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Review Article

ROLE OF PROCESS VALIDATION IN PHARMACEUTICAL INDUSTRY: AN OVERVIEW

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Abstract:
Drugs are the critical element in health care. They must be manufactured to the highest quality level. End product testing by itself does not guarantee the quality of the product. Quality assurance technique must be used. In pharmaceutical industry, process validation performs this task, ensuring that the process does what it purport to do. Validation is one of the important steps in achieving and maintaining the quality of the final product. If each steps of production process is validated we can assure that the final product is of the best quality. Process validation also emphasizes the role of objective measures and statistical tools & analyses and emphasizes knowledge, detection, and control of variability and gives assurance on consistent of quality/productivity throughout life cycle of product. Validation is the tool which establishes a high degree of assurance that all processes meet their intended specifications. Hence pharmaceutical validation becomes significant in pharmaceutical industry. This overview summarizes the various aspects of pharmaceutical validation. This paper represents an introduction and general overview of process validation of pharmaceutical manufacturing process.

Keyword: Process Validation, Process Validation Decision Tree, Change Control, Phase Of Process Validation

Introduction:

The word validation simply means assessment of validity or action of proving effectiveness.

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According to European community for medicinal products, validation is action of proving in accordance with the principals of good manufacturing practices that any procedure, process, equipment, material, activity or system actually leads to expected results.[1]

Pharmaceutical process validation is a key element in assuring that these quality assurance goals are met. It is through careful design and

validation of both the process and process controls that a manufacturer can establish a high degree of confidence that all manufactured units from successive lots will be acceptable. Successfully validating a process may reduce the dependence upon intensive in-process and finished product testing.[1] The principal objective of dosage form design is to achieve a predictable therapeutic response to a drug included in a formulation which is capable of large scale manufacture with reproducible product quality. To ensure product quality, numerous features are required, like chemical and physical stability, suitable preservation against microbial contamination if appropriate, uniformity of dose of drug, acceptability to users including prescriber and patient, as well as suitable packing, labeling, and validation.[2]

History of validation:

The concept of validation was first proposed by two FDA officials, Ted Byers and Bud Loftus, in the mid 1970's in order to improve the quality of pharmaceuticals.[3] It was proposed in direct response to several problems in the sterility of large volume parenteral market. The first validation activities were focused on the processes involved in making these products, but quickly extended to associated process of pharmaceutical. [1]

In the 1980s validation organizations were created and began interacting with the other traditional groups such as Research, Engineering, Production, Manufacturing, and Quality Assurance. [1]

Validation study inevitably leads to process optimization, better productivity and lower manufacturing cost. The investment made in validation, similar to the investment made in qualified people can only provide an excellent return.[4]

In a guideline, validation is an act of demonstration that any procedure, process, and activity will consistently lead to the expected result. It includes the qualification of system and equipment. The goal of the validation is to ensure that quality is built into the system at every step, and not just tested for at the end. As such validation activities commonly include training on production material and operation procedure, training of people involved and monitoring of the system whilst in production. In general, an entire process is validated and every object within that process parts is verified. The regulation also set out an expectation that the different production process are well defined and controlled, such that the result of that process will not substantially change over the time.[5,6]

THE REGULATORY BASIS FOR PROCESS VALIDATION:

In the early 1990s, the concept of preapproved inspection (PAI) was born and became one of its basic tenets of the assurance that approved validation protocols and schedules were generated during that comprehensive development.

There are several important reasons for validation of product and process.

- Manufacturers are required by law to confirm to CGMP requirements.
- Good business dictates that a manufacturer avoids possibility of rejection or recall.
- Validation helps to ensure products uniformity, reproducibility and quality. [6,7,8]

Once the concept of being able to pre-direct process performance to meet user requirements evolved, FDA regulatory officials established that there was a legal basis of requiring process validation. The CGMP regulations for finished pharmaceuticals 21CFR 210 and 211 were promulgated to enforce the requirements of the act, which states that: 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 purport or are represented to possess.[8]

Definition of validation:

USFDA defined process validation is as:"Establishing documented evidence which provides high degree of assurance that a specific process will consistently produce a product that meet in its predetermined specifications and quality characteristics."[9,10]

FDA definition of validation is as: "There shall be written procedures for production and process control designed to assure that the drug products have their identity, strength , quality , and purity they purport or are represented to possess."[4,5]

FDA Guidelines: "General principle of validation" MAY, 1987 "Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specification and quality attributes."

According to the FDA's current Good Manufacturing Practices (cGMP) control procedure shall be established to monitor output and to validate performance of the manufacturing processes that may be responsible for causing variability in the characteristics of In-process materials and the drug product.[5]

ICH guidelines defines as Process validation:

'Process validation is the means of ensuring and providing documentary evidence that processes within their specified design parameters are capable of repeatedly and reliably producing a finished product of required quality'.[11]

Need of Validation:[1,7,12]

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. [13,14]

