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INDUSTRIAL PROCESS VALIDATION OF TABLETS: A REVIEW

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ABSTRACT

The main purpose behind this review article is to present an overview and an idea behind the industrial process validation. Process validation is done in order to know whether the process is producing the final product with its predetermined specification and acceptance criteria. Traditional process validation's main objective continues to be the generation of a process which yields a product which meets pre-determined quality criteria. Quality is always an imperative prerequisite when we consider any product. Therefore, drugs must be manufactured to the highest quality levels. End-product testing by itself does not guarantee the quality of the product. Quality assurance techniques must be used to build the quality into the product at every step and not just tested for at the end. In pharmaceutical industry, Process Validation performs this task to build the quality into the product because according to ISO 9000:2000, it had proven to be an important tool for quality management of pharmaceuticals.

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INTRODUCTION

The principle objective of dosage form design is to achieve a predictive therapeutic response to a drug when they are produced in a large scale in an industry with reproducible product quality. To ensure product quality, numerous features are required such as physical and chemical stability, addition of stabilizers and other parameters are investigated to see whether they have influence on process parameters or not.

The New drug development is a lengthy process involving drug discovery, laboratory testing, animal studies, clinical trials and regulatory registration. To increase the efficacy and safety of the drug product after approval, many regulatory agencies such as the United States Food and Drug Administration (FDA) also require that the drug product be tested for its identity, strength, quality, purity and stability before it can be released for use. For this reason, pharmaceutical validation and

process controls are important in spite of the problems that may be encountered.[1]

General Concept: - The concept of Validation was first proposed by two Food & Drug Administration Official's, Ted Byers and Bud Loftus in the mid 1970's in order to improve the quality of the Pharmaceuticals[2]. Assurance of drug product is derived from careful attention to number of factors including selection of quality parts and materials, adequate product and product design, control of the process, in process and end- process testing. Due to the complexicity of the today's medical products, routine end product testing is not only sufficient to assure the quality of the end product testing. Some end product tests have limited sensitivity. So, in order to have adequate process testing at each stage, concept of process Validation have been occurred.

Necessity of Process Validation

Process Validation involves the systematic study of systems, facilities and processes aimed at determining whether they perform their intended functions adequately and consistently as specified. A validated process is one which has been demonstrated to provide a high degree of assurance that uniform batches will be produced that meet the required specifications and has therefore been formally approved. Validation in itself does not improve processes but confirms that the processes have been properly developed and are under control.. Adequate validation is benefial to the manufacturer in many ways[5].

1. It deepens the understanding of processes; decreases the risk of preventing problems and thus assures the smooth running of the process.
2. It decreases the risk of defect costs.
3. It decreases the risk of regulatory noncompliance.
4. A fully validated process may require less in-process controls and end product testing.

Validation should thus be considered in the following situations:

1. Totally new process;
2. New equipment;
3. Process and equipment which have been altered to suit changing priorities;
4. Process where the end-product test is poor and an unreliable indicator of product quality[6].

Responsible authorities for Process Validation: -

The validation working party is convened to provide progress, community and ultimately approve the entire effort including all of the documentation generated. The working committee should include the following members of the company who should have the good insight on the Companies Working.

1. Quality Assurance Head
2. Engineering Head
3. Production Head
4. Validation Specialist all discipline
5. Validation Manager. (Table 1)

General View of Process Validation.

Elements of Validation: - (Figure 1)

1. Planning: - Before the production starts, generally planning has to be done in accordance to the suitability of the process that has to be performed.

2. Installation Qualification: - It is documented evidence that all the aspects of the facilities, utility or equipment that can affect the product quality. A quality adheres to the approved specification and is correctly installed.

Important Installation Qualifications are as follows: -

- Installation Condition (Wiring, utilities and functionalities)
- Calibration, Maintaince, preventive cleaning schedule.
- Safety Features.
- Supplier documentation, drawing, prints and manuals.
- Software documentation.
- Spare part list.
- Environmental condition (Temperature, humidity and other condition).
- Equipment design features.

