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Process Validation of Solid Dosage Form

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Abstract Process validation is an essential part for the safety of drug products and also to maintain the quality of the products. It is a fundamental component for assuring the quality system used by pharmaceutical industries. Process validation is the key element to ensure the identity, purity, safety, and efficacy of drug products. The process validation precisely focused on the aim and method of analysis. The Process validation reduces product recalls and troubleshooting assignments which results in more economical manufacturing process and quality products. In this article an overview is given on process validation with special reference to solid dosage forms.

Keywords Process validation, Product recalls, Quality products, etc.

1. Introduction

Origin of risk management has a variety of sources and it is described and practiced by a variety of professionals.
A risk is a probability or threat of damage, loss or any other negative impact or occurrence that is may be caused due to internal or external vulnerabilities and that may be skipped by preemptive actions. The process of conducting risk management involves planning, identification, analysis and response planning, monitoring and control on the project.
Risk management involves identifying, assessing, controlling and analyzing threats to an organization's capital and processing for its betterment and progress.

1.1. Features of risk management

Failure to manage the risks in an organization can be caused due to inadequate risk recognition, insufficient analysis for significant risks and failure to identify suitable risk response.
Risk management examines the key components of risk management and how it can be applied. It examines the key components of risk management and how it can be applied. This process cannot be conducted in isolation. Risk management is designed in different ways in the range of standards, guides and other publications are available [1].

1.2. Scope

Risk management can be applied to different aspects of pharmaceutical quality. These aspects include development, manufacturing, distribution, inspection and submission/review processes throughout the lifecycle of drug substances, drug products, biological and biotechnological products including the use of raw materials, solvents, excipients, packaging and labelling materials in drug products, biological and biotechnological products [2].

1.3. Principles of Quality Risk Management

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.
- The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk [3].

1.4. General Quality Risk Management Process

Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the drug product across the product lifecycle. A model for quality risk management is outlined in the diagram (Figure 1.1). Other models could be used. The emphasis on each component of the framework might differ from case to case but a robust process will incorporate consideration of all the elements at a level of detail that is commensurate with the specific risk [4].

I. Initiating a quality risk management process

- Quality risk management includes systematic processes designed to coordinate, facilitate and improve science-based decision making with respect to risk.
- Define the problem and/or risk question, including pertinent assumptions identifying the potential for risk.
- Assemble background information and data on the potential hazard, harm or human health impact relevant to the risk assessment.

II. Risk assessment

Risk assessment consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards.

The steps include, risk identification, risk analysis and risk evaluation.

- **Risk identification-** It is a systematic use of information to identify hazards and risks that affects professionals. Information can include historical data, theoretical analysis, informed opinions, and the concerns of stakeholders.
- **Risk analysis-** It involves the estimation of the risk associated with the identified hazards. It is the process that focuses on the second and third questions, seeking the likelihood that risks identified in risk identification might occur and an ability to detect them.
- **Risk evaluation-** It compares the identified and analyzed risk against given risk criteria. A qualitative or quantitative process might be used to assign the probability and severity of a risk.

III. Risk Control

Risk control includes decision making to reduce and/or accept risks. The Purpose of risk control is to reduce the risk to an acceptable level. The amount of effort used for risk control should be proportional to the significance of the risk [5].

2. Validation

The concept of validation was first proposed by food and drug administrations, Ted Byers and Bud Loftus, in order to improve quality of pharmaceuticals.

The origins of validation in the global healthcare industry can be traced to terminal sterilization process failures in the early 1970s. Validation in the pharmaceutical, medical device, food, blood establishments, tissue establishments, and clinical trials.

2.1. Definition of Validation

"Establishing documented evidence, which provides a high degree of assurance that specific process, will consistently produce a product meeting its predetermined specification and quality attributes".