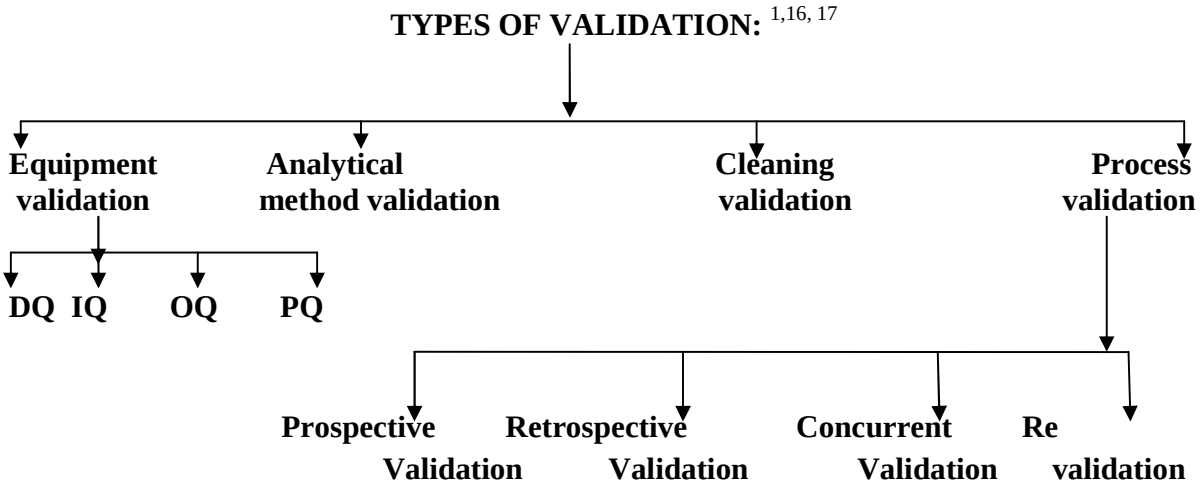
- Validation gives confidence over the product manufacturing process.
- It provides assurance to the product quality as per customer requirements.
- Validation is mandatory as per regulatory requirement.
- Following problems can occur if validation is not done:
  - Low process capability
  - Increased Scrap, Rework
  - Protracted production cycle times and low capacity utilization
  - Resolution of process related problems become slow and difficult
  - High cost of compliance Risk
  - Drug shortage,
  - Inconsistent quality of product, increased chance of Recalls
  - Delay in approval of new drugs
  - Quality problems confounding clinical trial data.

Significance of Validation:

Effective process validation contributes significantly to assure drug quality. The basic principle of quality assurance is that a drug should be produced that is fit for its intended use. The most compelling reasons to optimize and validate pharmaceutical productions and supporting processes are quality assurance and cost reduction. The basic principles of quality assurance have as their goal and the production of articles that are fit for their intended use.[1,15,16]

- It deepens the understanding of processes, decreases the risks and processing problem.
- It assures the smooth running of the process.
- It decreases the risks of defect and save costs.
- It decreases the risks of regulatory non-compliance.
- A fully validated process may require less in-process control and end product testing.
- It optimizes the process.

- It gives assurance of quality and safety.



1. **Equipment validation**:

Validation of equipment is known as qualification. There are 4 types of equipment validation/qualification.[18,19.20,21]

- Design Qualification(DQ)
- Installation Qualification(IQ)
- Operational Qualification(OQ)
- Performance Qualification(PQ)

Design Qualification (DQ):

It is a documented review of the design, at an appropriate stage in the project, for conformance to operational and regulatory expectation.

DQ check items are:

- ✓ GMP_S and regulatory requirement.
- ✓ Performance criteria.
- ✓ Facility for air flow, movement and pressure regimen.
- ✓ Reliability and efficiency.
- ✓ Commissioning requirement.
- ✓ Construct ability and installation of equipment.
- ✓ Maintenance and access to critical equipment and instrument.
- ✓ Safety and environment impact.

Installation Qualification (IQ):

It is also a documented verification that all aspects of a facility, utility or equipment that can affect product quality adhere to approved specification and are correctly installed.

Important IQ considerations are:

- ✓ Installation consideration (wiring, utility and functionality).
- ✓ Calibration, preventative maintenance, cleaning schedule.
- ✓ Safety features.
- ✓ Supplier documentation, prints, drawing and manuals.
- ✓ Software documentation.
- ✓ Spare parts list
- ✓ Environmental condition (such as clean room requirement, temperature and humidity).
- ✓ Equipment design features.

Operation Qualification (OQ):

It is documented verification that all aspects of a facility, utility or equipment that can affect the product quality during operation, and to ensure that each operational parameter remains within the predetermined range.

OQ considerations include:

- ✓ Process control limit(time, temperature, pressure, line speed and setup conditions)
- ✓ Software parameters.
- ✓ Raw material specification.
- ✓ Process operation procedures.
- ✓ Material handling requirements.
- ✓ Process change control.
- ✓ Training.
- ✓ Short term stability and capability of the process (latitude studies or control charts).
- ✓ Potential failure modes, action levels and worst-case condition (failure mode and effect).
- ✓ Fault tree analysis.

Performance Qualification (PQ):

It is documented verification that all aspects of a facility, utility or equipment perform as intended in meeting predetermined acceptance criteria.

PQ considerations include:

- ✓ Actual product and process parameters and procedures established in OQ.
- ✓ Acceptability of the product.
- ✓ Assurance of process capability as established in OQ.
- ✓ Process repeatability, long term process stability.

2. Analytical method validation:

Analytical validation is the evaluation of product quality attributes through testing, to demonstrate reliability is being maintained throughout the product life cycle and that the precision, accuracy, strength, purity and specification has not been compromise .[22,23]

3. Cleaning validation:

Cleaning validation is a documented process that proves the effectiveness and consistency in cleaning a pharmaceutical production equipment1. Validations of equipment cleaning procedures are mainly used in pharmaceutical industries to prevent cross contamination and adulteration of drug products hence is critically important. [22]

4. Process validation:

USFDA defines process validation as "Establishing documented evidence, which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre determine specification and quality attributes".[24,25]

Regulatory requirement for process validation:[26,27,28]

The basic principles of quality assurance have as their goal the production of articles that are fit for intended use. These principles may be stated as follows:

- Quality, safety and effectiveness must be designed and built in to the product.
- Quality can't be inspected or tested in to finished product.

Each step of the manufacturing process must be controlled to maximize the probability that the finished product meets all the quality and design specification.

