VALIDATION PROTOCOL:**

After preparing validation plan, subsequent step is to organize validation protocol. There is a minimum of the subsequent contents during a validation protocol.

a. Purpose and scope of validation

b. Responsibilities of every organizational units involved in validation

c. Sort of validation to be conducted

d. Number of process validation runs

e. Quality of materials utilized in the method

f. Description of process

g. All major equipment to be used, their type/design and their installation and operational qualification.

h. Critical process parameters and operating ranges

i. Sampling plans

j. Specification and test data to be collected.

k. Acceptance criteria to incorporate that validation has been successful measures to be taken within the event of process validation failure. [15]

**VALIDATION REPORT: -**

A composed report ought to be accessible after consummation of the approval. Whenever found satisfactory, it ought to be endorsed and approved (marked and dated). The report ought to incorporate in any event the accompanying.

1. Title and objective of study.

2. Reference to protocol.

3. Subtleties of material.

4. Gear.

5. Program and cycles utilized.

6. Subtleties of procedures and test techniques.

7. Results (contrasted and acknowledgment measures).

8. Suggestions on the breaking point and rules to be applied on future premise. [3]

**CONCLUSION:**

This article generally outlines the principles and approaches that considers appropriate elements of process validation for the manufacture of medicine, including active pharmaceutical ingredients (APIs or drug substances), collectively mentioned as drugs or products. And it incorporates principles and approaches that each one manufacturer can use to validate manufacturing process. From this study, it is often stated that process validation may a major requirement of cGMP regulation for finished pharmaceutical basis for releasing or rejecting product. It'll perform programs to work out whether or not the new information indicates the changes in product or process has occurred. Finally, it performs the analytical tests that are wont to generate the validation data required by the protocol.

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