It often includes the qualification of systems and equipment. It is a requirement for Good Manufacturing Practices and other regulatory requirements. Since a wide variety of procedures, processes, and activities need to be validated. The field of validation is divided into a number of subsections including the following:

- Process validation
- Cleaning validation
- Equipment validation
- Validation of analytical methods [6]

2.2. Purpose

Validation act as guidance that is intended to assist manufacturers in understanding quality management system requirements concerning process validation [7].

2.3. Scope

- Selecting raw material of desired quality
- Product designed as per expectations
- Processing designed as per desired quality attributes in the product
- Designing other parameters like control parameters, tolerance limits, acceptance limits, change control, etc.
- Process validation has general applicability to manufacturing (including servicing and installation) processes for medical devices. Specific recommendations for verification of design output and design validation are included in the global harmonization task force document covering design control.
- This guidance describes process validation activities in three stages;
- **Stage 1 – Process design**: The commercial manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities.
- **Stage 2 – Process qualification**: During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.
- **Stage 3 – Continued process verification**: Ongoing assurance is gained during routine production that the process remains in a state of control [8].

2.4. Principle Elements of Validation

(I) Documented evidence:

Validation requires thorough documentation. Everything that is not documented is considered incomplete.

(II) High degree of assurance:

The assumption is that a large software package as used in complex computerized systems is rarely free of errors. Frequently, there is a perception that validation means error-free. This assumption is wrong. During the validation process, everything realistically possible should be done to reduce errors to a high degree.

(III) Specific process:

The overall validation of software is process related, not product related. For example, the development and testing activities performed prior to releasing the software for manufacture are validated once for a series of products characterized by the serial number.

Some subparts of validation, such as the qualifications (installation, operation, and performance) are product-specific and have to be done for each system.

(IV) Consistency:

Validation is not a one-time event. The performance of the equipment has to be controlled during the entire life of the product [9].

2.5 Validation v/s Testing, Calibration, Verification & Qualification

There is still considerable misunderstanding on the differences between testing, calibration, verification, and validation.

(I) Testing:

Testing has been defined as: "A technical operation that consists of the determination of one or more characteristics or performance of a given product, material, equipment, organism, physical phenomena, process or service according to a specified procedure."Instrument testing is the process of executing experiments to measure the performance characteristics following documented procedures.

Examples are the measurement of the baseline noise of a detector, the precision of the injection volume of an injector, or the precision of a flow rate.

(II) Calibration

Calibration has been defined as "The set of operations which establish, under specified conditions, the relationship between values indicated by a measuring instrument or measuring system and the corresponding known values of the measured."

A well-known example of a device that has to be calibrated is the balance. A reference weight that is traceable to a national standard is measured and the result compared with the actual weight. The term calibration is sometimes used interchangeably with the term standardization. Calibration normally means to check against known standards, whereas standardization usually means to make uniform. For some equipment, the term calibrated is more appropriate; for other equipment, the term standardized is better. The word calibration is also frequently used in FDA regulations and inspection reports interchangeably with operational qualification of equipment.

(III) Verification

Verification has been defined as "Confirmation by examination and provision of evidence that specified requirements have been met." Performance verification of analytical instrumentation is the process of comparing the test results with the specification. It includes testing and requires the availability of clear specifications and acceptance criteria.

Examples are the same as for testing. The verification process ends with the generation and sign-off of a "Declaration of Conformity" of the instrument to specifications. Additionally, a sticker should be affixed to the instrument with the date of the last successful performance verification and the next scheduled performance verification.

(IV) Qualification

Qualification has been defined as "Action of proving that any equipment works correctly and leads to the expected results." The word validation is sometimes widened to incorporate the concept of qualification. Like verification, qualification is also part of validation and is product-specific [10].

