Module- 03

Validation- Validation is 'action of proving', in accordance with the principles of Good manufacturing practices that any procedures, process, requirement, material, activity or system actually leads to expected results.

US FDA Definition- Process validation is establishing documented evidence, which provides a high degree of assurance that a specified process will consistently produce a product meeting its pre-determined specifications and quality characteristics.

Need of validation

First, manufactures are required by law to conform to CGMP regulations. Second, good business dictates that a manufactures avoid the possibility of rejected or recalled batches. Third, validation helps to ensure product uniformity, reproducibility, and quality.

Equipment validation

Validation of equipments is known as qualification. Equipment validation is divided into installation Qualification (IQ), Operational Qualification (OQ), and Performance Qualification (PQ).

Design Qualification (DQ)

This outline the key features of the system designed to fulfill the user requirement.

Installation Qualification (IQ)

Simply IQ means is it correctly installed? An IQ documents prove that the installation of the unit has been correctly performed and that the installation specifications of the manufacturer have been met.

Operational qualification (OQ)

OQ is a series of tests that measure the performance capability of the equipment. After installation it must be ensured that the equipment can deliver operating ranges as specified in the purchase order.

Performance qualification (PQ)

PQ is defined as “the process to verify that the system is repeatable and consistently producing a quality product”

Types of Process Validation

Prospective validation: It is defined as the establishment of documented evidence that a system does what it claim to do based on pre-planned protocol. This validation is usually carried out prior to the introduction of new drugs and their manufacturing process.

This approach to validation is normally undertaken whenever a new formula, process or facility must be validated before routine pharmaceutical formulation begins. This is also known as pre-market validation and validation is completed prior to the manufacture of finished product that is intended for sale.

Retrospective validation: It is defined as the establishment of documented evidence that a system does what it claims to do based on review and analysis of historical data or existing information. This is achieved by the review of the historical manufacturing testing data to prove that the process has always remained in control.

Concurrent validation: It is similar to 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.

Revalidation

It is the repetition of a validation process or a specific part of it. This is carried out when there is any change or replacement in formulation, equipment, plant or site location, batch size and in the case of sequential batches that do not meet product and process specifications.

Process Validation

Following are the various steps toward process validation-

A. Documentation/Record Keeping
B. Evaluation of sources of variation
C. In-Process testing
D. Challenge
E. Approvals

A. Documentation/ Record Keeping

The first step toward process validation is to establish a record keeping system. The system of record keeping involves-

- SOPs
- Specifications
- Test Procedures
- Manufacturing Formulae and manufacturing instructions
- Approval Process

Standard Operating Procedures (SOPs)- SOPs are written procedures that describe how to perform basic operations in a plant. The procedures should be written in language that is simple enough for an untrained nonprofessional to understand as well as any new personnel with minimal experience should be able to understand and follow these procedures.

Importance of SOPs- It should always be remembered that more than one individual must capable of performing a given task; at times he or she will be on vacation or absent because of sickness. In addition, no individual should be relied upon to perform task from memory, as there is no guarantee that such operations will be performed as reproducibly as may be required. Certainly no two individuals performing an operation from memory will do it identically. Written SOPs are necessary to avoid these drawbacks. Also, a written record provides a history that can be read and studied if, for example, a product batch should fail and we seek to identify the cause.

They are applicable to many different phases of a manufacturing operation.

- **Cleaning-** There must be cleaning procedures, firstly for cleaning the walls, floors and ceilings. These procedures include frequency of cleaning. The different steps that are required and the cleaning agents acceptable for use must be mentioned. Different areas within a plant will require different SOPs. For example, a sterile filling room will require more elaborate cleaning than a warehouse.
- **Environment-** All plants must be kept free of rodents and insects. In operations such as an area to manufacture sterile products, there are requirements for control of air temperature, humidity, flow rates and patterns and particulate matter.
- **Maintenance and safety-** It cover the basic air handling systems, water systems, physical structures as walls and ceilings, waste removal system and the heating and cooling systems.
- **Equipment-** SOPs under these categories describe equipment cleaning. SOPs must describe step-by-step what is to be done, disassembly and assembly, frequency and acceptable

cleaning agents. These SOPs provide a detailed step-by-step sequence of operations to run equipment.

- **Personnel:** All personnel in a plant who are involved should have specific written job descriptions. There must be established rules and regulations regarding proper dress, i. e., uniforms and hats, safety glasses, eating and drinking, storage of personal articles and washing hands.