The validation working party defines process, coordination and ultimately, approves the entire effort, including all of the documentation generated. The working party would usually include the following staff members, preferably those with a good insight into the company's operation.[29,30,31]

- ❖ Head of quality assurance.
- ❖ Head of engineering.
- ❖ Validation manager.
- ❖ Production manager.

Table no.1 Department and their Responsibility

Department/designation	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.

Types of process validation:

On principle the guidelines generally categories process validation into four types of validation. [1,12,21,25,32]

1. Prospective Validation:

This refers to establishment of documented evidence prior to process implementation that a system does what it proposed to do based on preplanned protocol. This approach to validation is normally undertaken whenever the process for a new formula (or within a new facility) must be validated before routine pharmaceutical production commences. In fact, validation of a process by this approach often leads to transfer of the manufacturing process from the development function to production.

2. Retrospective Validation:

Retrospective validation is used for facilities, process and process controls in operation use that have not undergone a formally documented validation process. Validation of these facilities, processes and process controls is possible using historical data to provide the necessary documentary evidence that the process is doing what it is believed to do. Therefore, this type of validation is only acceptable for well-established processes and will be inappropriate where there have been recent change in the composition of product, operating processes, or equipment.

This approach is rarely been used today because it's very unlikely that any existing product hasn't subjected to the prospective validation process. It is used only for the audit of a validated process.

3. Concurrent Validation:

Concurrent validation is used for establishing documented evidence that a facility that a facility and process do what they purport to do, based on information generated during actual imputation of the process. This approach involves monitoring of critical processing steps and product testing of current production, to show that the manufacturing process is in state of control.

4. Revalidation:

Revalidation means repeating the original validation effort or any part of it, and includes investigative review of existing performance data. That approach is essential to maintain the validated status of the plant, equipment, manufacturing processes and computer system. Possible reasons for starting the revalidation process include:

- The transfer of a product from one plant to another.
- Change to the product, the plant, the manufacturing process, the cleaning process, or other changes that could affect product quality.

- The necessity of periodic checking of the validation result.
- Significant (usually order of magnitude) increase or decrease in batch size.
- Sequential batches that fail to meet product and process specification.
- The scope of revalidation procedures depends on the extent of the change and the effect upon the product.

Benefits of process validation:

The validation of process results in several advantages with respect to cost of manufacture, quality of the product, and profitability of the company. The specific advantages or benefits of process validation are mentioned below. [16,20,22,33,34]

- Increased throughput
- Reduction in rejections and reworks
- Reduction in utility costs
- Avoidance of capital expenditures
- Fewer complaints about process related failures
- Reduced testing in process and finished goods
- More rapid and accurate investigations into process deviations
- More rapid and reliable start-up of new equipment
- Easier scale-up from development work
- Easier maintenance of the equipment
- Improved employee awareness of processes
- More rapid automation.

The stages of Process Validation:

Generally the process validation activities are performed in three stages as mentioned below: [20,27,35,36,37]

Stage I: Process Design

The commercial process is defined during this stage based on 100 knowledge gained through development and scale-up activities.

Stage II: Process Qualification

During this stage, the process design is confirmed as 103 being capable of reproducible commercial manufacturing.

Stage III: Continued Process Verification

Ongoing assurance is gained during routine production that the process remains in a state of control.

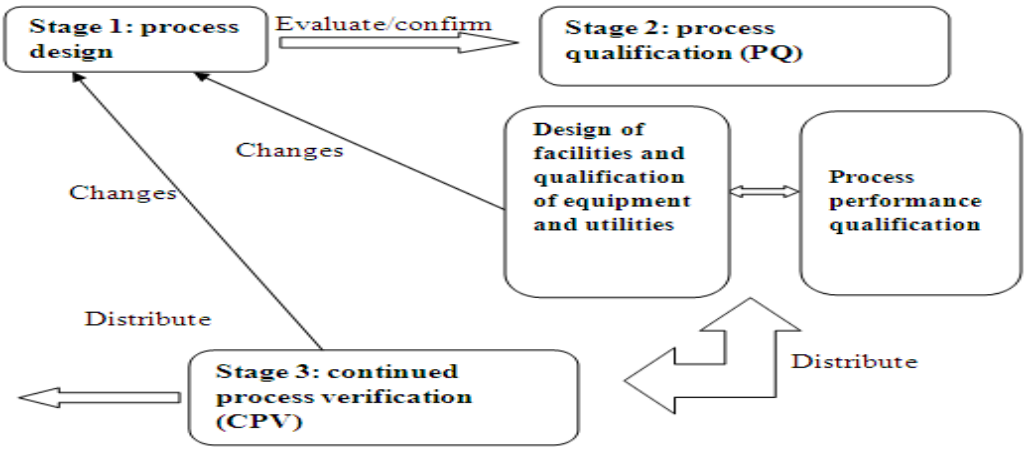


Fig:1 Stages of process validation according to FDA Guidance for Industry

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

Phase 1: Pre-validation phase or the Qualification Phase

Which covers all activities relating to product research and development, formulation, pilot batch studies, scale-up studies, transfer of technology to commercial scale batches, establishing stability condition, storage and handling of in-process and finished dosage forms, equipment qualification, installation qualification, master production documented, operational qualification, process capability.

Phase 2: Process Validation Phase (Process Qualification Phase)

It designed to verify that all establishing limits of the critical process parameter are valid and that satisfactory products can be produced even under the "Worst case" conditions.

Phase 3: Validation Maintenance Phase

Validation Maintenance Phase requiring frequently review of all process related documented, including validation audit reports to assure that there have been no change, deviation, failures, modification to the production process, and that all SOPs have been followed, including change control procedures. At this stage the validation team also assures that there has been no changes/deviation that should have resulted in requalification and revalidation.