3. **Operational qualification: -** It is a documented verification that all the aspects of the utility, facility or equipment that can affect product quality operate to intend throughout all anticipated range.
Operational qualification includes:

- Process controls limit.
- Software parameters
- Raw material specification.
- Process operating procedure.
- Material handling requirements.
- Process change control.
- Short term stability and capability of the process.
- Training.
- Fault tree analysis.
- Potential free modes, action level and worst case condition.

4. Process Qualification: - It is a documented verification that all the aspects of the utility, facility or equipment perform as intended in the predetermined acceptance criteria.
Process qualification consideration include: -

- Actual product and process parameters.
- Acceptability of the product.
- Assurance of process capability as established in operational qualification.
- Process repeatability and stability.

5. Process Monitoring: - During this stage, process monitoring is done whether all the condition are predetermined acceptance criteria of equipment and product or not.

6. Revalidation: - Revalidation is done whether there occur any change in –

- Equipment.
- Process
- Any other chemical parameters.

Types of Validation: -

a) Prospective validation
b) Concurrent validation
c) Retrospective validation
d) Revalidation
e) Analytical Validation
f) Equipment Validation

a) **Prospective Validation**

Prospective validation is done before product launching in market. This type of validation is used for introduction of new drug products and their manufacturing processes. Most validation efforts require some degree of prospective experimentation to generate validation support data. This is normally carried out in connection with introduction of new drug products and their manufacturing processes on three consecutive production size batches.[7]

The objective of prospective validation is to prove that the process will work in accordance with a validation master plan prepared for pilot-product (100X sizes) trials. In practice, usually two or three pilot production (100X sizes) batches are prepared for validation purposes[8].

b) **Concurrent Validation**

It is in-process monitoring of critical processing steps and end –product testing of current production which provides documented evidence to show that the manufacturing process is in a state of control. The concurrent validation is conducted to assure that a process does what it is supposed to do on the basis of information generated during actual implementation of the process.

c) **Retrospective Validation**

It is defined as the establishment of documented evidence that a system does what it purports to do on review and analysis of historical information. This type of validation process is done for a product already in distribution. When the system or processes are in place that have not been previously validated but are functionally well and consistently producing good products which are already in production, validation of such facilities or process is called retrospective validation and is achieved by review of historical manufacturing and testing data[9].

d) **Revalidation:**

Revalidation provides the evidence that changes in a process or the process or the process environment that are introduced do not adversely affect process characteristics and product quality. In revalidation facilities, systems, equipments and processes, including cleaning, are periodically evaluated to confirm that they remain valid. Revalidation becomes necessary in situations. Some of the changes that require revalidation are as follows:

1. Change in raw materials (physical properties such as density, viscosity, particle size distribution and moisture, etc. that may affect the process or product).
2. Changes in the source of active raw material manufacturer.
3. Changes in packaging material
4. Changes in process (e.g mixing time, drying temperature and batch size).
5. Change in plant or facility[10].

Process Validation: -

Process validation is" A documented program which provide a high degree of assurance that a process will continue to produce a product with its predetermined specification and standards". Process validation is called in several trouble shooting and in case of several product recalls[11].

Phases in Process Validation:

Phase 1: This is the pre- validation qualification phase which covers all activities relating to product research and development, formulation pilot batch studies, scale-up studies, establishing stability conditions and storage, and handling of in- process and finished dosage forms, equipment qualification, installation qualification master production document, operational qualification and process capacity.

Phase 2: This is the process validation phase. It is designed to verify that all established limits of the critical process parameter are valid and that satisfactory products can be produced even under the worst conditions.

Phase3: This is known as validation maintenance phase, it requires frequent review of all process related documents, including validation of audit reports, to assure that there have been no changes, deviations and modifications to production process and that all standards crepitating (SOPs),including change control procedures have been followed. At this stage the validation team comprising of individual representing all major departments also assures that there have been no changes/deviations that should have resulted in requalification and revalidation. A careful design and validation of system and process control 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 principles of good manufacturing practices (GMP) both in general and in specific reference to sterile product manufacture[12].

HOW VALIDATION IS DONE?

The basic principle is characterized by harmony between the results obtained and requirements, which includes/supports.

- Specified requirements and objectives
- Available means
- Choices which are justified in relation to objectives
- Each stage should begin when the previous stage is over.

Certain dispositions have to be taken into account as to

- How restrictions should be defined?
- How norms should be dealt with
- How modifications should be dealt with?

