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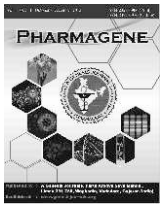

A Review On: Process Validation of Tablet Dosage Form With Risk Assessment Study

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Abstract:

Product quality is the mainstay of pharmaceutical industries and is derived from careful attention to a number of factors including selection of quality parts and materials, adequate product and manufacturing process design, control of the process variables, in-process and end-product testing. Process validation and risk assessment study are an integral part of quality assurance program in industries. By validating each step of production process we can assure that the final product is of best quality. This review provides information on objectives and benefits of process validation, types of process validation, major phases in validation and regulatory aspects. Guidelines and strategy for process validation of solid dosage form are also discussed andto minimize the errors and deviations of set quality attributes, avoiding rejections / minimizing rejections. Quality cannot be adequately assured by in process and finished product testing. It should be built into the various stages of manufacturing process. Risk assessment was done in order to minimize failure mode. During risk assessment, failure modes were identified, analysed and evaluated by setting current control.

Key Words : Quality, Process variables, Process validation, Risk assessment.

Introduction :

RISK ASSESSMENT

Risk assessment can be defined as systematic process of organizing information to support a risk decision to be made within a risk management process.

PRINCIPLE

Two primary principles of quality risk management are:

The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient; and

The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk.

-It consists of the identification of hazards and the analysis and evaluation of risk associated with exposure to those hazards. It consists of the identification of hazards and the analysis and evaluation of risk associated with exposure to those hazards.

In the subsequent risk analysis the following basic questions should be addressed:

- What is the nature of possible hazards?
- What is the probability of their occurrence and how easy is it to detect them?
- What are the consequences (the severity)?

Potential hazards in relation to at least the following should be considered:

- Materials and ingredients;
- Physical characteristics and composition of the product;
- Processing procedures;
- Microbial limits, where applicable;
- Premises;
- Equipment;
- Packaging;
- Sanitation and hygiene;
- Personnel- human error; and
- Risk of explosions.

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Overview of a typical quality risk management process

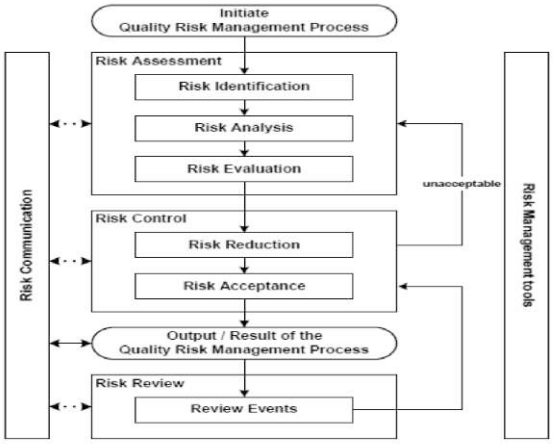

Figure: Quality risk management process

VALIDATION

In the mid 1970's , Food and Drug Administration (FDA) officials, Ted Byers and Bud Loftus first proposed the concept of validation in order to improve the quality of pharmaceuticals.

"Validation is an act of demonstrating and documenting that any procedure, process, and activity will consistently lead to the expected results."

VALIDATION PRINCIPLE

The basic principle of quality assurance is that a drug should be produced that is fit for its intended use. In order to meet this principle, a good understanding of the processes and their performance is important. Quality cannot be adequately assured by in-process and finished product inspection and testing but it should be built into the manufacturing processes.

These processes should be controlled in order that the finished product meets all quality specifications. Therefore, building of the quality requires careful attention to a number of factors, such as the selection of quality materials/components, product and process design, control of processes, in-process control, and finished product testing. Careful design and validation of system and process controls can establish a high degree of confidence that all lots or batches produced will meet their intended specifications.

PROCESS VALIDATION

As per ICH : "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 the required quality."

As per WHO: "Validation is documented act of proving that anyprocedure, process, equipment, material, activity or system actually leads to the expected results." Validation act of proving, in accordance of GMPs that any process actually leads to expected results. Documented evidence that the process, operated with in established parameters, can perform effectively reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes.

As per USFDA: "Process validation is establishing documented evidence which provides a high degree of assurance that a specific process will continuously produce a product meeting its predetermined specifications and quality attributes."

Above definition is as per 1987 guideline. The revised guideline was published in January 2011.As per 2011 guideline

"Process validation is defined as the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product."

The FDA considers process validation necessary because

It makes good engineering sense.