Change Control: [15,18,25, 29,39,40]

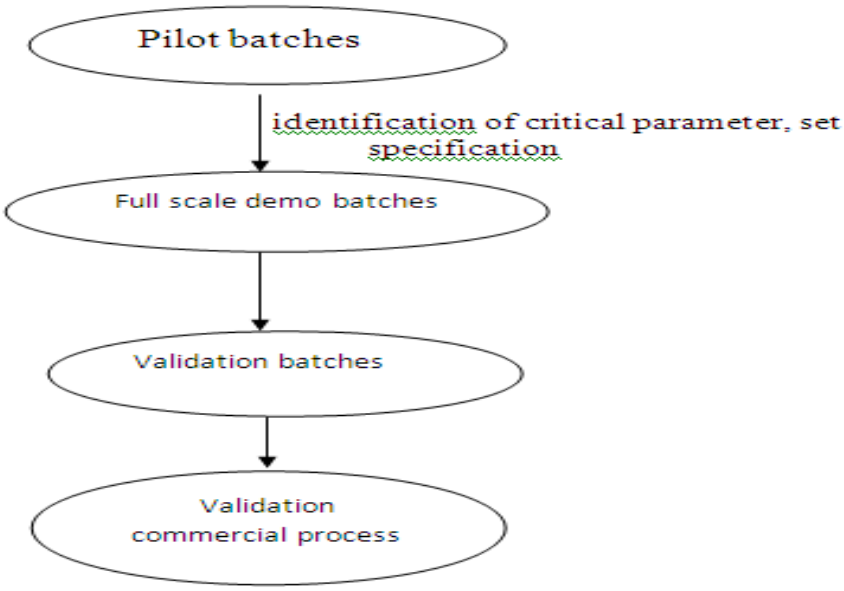
Written procedure should be in place to describe the actions to be taken if a change is proposed to a product component, process equipment, process environment, processing site, method of production or testing or any other change that may affect product quality or support system operation.

All change must be formally requested, documented and accepted by the validation team. The likely impact/risk of the change on the product must be assessed and the need for extent of re-validation should be determined.

Commitment of the company to control all changes to premises, supporting utilities, system, material equipment and processes used in the fabrication/ packaging of pharmaceutical dosage forms is essential to ensure a continued validation status of the system concerned.

The change control system should ensure that all notified or requested change are satisfactorily investigated, documented and authorized. Products made by processes subjected to change should not be released for sale without full awareness and consideration of the change by the validation team. The team should decide if a re-validation must be conducted prior to implementing the proposed change.

Development of process validation:[33]



Pilot Scale-Up and Process Validation:
The following operations are normally carried out by the development function prior to the preparation of the first pilot-production batch. The development activities are listed as follows: [1]

- Formulation design, selection, and optimization
- Preparation of the first pilot-laboratory batch.
- Conduct initial accelerated stability testing.
- If the formulation is deemed stable, preparation of additional pilot laboratory batches of the drug product for expanded non-clinical and/or clinical use.
- The pilot program is defined as the scale-up operations conducted subsequent to the product and its process leaving the development laboratory and prior to its acceptance by the full scale manufacturing unit.
- Thus, product and process scale-up should proceed in graduated steps with elements of process validation (such as qualifications) incorporated at each stage of the piloting program.

Laboratory Batch:
The first step in the scale-up process is the selection of a suitable preliminary formula for more critical study and testing based on certain agreed-upon initial design criteria, requirements and/or specifications. The work is performed in the development laboratory.

Laboratory Pilot Batch:
After the laboratory batch is determined to be both physically and chemically stable based on accelerated, elevated temperature testing (e.g., 1 month at 45°C or 3 months at 40°C or 40°C/80% RH), the next step in the scale-up process is the preparation of the laboratory pilot batch.

Pilot Production:
The pilot-production phase may be carried out either as a shared responsibility between the development laboratories and its appropriate manufacturing counterpart or as a process demonstration by a separate, designated pilot-plant or process-development function.

Prerequisites for Successful Validation: [20,33,41,42,43]

There are thirteen tools or elements that are required for conducting effective validation.

Each are presented and discussed in the following section.

1. Information:

The single most important element required is a good understanding of what is validation .this understanding activity goes beyond the basic definition of validation, beyond the concept of "requiring a minimum of three runs". The understanding must be anchored by sufficient years of practical experience and knowledge. It will permit sound and logical decisions, even under the most intense situation.

Given the regulated drug manufactures must perform validation, it is very important that understanding be shared throughout the organization.

Why can't the laboratory use the piece of equipment undergoing validation?

Why can't the facility be used before the laboratory has completed analysis of the microbial data?

Why are validations so expensive?

If the entire company is fairly educated on what validation entails, less time will be required defending validation actions.

2. Communication:

One of the methods of improving environmental understanding is through communication. Communication is essential for any activity that requires more than one resource to complete. This point is understandable consideration that conducting effective validation involve multi-department.

One of the keys to proper communication is locating the communication vehicle. Most organization communicates through one or more of the following methods.

- Conversations.
- Memos.
- Periodic meeting.
- Training sessions.

3. Experience: A firm must have good resource in validation experience in order to execute their validation program successfully.

4. Cooperation and focus:

Multitude of department that sometimes interact during the course of executing validation program are project management, accounting, validation, quality control, facilities, project engineering, process engineering, quality assurance, regulatory etc. it is safe to assume that these department have an array of priorities and typically they are not the same as validation's. The cost of validation will undoubtedly increase because more time will be spent seeking approvals. Likewise, time will be spent justifying and writing the explanation for why a sample was not initially collected. Cooperation is essential and critical. Therefore, each member must be focused on the overall tasks, and willing to cooperate 100%.

5. Resource:

In reality, it does not matter how much knowledge, experience and understanding a firm has, if they don't allocate the proper resources for conducting effective validation.