Controlling the evolution will involve

- Setting data for decision making
- Evaluation before decision making
- Justifying the decision
- Follow-up

The following scheme may be suggested

- Aim versus objective

- Process as a whole and flow diagram
- Challenging the critical process variables
- Validation protocol
- Protocol versus report: procedures, sampling, testing, reporting and results.
- Evaluation and recommendations including frequency for re validation.

Validation Master Plan: -

The Validation Master Plan is a document that describes how and when the validation program will be executed in a facility. Even though it is not mandatory, it is the document that outlines the principles involved in the qualification of a facility, defines the areas and systems to be validated and provides a written program for achieving and maintaining a qualified facility with validated processes. It is the foundation for the validation program and should include process validation, facility and utility qualification and validation, equipment qualification, cleaning and computer validation. The regulations also set out an expectation that the different parts of the production process are well defined and controlled, such that the results of that production will not substantially change over time

VALIDATION PROTOCOLS

Protocols should specify the following in detail

- General information
- Objective
- Background/revalidation
- Summary of development and technical transfer (form R&D or another site activity to justify in process testing and controls: any previous validations. Before formal cleaning validation programs were instituted, visual inspection was the primary means of determining equipment cleanliness.
- List of equipments and their qualification status
- Facilities qualification
- Process flow chart
- Manufacturing procedure narrative
- List of critical processing parameters and critical excipients
- Sampling, test and specification
- Acceptance criteria[14]

STRATEGY FOR VALIDATION OF METHODS

The validity of a specific method should be demonstrated in laboratory experiments using samples or standards that are similar to the unknown samples analyzed in the routine. The preparation and execution should follow a validation protocol preferably written in a step-by-step instruction format as follows.

- Develop a validation protocol or operating procedure for the validation
- Define the application purpose and scope of the method;
- Define the performance parameters and acceptance criteria
- Define validation experiments
- Verify relevant performance characteristics of the equipment
- Select quality materials, e.g. standards and reagents;
- Perform pre-validation experiments;
- Adjust method parameters and/or acceptance criteria, if necessary;
- Perform full internal (and external) validation experiments;
- Develop SOPs, for executing the method routinely;
- Define criteria for revalidation
- Define type and frequency of system suitability tests and/or analytical quality control (AQC) checks for the routine; and
- ·Document validation experiments and results in the validation report.

CRITICAL FACTORS AND SAMPLE THIEF

Critical factors which affect conducting effective process validation

- The quality system (infrastructure) should support the validation effort by way of document control, calibration, preventive maintenance, etc.
- All the critical points of the process should be clearly identified

- The process should run using the extremes of the system at the critical points (worst case).
- Adequate run (data) are required to provide statistical support to demonstrate product consistency.
- The execution of the protocol should follow the requirements of the validation document, where all deviations from the validation document well recorded and followed up properly.
- Before approving validation the area should be conformed for the requirement of validation[15].

SAMPLE THIEF

A significant improvement in sampling can be achieved with the use of sample thief, sometimes known as a grain thief of historical reasons. This device consists of 2 tubes one fitting tightly inside the other and with oolong holes cut through the tubes in corresponding positions. One end of the outer tube is fitted to a point to facilitate is insertion in to a bulk powder, the sampling procedure consists of rotating the inner tube to close the holes, inserting the device into the powder, rotating the inner tube to open the holes, allowing the powder to enter the device, rotating the inner tube once more to close the wholes and finally removing the thief from the bulk powder. The thief sampling is better method than merely scoping off the top of a bulk powder, it is still an inferior technique.

Pre requisite For Process Validation: -

Before Process Validation can be started, manufacturing instruments as well as control instrument as well as formulation must be qualified. This involves the study of the active drug ingredient with the excipients and the final product including the packing material as well as stability Studies. Other manufacture facility such as air, temperature, Nitrogen supply and sanitation facility. Proper training and motivation of personal are pre requiste are necessary for successful Validation[16].

