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A SIMPLIFIED REVIEW ON PROCESS VALIDATION IN PHARMACEUTICAL INDUSTRY.

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Abstract: Now a days validation of all major pharmaceutical systems and processes are very essential. Process validation is nothing but the documented verification of specific processes and systems against required specification. It is one of the important processes in the pharmaceutical industry. It is compulsory to comply with national and international standards of USFDA & other major regulatory bodies. Any validation process requires complete documentation that complies with standard operating procedures & ongoing operations. It is an integral part of the quality assurance system in pharma industries. By validating all process, we can be assured about final product in terms of quality.

KEY WORDS: Process Validation, Pharmaceutical Industry, Documentation, Quality Assurance.

INTRODUCTION: Every pharmaceutical industry wants their manufacturing products at required quantity & the desirable quality. For this Validation plays a key role in entire pharmaceutical industry. Validating a process provides a high degree of assurance that the process will result in a product that consistently meets all the acceptance criteria & predetermined requirements and specifications.

The FDA in "Guidelines on General Principles of Process Validation" 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 predetermined specifications and quality characteristics". According to EMEA, "Process validation can be defined as documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medical product meeting its predetermined specifications and quality attributes"

BENEFITS OF PROCESS VALIDATION:

- Consistent through output.
- Reduction in rejections and reworks.
- Reduction in utility cost.
- Avoidance of capital expenditures.
- Fewer complaints about process related failure.
- Reduced testing process & finished goods.
- More rapid and accurate investigations into process deviation.
- More rapid and reliable start-up of new equipment.
- Easier scale -up from development work.
- Easier maintenance of equipment.
- Improve employee awareness of processes.
- More rapid automation.

STRATEGIES FOR PROCESS VALIDATION:

The strategy selected for process validation should be simple & straight forward.

1. The use of different lots of raw materials should be included.
2. Batches should be run in succession & on different days & shifts.
3. Batches should be manufactured in the equipment and facilities designed for eventual commercial production
4. Critical process variables should be set within their operating ranges & should not exceed their operating ranges and should not exceed their upper and lower control limits during process operation.
5. Failure to meet the requirements of validation protocol with respect to process input & output control should be subjected to process requalification and subsequent revalidation following a thorough analysis of process data and formal discussion by the validating team.

IMPORTANCE OF PROCESS VALIDATION:

- Improve the use of technology.
- Improve the business benefits.
- Improve operational efficiency.
- Improve compliance with regulations.
- Reduce the risk of failure.
- Reduce the cost.
- Process optimization.
- Increased customer satisfaction.

PHASES OF PROCESS VALIDATION: All the relevant activities related to validation studies may be classified into 3 phases.

Phase 1 – It is also known as 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 conditions, storage and handling of in-process & finished dosage forms, Equipment qualification, Installation qualification, master production documents, Operational qualification, Process capability.

Phase 2 – It is also known as Process validation phase, which is designed to verify that all established limits of the critical process parameters are valid and that satisfactory products can be produced even under the worst case conditions.

Phase 3 – It is also known as Validation maintenance phase, which requires frequent review of all process related documents, including validation audit reports to assure that changes have not made, no deviations, no failures & no modifications have been done to the production process & that all SOPs have been followed, including change control procedures.

INDUSTRIAL PROCESS EVALUATION AND SELECTION:

VALIDATION OF MIXING: Mixing is also called blending. It ensures production of uniform mixture of active pharmaceutical ingredients and excipients that do not segregate post blending. So, this process is examined thoroughly and validated. Materials having similar physical properties will be easier to form a uniform mix as compared to different properties.

PARAMETERS TO BE CONSIDERED**:**

- Mixing or blending technique.
- Mixing or blending speed.
- Mixing or blending time.
- Drug uniformity.
- Excipient uniformity.
- Equipment Capacity/load.

GRANULATION: If a powder blend's properties do not suit direct compression tableting, manufacturers will turn into granulation process to create the desired flowability & low dust ability. These characteristics are required to minimize tablet weight variations & ensure high density for high tablet filling weight & high mouldability for hard tablet manufacture. It is more time-consuming technique compared with direct compression and there is also risk of product cross-contamination & product loss during granulation, drying & sieving.

- **WET GRANULATION:** In wet granulation, a liquid binder solution is combined with a bed of mixed powders to mass the particles together into granules. The damp mass is then screened, dried and milled to the desired size. Different types of wet granulation techniques can be used such as low shear, high shear or fluid bed. Each technique will produce granules with different physical properties and will require monitoring of different processing parameters.

  PARAMETERS TO BE CONSIDERED:

  - Binder addition.
  - Binder concentration.
  - Amount of binder solution/granulating solvent.
  - Binder concentration.
  - Amount of binder solution/granulating solvent.
  - Binder solution/granulating solvent addition.
  - Mixing time.
  - Granulation end point.

- **DRY GRANULATION**: In the dry granulation method the granulation is formed not by adding a binder. Here compacting large mass of the mixture and subsequently crushing and sizing these pieces into smaller granules takes place. The primary powder particles are aggregated under a high pressure. There are two main processes. Either a large tablet (known as a slug) is produced in a heavy-duty tablet press, which is called slugging or the powder is squeezed between two rollers to produce a sheet of material (roller compaction).

WET MILLING: The wet granulation might need to be milled to break up the lumps and enhance drying of the granulation. Wet granules that have a wide aggregate range can lead to inefficient drying.

FACTORS TO BE CONSIDERED:

- Equipment size & capacity.
- Screen size.
- Mill speed.
- Feed rate.

DRYING: The type of drying technique (e.g., tray, fluid bed and micro wave) required for the formulation needs to be determined and justified. The type of technique may be dependent on such factors as drug or formulation properties and equipment availability. Changing dryer techniques could affect such tablet properties as hardness, disintegration**,** dissolution & stability. The optimal moisture content of the dried granulation needs to be determined. High moisture content can result in tablet 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 such state-of-the art techniques as **Near infrared** spectroscopy.

FACTORS TO BE CONSIDERED**:**

- Inlet/outlet temperature.
- Air flow.
- Moisture uniformity.
- Equipment capability/capacity.

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. In adequate flow can result in" rat holling" in the hopper and segregation of the frame in hopper frame. This can cause tablet weight & content uniformity problems. As for the compressibility properties of the formulation, it should be examined on an instrumental tablet press.

FACTORS TO BE CONSIDERED**;**

- Tooling
- Compression speed
- Compression force

The following in process tests should be examined during the compression stage:

- Appearance
- Hardness
- Tablet weight
- Friability
- Disintegration

TABLET COATING: Tablet coating can occur by different techniques (e.g., sugar, film or compression). Film coating has been the most common technique over recent years. Tablet may be coated for various reasons like stability, taste making, controlled release, product identification, safety material handling etc.

PARAMETERS TO BE CONSIDERED**;**

- Tablet properties
- Equipment type
- Coater load
- Pan speed
- Spray guns
- Tablet flow
- Inlet/outlet temperature and air flow
- Coating solution
- Coating weight
- Residual solvent level

CONCLUSION: Process validation is one of the major protocols in pharmaceutical industry. It is very useful because it confirms that all the works have been done properly and systematically. The goal of the process validation to create a manufacturing process that consistently produces a drug product with minimal variation that goes with the quality criteria of purity, identity and potency. It can be stated that it is major requirement of CGMPs regulation for the process efficiency and sturdiness from the review validation data on pharmaceutical process validation. It is concluded from the simplified review that process validation is essential for a pharmaceutical industry and if any improvements will be available in process validation, it will be much better & useful.

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