Specifications: It describes the characteristics of a particular material. Specifications must be written for each raw material, packaging component, in-process material and finished product. Specifications are an important tool in validating a raw material or a process.

Test Procedures are written procedures that provide the step-by-step details of how to perform the tests indicated in specifications or SOPs. They indicate the reagents to be used, sources of the chemicals, how the reagents are to be prepared and shelf life of the reagents. Apparatus to be used and special handling and precautions to be followed are also described.

Manufacturing Formulae & **Manufacturing Instructions-** A master formula generally represents weight or volume of each raw material per unit of finished product and also weight or volume of each raw material per standard batch size. Manufacturing Instructions are the written directions that personnel follow to prepare product batches. They describe in sufficient detail and step by step, the operations to be performed, providing blank spaces for personnel to record the operations that they perform.

Approval Process is the last and most important part of record-keeping. All documents must be approved before they are used. If they require a change, the documents must again be approved before the change is implemented.

B. Evaluation of source of variation

The second step toward process validation is to evaluate all possible sources of variations in the process. In validation, it is important to identify all source of variation that is possible from materials, machines, methods and men.

a. Materials- This includes review of all raw material and packaging components utilized to prepare and package a product.

b. **Machines-** This includes all equipment, apparatus and instruments used to prepare used to prepare and test a product. Reactivity of all equipment parts that contact the product must be evaluated to be sure that there is no additive or absorption effect.

c. **Methods**- Procedure must be in sufficient detail so that their use by different personnel with different techniques will enable the operations to be performed reproducibly.

d. **Men-** This includes all personnel involved in manufacturing/testing a product. Personnel who are improperly trained and/or who lack certain expertise can cause serious problems in a manufacturing operation.

C. In-Process Testing

It is the requirement of CGMP. In-process testing means that a product batch is evaluated at specified critical stage of the manufacturing process to assure that the batch is being manufactured as predetermined in the manufacturing batch records.

D. Challenge

The fourth step toward process validation is to challenge and then evaluate the process. The challenge batches are prepared by introducing only one variable into one batch to study the effect of that variable on the formulation. The information generated will be helpful in the future when product batches are prepared and such deviations occurs.

E. Approvals

The last step toward process validation is to document everything that is done to follow established procedures and protocols as closely as possible and not to make change without proper documentation and approval.

Validation of Solid Dosage Forms

A. Validation of raw material

The validation process of a solid dosage form begins with validation of the raw materials: both active ingredients and excipients. Variation in raw materials is one of the major causes of product variation or deviation from specification. For example, poor water soluble drug required micronization to achieve rapid dissolution and in vitro availability. If the milling or micronizing process is not controlled and properly validated, irregular particle size and blend distribution will result in content uniformity problems of the final dosage form.

Volume of granulating solution or binder must be validated. A greater volume of granulating agent will be needed to wet mass a powder bed comprised of finely divided particle than is needed for coarser particles of the same substance.

If the particle size/surface area ratio is not controlled and a specific amount of granulating solution is not stated in the product manufacturing directions, then overwet granules, resulting in insufficient dried product; or it will be too dry and will not form proper particle aggregates, resulting in poor tablet compressibility, and content uniformity problems with the final dosage form.

Control of amount of lubricant is also required. Hydrophobic coating of magnesium stearate delays the disintegration and dissolution of the final tablet. Lubricant having small particle size and greater surface area, more efficiently coats the surface of the particles, thus creating more hydrophobicity and drug-released problems. It is critical to validate the particle size/surface area characteristics of grade of magnesium stearate.

B. Process Variables

Major processing variables in solid dosage forms are evaluated. The various steps and process critical parameters during validation of tablet are given below-

Step	**Purpose**	**Critical parameter(s) to be checked**
Mixing/ Blending	Homogenous Mixture	Mixing time and speed
Granulation	Convert powder to granules	Solvent used and time of addition
Drying	Reduce moisture content to proper level for compression	Inlet/outlet temperature and drying time
Milling	Reduce particle size of dried granulation	Mill speed and feed rate
Lubrication	Provide granules suitable flow and compressibility	Mixing time and speed
Tablet compression	Manufacture of compressed tablets	Machine speed and compression force
Tablet coating	Coating of tablet	Pan speed, inlet/ outlet temperature, spray rate