Resource mean personnel who will plan and execute, equipment on which validation will be performed on, materials with which to conduct validation, laboratories that will perform necessary analysis, funding to pay the validation and times in which to perform validations. Validations can often begin, but can't be completed if any one of these resources is missing.

6. Budget:

It is important to understand that a successful validation must be done completion; typically, it should not be limited by a budget assembled by personnel who have no appreciation for what is required to successfully complete validation. Further, it is important to understand that validation cost money.

Consideration of how projects are funded within corporation. Each department has to prepare an annual budget for anticipated expenses. It is very important the anticipated costs are shared with upper management to assure that the ample support or funding exists. From a corporate standpoint, each one of the validation elements requires time, and therefore has an associated cost. Thus, it is essential that they are reflected in the validation budget.

7. Plan:

Conducting validation within most companies will involve a number of department and disciplines. These disciplines need a plan in order to get good team synergy. Further, this plan must be communicated in order to be accepted and successful.

- When should the analytical laboratory receive the samples?
- How should a deviation be handled?
- How will chamber temperatures be monitored?
- When will the first event occur?
- Will manufacturing assistance be required to execute the validation protocol?

It is essential that the lead validation resource know the answer to each of the above question, and assures that are shared in pre-validation planning sessions.

8. Training:

Training is essential for any successful validation. Typically this training initiates within the validation group. It is essential that the lead validation resource for a given validation project initiate, facilitate, coordinate and/or communicate the need for resource training as required by validation event. Actually, the requirement for training goes beyond the act of teaching. The regulating bodies require proper documentation be assembled and maintained to serve as proof that key resource have undergone required training.

9. Standard Operating Procedures (SOPs):

SOPs capture activities that routinely occur within an organization departments charged with abiding by or following these SOPs must first be trained against these SPOs. Many SOPs are typically the off spring of a successful validation. In most cases, equipment operation SOPs are drafted for use during the initial phase of qualification. These SOPs often are not finalized until after the equipment OQ event. A case in point would be an SOPs for set-up and operation of a new piece of equipment. Often, the vendor manuals or the specification will convey how the equipment is operated. In the OQ phase, this information is usually transcribed for use in the form of a draft SOP. Once the OQ steps are completed, the result should be an SOP that is finalized approved, trained upon and implemented for routine use.

The expectation is that these SOPs are finalized before the equipment is used to support process validation.

10. Solid Quality Control Lab Support:

During most validation handled by the QC group. QC is expected to provide result in timely manner. So often the wait for the receipt of analytical results causes the entire validation project to come to halt. Because validations are based on the result obtained.

In addition, QC input in required during protocol preparation. If the QC lab lacks organization, maturity, technical competency, appropriated methods etc. An initiative has to be undertaken to attain laboratory support through contract laboratory.

11. QA Support:

All validation resource may not be the best for adhering to compliance procedures. It is therefore up to QA to thoroughly policy the protocols before, during and after execution. This policing must be against internal SOPS and external regulation. The expectation is

that QA will enforce any relevant compliance issues, and will there by prevent an unwanted discovery by auditing bodies. If an auditor uncovers a number of compliance issue, the department that will often be held accountable is QA. If must be understood that a good QA resource often is not a resource that most other departments would choose as their best buddy during working hours. However, their value to success of the organization validation must not be minimized.

12. Permission to conduct preliminary runs (Trials/ engineering runs, Demonstration etc.):

When a system undergoes validation, the desire is that its operation is then faultless. Validations require practice. Given the fact that validation is typically expensive, it should be understood that anything that would assure that costs are minimized would be an asset. Therefore, it is advisable that permission be attained to perform some form of preliminary runs. These runs can be used to provide operator training, to investigate values recommended by specification or vendors equipment manuals, and/or explore any limits proposed for validation.

13. Realistic Completion Dates:

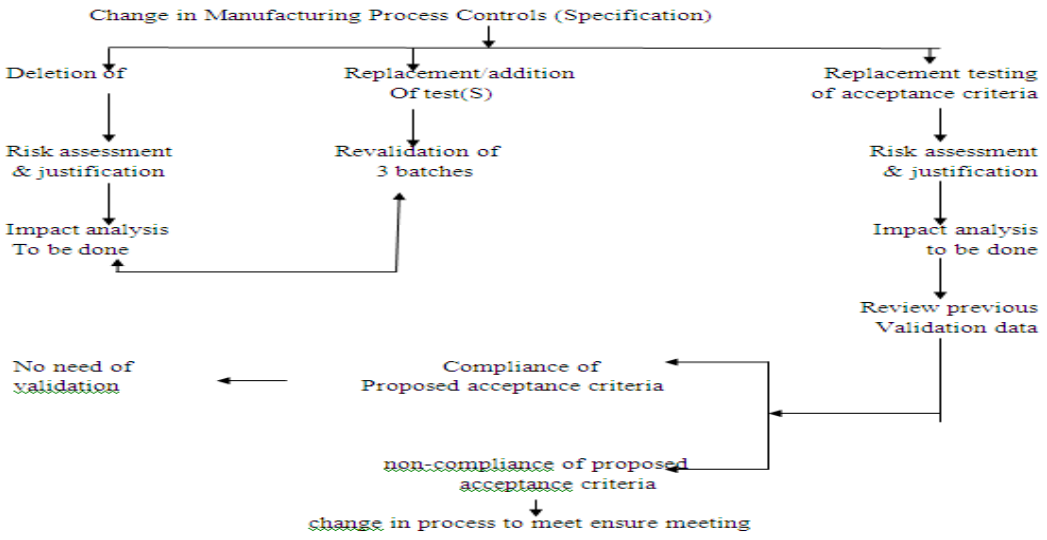
Typically, the expectation is that once the requisite time has been allotted to complete three runs, the system under validation is released and ready for use. Unfortunately, this is rarely the case. For example, a cleaning validation activity will require time to complete the following activities, including:

- Training
- Conducting cleaning events.
- Gather cleaning samples.
- Obtain the microbial challenges result.
- Evaluate result.
- Write conclusion.
- Seek and attain post execution approval.