It results in fewer product recalls and troubleshooting assignments in manufacturing operations.

It results in more technically and economically sounds products and their manufacturing processes.

TYPES OF PROCESS VALIDATION

Prospective validation

It is conducted for new product / modified production process before the process is put into commercial use.

It establishes documented evidence prior to process implementation that a system does what it proposed to do based on preplanned protocols. 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.

Prospective validation is carried out during the development stage by means of a risk analysis of the production process, which is broken down into individual steps. Each step should be evaluated on the basis of past experience to determine whether they might lead to critical situations.

Where possible critical situations are identified, the risk is evaluated, the potential causes are investigated and assessed for probability and extent, the trial plans are drawn up, and the priorities set. The trials are then performed and evaluated, and an overall assessment is made. If, at the end, the results are acceptable, the process is satisfactory. Unsatisfactory processes must be modified and improved until a validation exercise proves them to be satisfactory. This form of validation is essential in order to limit the risk of errors occurring on the production scale, e.g. in the preparation of injectable products.

Retrospective validation

Retrospective validation is used for facilities, processes, 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 changes 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 been subjected to the Prospective validation process. It is used only for the audit of a validated process.

Concurrent validation
Concurrent validation is used for establishing documented evidence that a facility and processes 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 end product testing of current production, to show that the manufacturing process is in a state of control.

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

The transfer of a product from one plant to another.

Changes to the product, plant, manufacturing process, Batch size, cleaning process, or other changes that could affect product quality.

The necessity of periodic checking of the validation results.

IMPORTANCE OF VALIDATION
- ✓ Reduction of quality costs
- ✓ Process optimization
- ✓ Assurance of quality
- ✓ Safety

Reduction of quality costs
✓ Preventive costs: These are the costs incurred in order to prevent failures and/or reduce the appraisal costs. They involve the following:
- Quality planning & Vendor approval system
- Training
- Documentation, SOPs, monographs
- Preventive maintenance
- Calibration & Sanitation
- Annual review of data or trend analysis

✓ Appraisal costs: These are costs of inspection, testing and quality evaluation.

✓ Internal failure costs :
- Rejects and Reworks
- Re-inspection and Retests
- Wastage/ Scrap

✓ External failure costs :
- Recalls
- Complaints
- Returns due to quality related problems

Process optimization
Optimization means make the process effective, efficient, perfect as possible at the minimum cost. Trained, qualified people are a key element in any process and thus have the greatest impact on improving efficiency and productivity.

Assurance of quality
Validation is an extension of the concepts of quality assurance since close control of the process is necessary to assure product quality and it is not possible to control a process properly without thorough knowledge of the capabilities of that process.

Without validated and controlled processes, it is impossible to produce quality products consistently. End product testing, in the absence of validation, gives little assurance of quality for various reasons, among which are:

- Very limited sample size.
- The limited number of tests performed on a sample. For example, it is impractical to test for all potential impurities or contaminants.
- The limited sensitivity of the test.

Safety
Validation can also result in increased operation safety.

The pharmaceutical industries are concerned about validation because of the following reasons.
i) Assurance of quality
ii) Cost reduction
iii) Government regulation

ELEMENTS OF PROCESS VALIDATION
Design Qualification (DQ)
It is documented review of the design, at an appropriate stage of stages in the project, for conformance to operational and regulatory expectations. Design qualification (DQ) defines the "functional and operational specifications of the instrument and details the conscious decisions in the selection of the supplier."

DQ Check Items:
- GMPs and regulatory requirements
- Performance criteria
- Facility air flow, movement flow & pressure regimes
- Reliability & efficiency
- Safety & environment impact
- Construct ability & installation of equipment
- Maintenance & access to critical equipment & instrumentation
- Commissioning requirements

Installation Qualification (IQ)
It is documented verification that all aspects of a facility, utility or equipment that can affect product quality adhere to approved specifications and are correctly installed. IQ is established by objective evidence that all key aspects of the process equipment and ancillary system installation adhere to the manufacturer's approved specification and that the recommendations of the supplier of the equipment are suitably considered.

Important IQ considerations are:

- Installation conditions (wiring, utilities and functionality)
- Calibration, preventive maintenance, cleaning schedules
- Safety features
- Supplier documentation, prints, drawings and manuals
- Software documentation
- Spare parts list
- Environmental conditions (such as clean room requirements, temperature and humidity)
- Equipment design features (i.e. materials of construction, cleanability)

Operational Qualification (OQ)
It is documented verification that all aspects of a facility, utility or equipment that can affect product quality operate to Intend throughout all anticipated ranges. OQ is established by objective evidence that process control limits and action levels which result in product that meets all predetermined requirements.