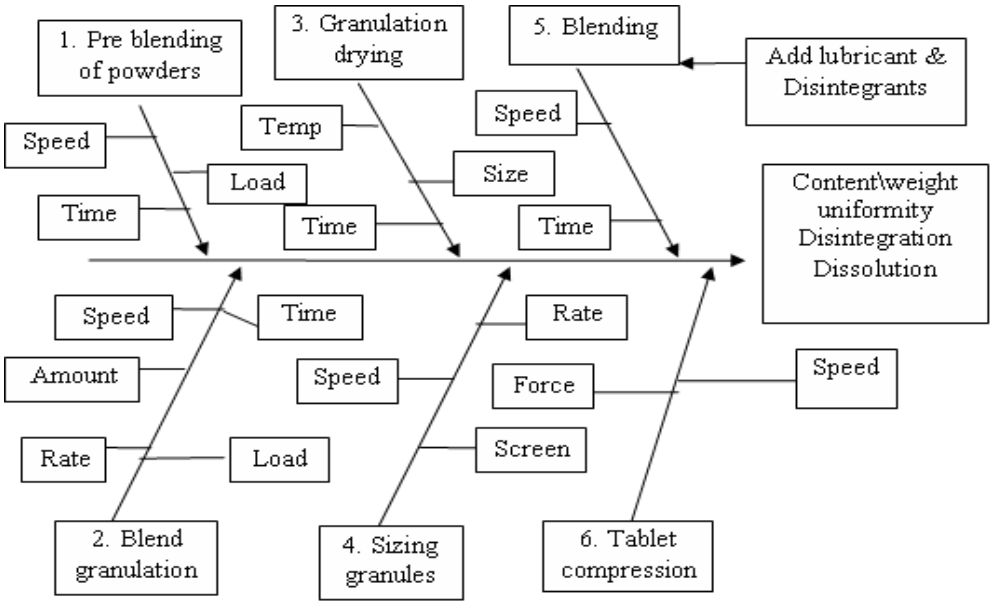
1. Mixing or blending- Review the time of mixing. The extensive blending causes demixing and segregation of components. Determine time of un-mixing, i.e., time to lose uniformity. Powder blends and granulations can segregated on blending as a result of particle size or density differences. For example, in a direct compression formula in which the active agent is micronized (5 microns) and the excipients are granular (500-1000 microns). Content uniformity is usually performed to determine the uniformity of drug throughout the mix or blend.

The lubricant needs to be distributed uniformly in the mixture/granulation. Uneven distribution of the lubricant can result in picking and sticky problems during compression.

2. **Granulation-** The type of wet granulation technique used must be determined. It may be low shear (e.g., Hobart), high shear (e.g., Diosna, GEI-Collette) or fluid bed (e.g., Glatt, Fluid Air). Each technique will produce granules with different physical properties and will require monitoring of different processing parameters. Wet granulation parameters to be considered during development and validation are:

Binder Concentration- Adequate binder concentration is required to agglomerate particles to achieve good granulation flow and compressibility.

Amount of binder or solvent solution that is required to granulate the material must be validated. Too much binder or solvent solution will over wet the materials and prolong the drying time.



Processing steps and in-process variables during tablet manufacture

(Also known as Cause- effect or Fish Bone Diagram)

3. **Drying-** The type of drying technique (e.g., tray, fluid bed, and microwave) required for the formulation needs to be determined and justified.

Determine the optimal moisture content of the dried granulation. High moisture content can result in tablet picking or sticking to tablet punch surfaces and poor chemical stability as a result of hydrolysis. An over dried granulation could result in poor hardness and friability. Moisture content analysis can be performed using the conventional loss-on-drying techniques or newer techniques such as infrared or radio-frequency drying. The proper air flow is needed to remove moisture from the wet granulation. Load to be dried must be validated. The greater the load, the more moisture that will have to be removed on drying.

4. Milling operation for dried granulation- The milling operation reduces the particle size of the dried granulation. The resultant particle size distribution will affect such material properties as flow, compressibility, disintegration, and dissolution.

5. **Lubrication-** What kind of lubricant should be used and check the compatibility of lubricant with other ingredients. Too much lubricant will form hydrophobic layer on the tablet resulting in dissolution problems.

6. **Tablet compression-** Compression is a critical step in the production of a tablet dosage form. The materials being compressed will need to have adequate flow and compression properties. The material should readily flow from the hopper onto the feed frame and into the dies. Inadequate flow can result in “rat holing” in the hopper and/or segregation of the blend in the hopper/feed frame. This can cause tablet weight and content uniformity problems.