2.6 Elements of Qualification

- **Design Qualification (DQ):** Documented verification of the design of equipment and manufacturing facilities. It is documented review of the design, at an appropriate stage of stages in the project, for conformance to operational and regulatory expectations. DQ defines the "functional and operational specifications of the instrument and details the conscious decisions in the selection of the supplier."
- **Installation Qualification (IQ):** Documented verification of equipment or system design and adherence to manufacturer's recommendations. 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.
- **Operational Qualification (OQ):** Documented verification of equipment or system Performance in the target operating ranges. It includes all aspect of facility, utility or equipment that can affect product quality operate to intend throughout all anticipated ranges. OQ is defined as documented action of demonstrating

that process equipment and ancillary systems work correctly and operate consistently in accordance with established specifications.

- **Performance Qualification (PQ):** Documented verification that equipment or systems operate as expected under routine production conditions. The operation is reproducible, reliable and in a state of control. It is documented verification that all aspects of a facility, utility or equipment perform as intended in meeting predetermined acceptance criteria. It involves establishing documented evidence that the process is effective and reproducible [11].

2.7 Significance of Validation

To show that a process can "consistently produce what it purports to do" validation is vital requirements for any pharmaceutical industry. The four basic reasons for validation are compliance, quality assurance, economics and regulatory requirements.

(I) Compliance

Pharmaceutical manufacturers are directed by GMP and CGMP guidelines, which they are bound to follow. Validation is the medium with which compliance to these guidelines is attained and presented in a systemic way. Validation requirements in industry is supported by EC, GMP, WHO and further supported by FDA Guidelines on general principles of process validation.

(II) Quality assurance

A successful validation provides high degree of assurance up to consistent level of quality, therefore the second and most compelling reason for validation should be to guarantee, as far as possible that all processes and equipment in the pharmaceutical manufacturing process are being used in a way that will ensure the safety, integrity, purity, quality and strength of a product for use by the general public.

(III) Economics

Due to successful validation, there is decrease in sampling and testing procedures, similarly it leads to decrease in rejections and retesting and results into cost-saving benefits. Aside from the above reasons, validation is essential business practice. It prompts appraisal and reappraisal of every activity involved in a process and, almost inevitably, improvements are made. As a result of these validation activities, indirect economic benefits may arise.

(IV) Regulatory requirements

Fourth, and certainly foremost, among the reasons for validation is that it is a regulatory requirement for virtually every process in the global health care industry-for pharmaceuticals, biologics, and medical devices. Regulatory agencies across the world expect firms to validate their processes [12].

2.8. Benefits of Validation

(I) Quality

- Customer – patient satisfaction. It has been built into the product.

(II) Understanding equipment, system and process

- Process improvement, technology transfer, rapid failure investigations.
- Improve employee awareness and increased outputs.
- Easier maintenance of the equipment.
- Fewer complaints about process related failures.
- Easier scale-up from development work.

(III) Regulatory benefits

- Successful inspections.
- Approved products.
- Ability to export.

(IV) Cost reduction

- Fewer rejects and reworks and avoidance of capital expenditures.

- Increased efficiency, shortening lead time resulting in lower inventories.
- Longer equipment life by operating the equipment as per manufacture's specification and the establishing of cost effective preventive maintenance schedules.
- Reduction in utility costs.

(V) Time saving

- Possible reduced testing of raw materials bulk formulations and finished products.
- Reduced testing in process and finished goods.
- More rapid and accurate investigations into process deviations.
- More rapid and reliable startup of new equipment.
- More rapid automation [13].

2.9 Validation Process

- Pre- Validation activities
- Validation Protocol Preparation
- Validation Protocol review and approval
- Protocol execution
- Data analysis
- Validation report and sign- off
- Revalidation

(in case of change control) [14]

4. Process Validation

Process validation includes a series of processing activities carried out over the lifecycle of final product

4.1 Objective: The objective of this exercise is to develop a Process validation protocol to validate the standardized process and have documented evidence to ensure that critical process variables established during standardization are checked during validation. Also to demonstrate the process capability on equipment and utility ensuring that the product meets its predetermined specifications and quality attributes.