Approaches to Process Validation[18]: -

There are two basic processes for the process of validation itself. These are the experimental approaches and these approaches are based on the analysis of the historical data. The experimental approaches which are valid for both prospective as well as Concurrent validation analysis are as follows:

1. Extensive Product testing.
2. Simulation Process trials.
3. Challenge/ Worst case trials
4. Controls of Physical parameters (Mostly Physically)

These approaches involve the extensive sampling, far beyond that called for in routine testing and often for certain parameters only. Thus, for instances, several hundred tablets are sampled to determine unit dose uniformity. This data is then statistically treated to verify the normality of the distribution and then to now the deviation of unit dose from average weight. Confidence limit for individual approach as well as for homogeneity is also estimated. Strong assurance is needed that the samples taken at random should meet the regulatory requirement if the confidence limit is well within the compendia specification.

Industrial Process over view of Tablet Manufacturing: -

Steps and process critical parameters during process validation of tablet manufacturing process are as follows: - (Table 2)

The Validation Report: -

A summary report should be available for the review after the compilation of validation report. After completion, the report should be dully approved and authorized. The summary report should include at least following: -

1. Title and objective of the study.
2. Reference to the protocol.
3. Details of the equipment.
4. Details of the materials
5. Details of test procedure and methodology.
6. Programmes and cycle used.

7. Result (Compared with acceptance criteria)
8. Any Recommendation[17].

Conclusion: - From the study, it is concluded that pharmaceutical process validation is an essential requirement of cGMP guidelines for the finished product specification. All the parameters tested during the process should be an indicator of tablet dosage form indicator. Scientific information obtained during the process helps to form the Comprehensive validation report. Continue knowledge of pharmaceutical process validation helps industries to form the good end product and regulatory requirement should also be accomplished. Finally it is concluded that process validation is an integral part of Quality assurance for pharmaceutical industries as end product testing should not be sufficient for effective product delivery.

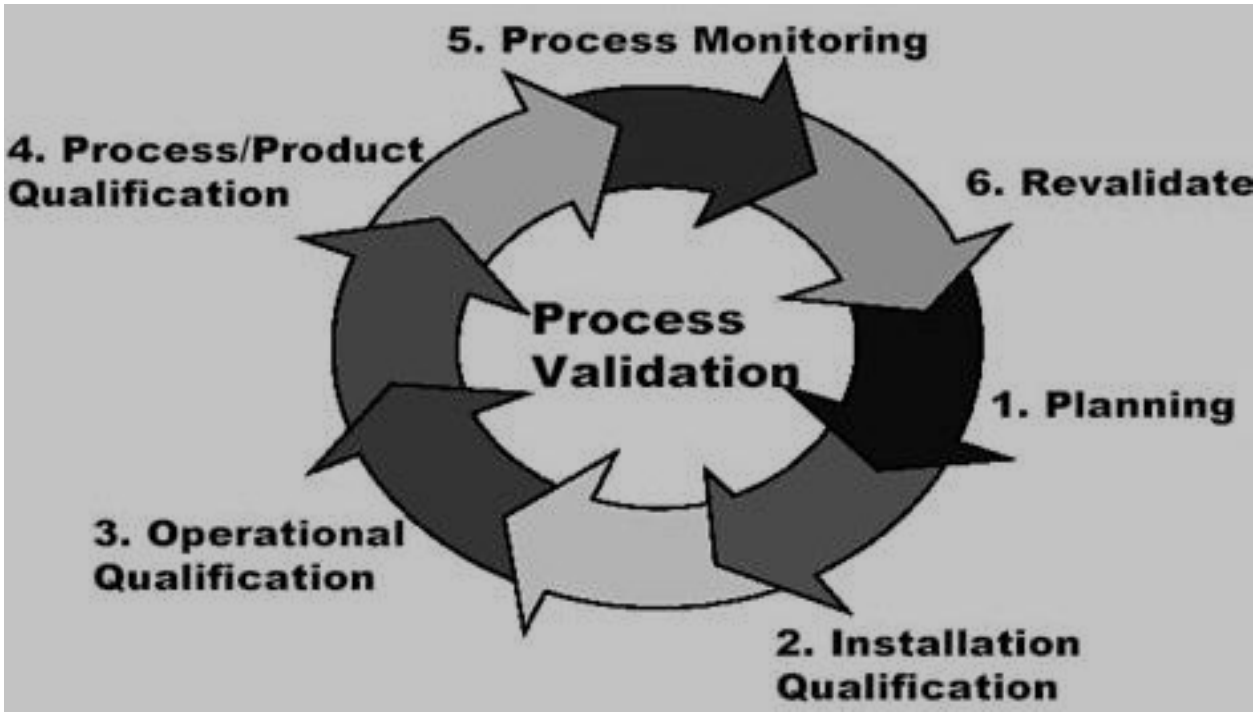
Table: `1 showing department roles in Process Validation.