Tablet machine rpm affect dwell time (the time the powder mass is under compression by the tablet punches), which can ultimately affect hardness, friability; dissolution, etc. in general, an increased dwell time will result in a harder tablet.

7. **Tablet coating-** Tablet properties such as hardness, shape are important to obtain a good film-coated tablet. The tablet needs to be hard enough to withstand the coating process. If tablet attrition occurs, the tablets will have a rough surface appearance. For tablet shape, a round tablet

will be easier to coat than tablets will multiple sides or edges because of the uniformity of the surface.

Pan speed- This will be interrelated to other coating parameters, such as inlet temperature, spray rate, and flow rate.

Spray Pattern- Spraying too fast will cause the tablets to become over wet, resulting in clumping of tablets and possible dissolution of the tablet surface. Spraying too slowly will cause the coating materials to dry prior to adhesion to the tablets. This will result in a rough tablet surface and poor coating efficiency. The concentration and viscosity of the coating solution will need to be determined.

C. Equipment evaluation- Review the working capacity of equipment. How long can the equipment operate without routine maintenance. Does the equipment require particular tooling? What is the shape of the coating pan, oval, mushroom, round? The shape characteristic will affect the degree of agitation and direction of tablet flow in the pan.

Validation of Suspension

Manufacturing of the products and their procedure must be reviewed to minimize contamination. Observe the addition of drug substance and powdered excipients to manufacturing vessels to determine if operations generate dust. Observe the systems and the efficiency of the dust removal system.

Equipment- Equipment should be of sanitary design. This includes sanitary pumps, valves, flow meters and other equipment, which can be easily sanitized. To facilitate cleaning and sanitization, manufacturing and filling lines should be identified and detailed in drawings and SOPs.

Raw materials- The physical characteristics, particularly the particle size of the drug substance, are very important for suspensions. For syrups, elixir or solution a dosage form in which there is nothing suspended, particle size and physical characteristics of raw materials are not that important. Raw materials of a finer particle size may dissolve faster than those of a larger

particle size when the product is compounded. Review the physical specifications for any drug substance, which is suspended in the dosage form.

Manufacturing- For oral suspensions, there is the additional concern with uniformity, because of the potential for segregation during manufacture and storage of the bulk suspension, during transfer to the filling line and during filling. There should be established procedures and time limits for such operations to address the potential for segregation or settling as well as other unexpected effects that may be caused by extended holding or stirring.

For oral solutions and suspensions, the amount and control of temperature is important from a microbiological as well as a potency aspect. For products in which temperature is identified as a critical part of the operation, the documentation of temperature must be reviewed. There are also some oral liquids, which are sensitive to oxygen and have been known to undergo degradation. The manufacturing of such products might require the removal of oxygen. Such products might also require storage in sealed tanks, rather than those with loose lids.

Oral Suspensions Uniformity- Depending upon the viscosity, many suspensions require continuous or periodic agitation during the filling process. If delivery lines are used between the bulk storage tank and the filling equipment, some segregation may occur, particularly if the product is not viscous. Review the procedures for filling and diagrams for line set-up prior to the filling equipment. Good manufacturing practice would call for testing bottles from the beginning, middle and end to assure that segregation has not occurred. In-process testing for suspensions might also include an assay of a sample from the bulk tank, more important, may be testing for viscosity.

Product Specifications- Important specifications for the manufacture of all solutions include assay and microbial limits. Additional important specifications for suspensions include particle size of the suspended drug, viscosity, pH, and in some cases dissolution. Viscosity can be important from a processing aspect to minimize segregation. There should be no stable cake formation and viscosity should be optimum to minimize segregation.

Stability- One area that has presented a number of problems includes the assurance of stability of oral liquid products throughout their expiry period. Interactions of products with closure systems are possible, liquids and suspensions undergoing stability studies should be stored on their side or inverted in order to determine whether contact of the drug product with the closure system affects product integrity.

Packaging- Problems in the packaging of oral liquids have included potency (fill) of unit dose products, accurate calibration of measuring devices such as droppers that are often provided. Problem in the packaging of Oral Liquids is the lack of cleanliness of containers prior to filling. Fibers and even insects have been identified in containers, and particularly plastic containers used for these products. Many manufacturers utilize compressed air to clean containers. Review the systems for the cleaning of containers.