Therefore, it should be relatively easy to see it requires much longer than the three, basic runs. Validation resources typically provide input on validation task. The firm must understand that this is often a lose/lose situation because if the planning resource is overly optimistic, disappointment will result when the completion date is not met.

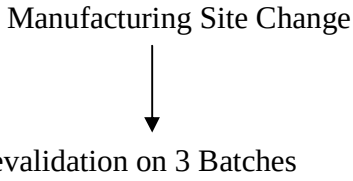
Process Validation Decision Tree:[20]

(i) Process Validation Decision Tree for change in process controls of manufacturing process of drug products:

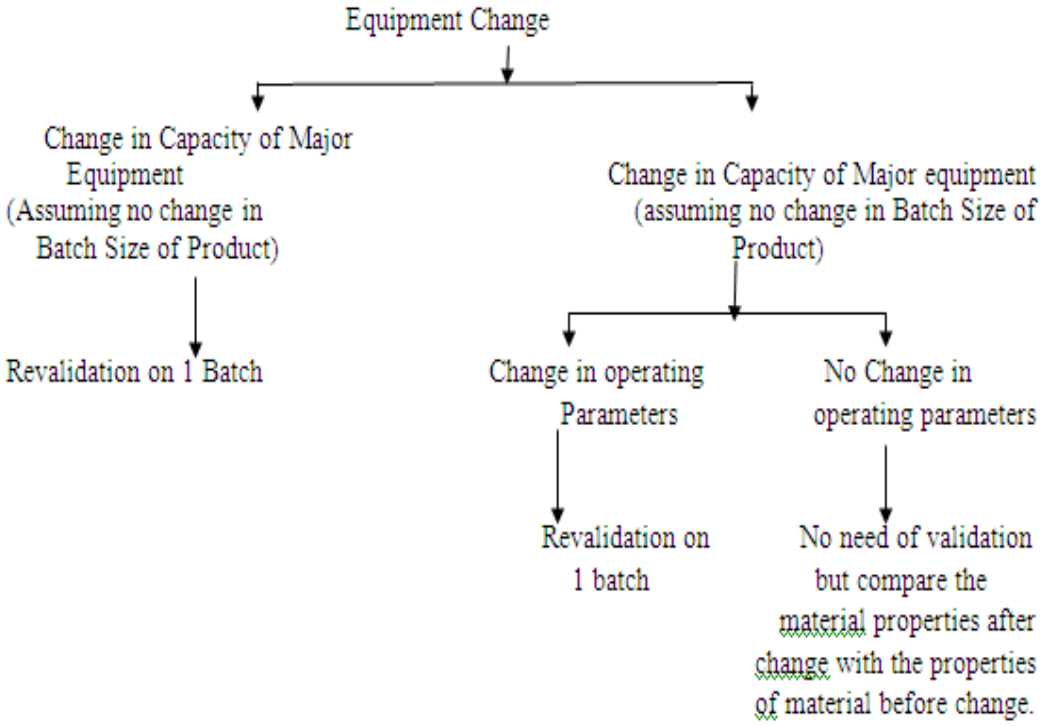


(ii)

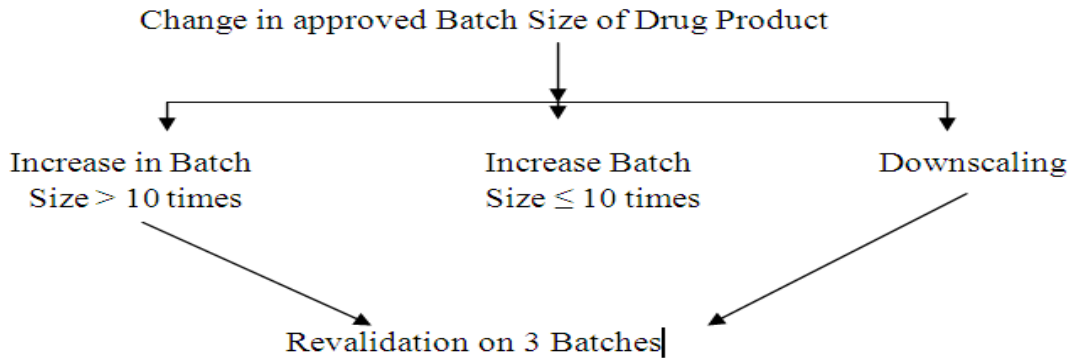
Process Validation Decision Tree for Change in Manufacturing Site of Drug Product:



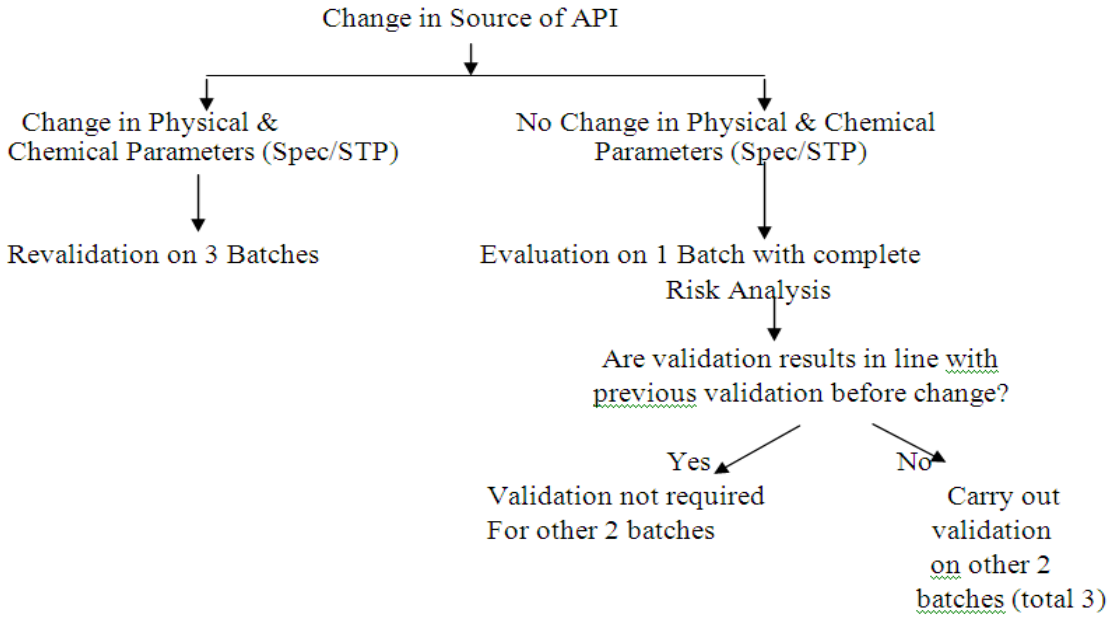
(iii) Process Validation Decision Tree for Change in Equipment:



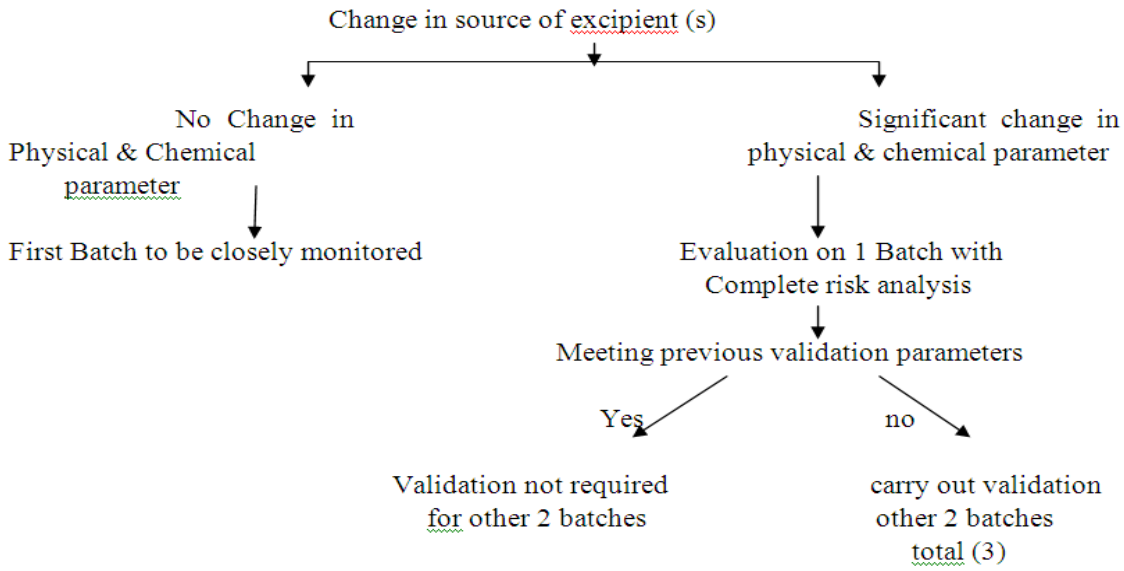
(iv) Process Validation Decision Tree for Change in Batch size of drug product:



(v) Process Validation Decision Tree for Change in Source of Active Pharmaceutical Ingredients (API).



(vi) Process Validation Decision Tree for Change in Source of Excipient(s).



Validation: types of document:[44]

- **Validation Master Plan.**
- **Validation protocol.**
- **Validation report.**

Validation Master Plan: [3,31,45,46,47]

A validation master plan is a documented that summaries 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 operation procedures. All observations must be documented and where

possible must be recorded as actual numerical result.

The validation master plan should provide an overview of the entire validation operation, its organizational structure, its content and planning. The main elements include the list/inventory of the items to be validated and planning schedule. All validation activities relating to critical technical operation, 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 validation 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 documented such as policy documented, SOP's and validation protocol and reports.

Format and content should include:[20]

- Introduction: Validation policy, scope, location and schedule.
- Organizational structure: personnel responsibilities.
- Plant/Process/Product description: rational for inclusions or exclusions and extent of validation.
- Specific process considerations that are critical and those requiring extra attention.
- List of products /Processes/Systems to be validated summarized in a matrix format, validation approach.
- Re-validation activities, actual status and future planning.
- Key acceptance criteria.
- Documentation format.
- Reference to the required SOP's.

Validation Protocol:

A written plan of actions stating how process validation will be conducted; it will specify who will conduct the various tasks and define testing parameters; sampling Plans, testing methods and specifications; will specify product characteristics, and equipment to be used. It must specify the minimum number of batches to be used for validation studies; it must specify the acceptance criteria and who will sign/approve/ disapprove the conclusions derived from such a scientific study.[18,20,30,45]

Objective: [44,48]

- Background/revalidation activities
- Summary of development and technology transfer (for R & D or another site) activities to justify in process testing and controls any previous validations.
- List of equipment and qualification status
- Facilities qualification
- Process validation
- Manufacturing procedure narrative
- List critical processing parameters and critical excipients
- Sampling, tests and specifications
- Acceptance criteria

Validation report:

The validation report should contain the approved validation ,protocol, tabulated or graphical results ,process monitoring and analytical results of the validation batches. process validation report shall be prepared by compiling the analytical results and raw data generated during validation. Analytical results an draw data shall be verified against acceptance criteria. [20,21,38,49]

The main components of the report are as follows : [15,20,44]

- Cover page.
- Over view.
- Product name.
- Description of the process being validated.
- Location.
- Number of batches being validated.
- Validation study plan.
- Scope.
- Results.