Department/ Designation	Responsibility
Manager Production	Responsible for production of Batches and review of protocols and report.
Manager QC	Responsible for analysis of Sample
Executive QC	Responsible for Sample collection and Submission to QC.
Manager Maintaince	Provide Engineering Support.
Executive production	Responsible for preparation of protocols and manufacturing of production Batches
Manager QA	Responsible for protocol authorization and summary preparation.

Table: - 2. Manufacturing stage table

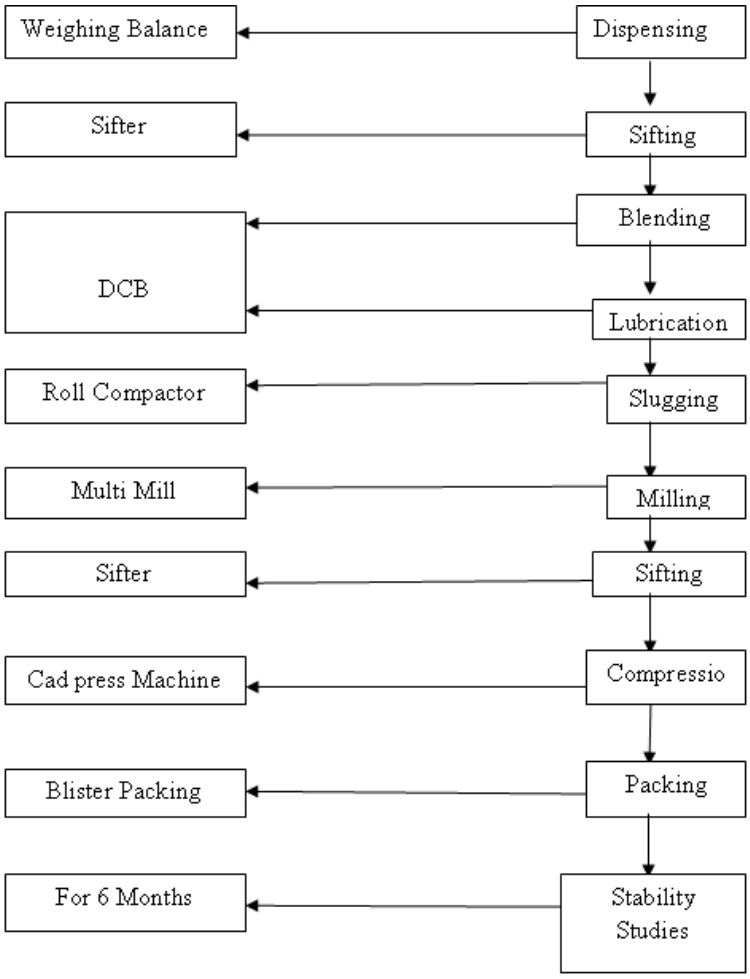
S.No.	Stage	Parameters Tested
1.	Mixing	Mixing Time, Mixing Speed, Drug Uniformity.
2.	Wet Granulation	Binder addition, Binder Concentration, Amount of Bonder add, Rate at which binder add,
3.	Wet Milling	Equipment Size and capacity, Feed Rate, Mill speed, Screen Size.
4.	Drying	Drying Rate, Temperature, Air flow, Moisture rate, Equipment capacity,
5.	Milling	Mill Type, Mill speed, Screen size, feed rate
6.	Lubrication	Mixing time, amount of lubricant added
7.	Compression	Tooling, Compression speed, Ejection force,, Hardness, Friability, Appearance, Disintegration Time, Weight Variation.
8.	Tablet Coating	Equipment Type, Coater Load, Pan speed, Spray Gun, Tablet flow, Input-output air flow, Coating Solution, Tablet weight, Solvent added

Figure: 1



PROCESS FLOW CHART

Figure: 2



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