4.2 Scope: The scope of the Process validation of formulation defines the procedural aspects to be followed while carrying out Process validation activity that includes prerequisites before commencing the actual work like, Master formula and process, approved vendors and characteristics of raw materials. Also it defines the acceptance criteria, re-validation criteria and justification for critical process parameters.

4.3 Process validation is divided in four types

(I) Prospective validation
(II) Retrospective validation
(III) Concurrent validation
(IV) Revalidation

(I) Prospective validation

Conducted prior to the marketing of either a new product or a product made under a modified production process, where the modifications are significant and may affect the product's characteristics. This validation can be performed for all new equipments, products and processes. It is a proactive approach of documenting the design, specifications and performance before the system is operational. This is the most defendable type of validation.

(II) Retrospective validation

This is establishing documented evidence that the process is performed satisfactory and consistently over time, based on review and analysis of historical data. This validation conducted for a product already being marketed, and is based on extensive data accumulated over several batches. The source of such data is production and QA/QC records. The issues to be addressed here are changes to equipment, process, specifications and other relevant changes in the past.

(III) Concurrent validation

Concurrent validation establishes documented evidence that a process does what it purports to do base on information generated during actual implementation of the process. In this validation, current production batch is used to monitor processing parameters. It gives assurance of the present batch being studied, and offers limited assurance regarding consistency of quality from batch to batch. This is performed in two instances, i.e., for existing equipment, verification of proper installation along with specific operational tests is done. In case of an existing, infrequently made product, data is gathered from at least three successful trials

(IV) Revalidation

It refers to repeated validation for an approved process or part of the process carried out either periodically or after change in the process to ensure that such change bears no adverse effects on product quality [15].

Conditions that require revalidation studies are:

- Changes in critical component
- Change in facility or plant
- Increase or decrease in batch size
- Sequential batches that fail to conform product and process specifications [16]

5. Process Validation of Solid Dosage Forms

Process validation establishes the flexibility and constraints in the manufacturing process controls to attain the desirable attributes in the drug product while preventing undesirable properties.

This is an important concept, because of support and define the validation, which is a systematic approach to identifying, measuring, evaluating, documenting, and re-evaluating a series of critical steps in the manufacturing process that require control to ensure a reproducible final product.

5.1. Strategy for industrial process validation of solid dosage forms

The following five points gives strategy for process validation:

- The use of variety raw materials should be included. i.e. active drug substance along with major excipients.
- Batches should be run in systematic manner and on different days and shifts (the latter condition, if appropriate).
- Batches should perform manufacturing processes on the equipment and facilities designed for eventual commercial production.
- Critical process variables should be set within their operating ranges and should not exceed their upper and lower control limits during process operation. Output responses should be well within finished product specifications.
- Failure to meet the requirements of the Validation protocol with respect to process input and output control should be subjected to process prequalification and subsequent revalidation following a thorough analysis of process data and formal discussion by the validation team.[17]

6. Process Validation at Different Stages of Tablet Manufactured by Direct Compression

- Validation of shifting process.
- Validation of blending process.
- Validation of lubrication process.
- Validation of compression process.
- Validation of coating process.
- Validation of packing process.
- Validation of finished product [18].

7. 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
- Specialist validation discipline: all areas [19].

8. Change Control

Change control is defined as "a formal system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect a validated status. The intent is to determine the need for action that would ensure and document that the system is maintained in a validated state."Change control is a lifetime monitoring approach [20].

9. Validation Master Plan

It is important to draw up a summarized document that describes the whole project. It has become common practice in the industry to develop a "validation master plan" (VMP).It is a document providing information on the company's validation work programme. It should define details of and timescales for the validation work to be performed [21].

Summary and Conclusion

From an overview, it can be stated that process validation is the key element to ensure the identity, purity, safety, and efficacy of drug products. It is mandatory to conduct in pharmaceutical organization for its betterment and to get desired quality products. Various types and elements of process validation are utilized as per requirement and conditions. Observed sample values are compared with standard specifications to meet desired quality product.

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