OQ considerations include:
- Process control limits (time, temperature, pressure, line speed and setup conditions)
- Software parameters
- Raw material specifications
- Process operating 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 conditions (Failure Mode and effects)
- 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:
- Process repeatability, long term process stability
- Acceptability of the product
- Assurance of process capability as established in OQ
- Actual product and process parameters and procedures established in OQ.

PHASES OF PROCESS VALIDATION
The activities relating to validation studies may be classified into three phases:

Phase 1:
Pre-Validation Phase or the Qualification Phase (process design), 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 and finished dosage forms, equipment qualification, installation qualification, master production documents, operational qualification, process capability.

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

Phase 2:
Process Validation Phase (Process Qualification phase) 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.

During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.

Phase 3:
Validation Maintenance Phase requiring frequent review of all process related documents, including validation audit reports to assure that there have been no changes, deviations, failures, modifications 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 have been no changes/ deviations that should have resulted in requalification and revalidation. Ongoing assurance is gained during routine production that the process remains in a state of control.

THE REGULATORY BASIS FOR PROCESS VALIDATION
Once the concept of being able to pre-directs process performance to meet user requirements evolved, FDA regulatory officials established that there was a legal basis of requiring process validation. The ultimate legal authority is in section 501(a)(2)(B) of the FD&C Act, which states that a drug is deemed to bead ultimate differ the methods used in or the facilities or controls used for its manufacture, processing, packing or holding do not conform to or administrated in conformity with CGMP. 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.

RESPONSIBLE AUTHORITIES FOR VALIDATION:
The validation working party is convened to define progress, coordinate and ultimately, approve 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.
- Head of quality assurance
- Head of engineering
- Validation manager
- Production manager

The responsibilities of each personnel of department are as follow:

Table 1 Responsibility

Designation/ Department	Responsibility
Manager – production	Responsibility for manufacturing of batches and review of protocol and report.
Manager – QC	Responsible for analysis of sample collected.
Executive QC	Responsible for sample 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.

Process Flow Chart

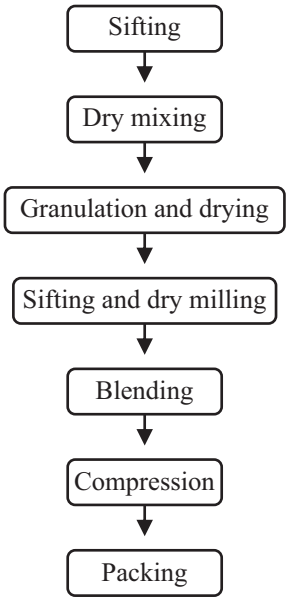

Figure 4.1 process validation flow Chart

Table 2 Steps for validation and critical parameters

Sr no.	Steps	Control variable	Critical parameter to be checked
1	Dry mixing	Impeller speed	Mixing time, mixing speed
2	Binder preparation and addition.	Temperature, solvent used	Mode and time of addition
3	Drying inlet/outlet temp. and time	Inlet/ outlet temperature and drying time	Initial drying, drying time
4	Lubrication	Blender/ granulator speed	Mixing time and speed
5	Compression	Pressure and turret speed	Machine speed and pressure

CONCLUSION

It can be stated that process validation is major requirement of cGMPs regulation for the process efficiency and sturdiness from the review validation data on pharmaceutical process validation and process control variables of tablets manufacturing processes in industry. Validation is the commonest word in the areas of drug development, manufacturing and specification of finished products. It also renders reduction in the cost linked with process monitoring, sampling and testing. The validation should start with active pharmaceutical ingredient (API) characteristics so that this material will be uniform batch after batch, providing a solid footing upon which the dosage form will be built. The parameters chosen must be relevant indicators of a controlled process. It is not sufficient merely to devise a test and set specifications for it; rather, it is desirable to show a cause and effect relationship between the parameter tested and control of the quality and/or process output. For the tableting procedure, the steps studied include powder blending, granulation, particle size, and lubrication with compression. Such step-wise studies have brought light into the impact of the parameters and increased the understanding of the respective processes and to collect a complete and rational database for the building of validation evidence.

It is concluded from the review that pharmaceutical validation and risk assessment study are important to assure that the drug product can meet standards for the identity, strength, quality, purity and stability.

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