- Discussion.
- Recommendations.
- Conclusion.

Sampling procedure:

All validation samples with the exception of the unit dose blend sample and tablet manufacture shall be placed in clean container and labeled as follows:

- Product name.
- Batch size.
- Batch number.
- Lot number.
- Manufacturing date.
- Expiry date.
- Stage.
- Sampled by/Date.

Unit dose blend sample:

These samples shall be taken in accordance with SOP. The sample shall be placed in container or sampling poly bag and labeled as follows:

- Product name.
- Batch number.
- Sample location number.
- Sample type.
- Sign/Date.

Sampling Device: [33]

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 along holes cut through the tubes in corresponding positions. One end of the outer tube fitted to a point to facilitate is insertion in to a bulk powder the sampling procedure consists of rotating the inner tubeto 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 wholes and finally removing the thief from the bulk powder The thief sampling is better method than merely scoping off it is still an inferior technique the top of a bulk powder Even through most thieves have relatively sharp ends; the very act of plunging the thief through the bulk powder must perturb the sample to some degree. A compression force of the thief as propagates ahead it is pressed into the bulk thus potentially of the bulk changing the strata and altering the wall of powder at the outer walls of the thief. Furthermore, because large particles will flow more easily than will small particles, an opened thief is liable to be filled preferentially with the coarse fraction of the particle distribution.

Working procedure by sample Thief

The sleeve rotates so that the interior compartment is isolated from the bulk powder, while in the closed position, the thief is plunged into the central mass of the powder. Once the thief is at the desired position, the unit is rotated so that the interior compartment is now exposed to bulk powder. Powder flows into the thief compartment of its own accord. Once the interior compartment of the thief is filled, the sleeve of the thief is rotated so that the interior compartment is again isolated from the bulk powder. The thief is then withdrawn from the powder, and the sample is analyzed.

Sampling Thief used for sampling of powder and granules.

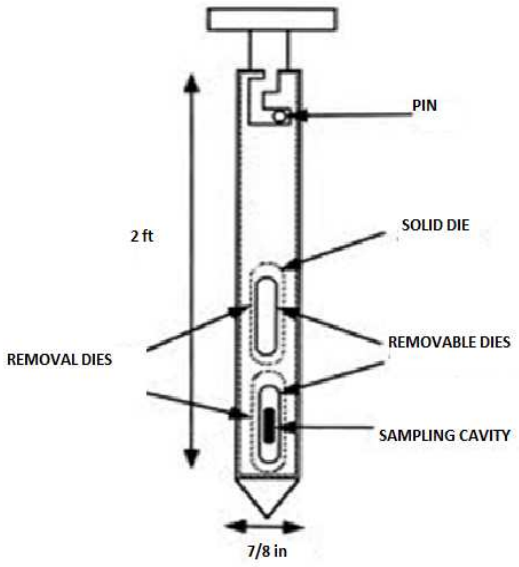


fig no.2 sampling thief

Diagrametic presentation of sampling:

Fig no.3 Diagrammatic Presentation of sampling

Table no.2 Sample summary of solid dosage form

Stage	Location	Sample size	Sample type	Frequency	Test
Raw Material	Raw material drum	As per specification	Sample of raw material	Prior to dispensing	Assay, LOD Moisture content,
Granulation	RMG	100.0 mg 30 g	10 location(top middle, bottom) composite	At the end of 7 Min. drying mixing	Assay Bulk Density
Dried granule	FBD	1. Approx 2-5 g 2.Approx 2-5 g	Composite 7 location	During drying At the end of drying process	LOD at 105^0c on IR moisture balance LOD
Lubrication	Bin blender	100-300 mg 30 g	10 location composite	At the end of blending process At the end of blending process	Blend uniformity(Assay) Assay LOD Particle size Bulk density, Tapped density
compression	Compression machine	100 tablets	Individual tablet(LHS& RHS)	1. Minimum hardness at optimum speed. 2. Maximum hardness at optimum speed. 3. Minimum RPM at at optimum speed. 4.Maximum RPM at optimum speed 5.Full hopper, half hopper, end hopper. 6.At regular interval	Appearance, hardness, thickness, friability, Disintegration time, Average wt. ,uniformity of wt.,

coating	Coating pan	80 tablet	Composite sample	End of coating	Average wt Thickness DT Uniformity of weight
Packing	After packing	Qty. w.r.t. Complete one cycle	blister	1. At low sealing temp. and high speed 2. At high sealing temp. and low speed 3. At low sealing temp. and low speed 4. At high sealing temp. and high speed	Leak test, Physical parameter, Assay

Conclusion

From study, it can be stated that Process validation is a major requirement of cGMP regulation for finished pharmaceutical products. It is a key element in assuring that the quality goals are met. Successfully validating a process may reduce the dependence upon intensive in process and finished product testing. Finally, it can be concluded that Process validation is a key element in the quality assurance of pharmaceutical product as the end product testing is not sufficient to assure quality of finished product.

The quality assurance of pharmaceutical product involves a number of factors. The complexity of modern day medical products requires more than the routine end product testing, as the end product testing is not sufficient to assure quality of finished product. The review highlights various aspects on process elements, regulatory requirements, and validation documentation that are considered by regulatory agencies. The particular requirement of process validation will vary according to the nature of the pharmaceutical product and type of process. The broad concepts stated in this review have general applicability and provide an acceptable framework for building a comprehensive approach for the validation.

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