Process Validation

Learning objectives

Students will be able to:

1. Explain the historical events that led to the development of process validation in the pharmaceutical industry.
2. Differentiate between FDA and EMA definitions of process validation and understand its scope.
3. Identify the types and approaches of process validation along with the Validation Master Plan.

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1. Introduction

In the field of pharmaceuticals, the development of process validation has been significantly impacted by a series of historical incidents. These events often arose from drug-related controversies that had a profound impact on the industry. We will take a journey through a historical timeline that illustrates some of these noteworthy occurrences, each underscoring the importance of robust process validation.

Incident	Year	Reason	Impact
Elixir Sulfanilamide Tragedy	1937	Contaminated elixir of sulfanilamide	More than 100 deaths
Cutter Incident	1955	Contained live polio virus	40,000 cases of paralysis, 10 deaths
Tylenol murders	1982	Tylenol capsules laced with KCN	7 deaths
Heparin Adulteration	2008	Heparin contaminated with counterfeit ingredient (over-sulfated chondroitin)	81 deaths
Valsartan Incident	2012-2018	Valsartan contaminated with N-nitrosodimethylamine (NDMA)	Increased risk of cancer

Additionally, in the period 2019-2023, the United States alone witnessed a staggering 6948 drug recalls. These recalls may be prompted by various factors, including safety concerns, mislabeling, contamination, and deviations in strength or potency. As we delve into the world of process validation, we recognize the imperative need to prevent such incidents and ensure the highest quality and safety standards in pharmaceutical production.

2. Definitions of Process Validation

FDA Definition of Process Validation (cGMP- Guidance for Industry Process Validation: General Principles and Practices: 2011): The U.S. Food and Drug Administration (FDA) defines process validation 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."

EMA Definition of Process Validation (GMP-Annex 15: 2015): The European Medicines Agency (EMA) defines process validation as "the documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes."

Process validation covers the following categories of drugs:

- Human drugs
- Veterinary drugs
- Biological and biotechnology products
- Finished products and active pharmaceutical ingredients
- The drug constituent of a combination (drug and medical device) product

3. Types of process validation based on timing

i. *Prospective Validation*: Validation done before new product launch to ensure the process consistently meets quality standards.
ii. *Concurrent Validation*: Ongoing validation during regular production to maintain product quality and consistency.
iii. *Retrospective Validation*: Validation of processes with a history of production to confirm their consistency and safety. This type is no longer considered acceptable.

4. Types of Process Validation based on approaches

a. Traditional validation approach

Approach Objective:

- Confirm the capability of a manufacturing process for consistent production of quality products.

Validation Batches:

- Typically, a minimum of 3 consecutive batches under routine conditions for validation.

Protocol Preparation:

- Develop a process validation protocol.
- Define critical process parameters (CPP), critical quality attributes (CQP), and acceptance criteria.
- Base criteria on development data or documented process knowledge.

Process validation protocols should include, but are not limited to the following:

i. A short description of the process;
ii. Functions and responsibilities;
iii. Summary of the CQAs to be investigated;
iv. Summary of CPPs and their associated limits;
v. Summary of other (non-critical) attributes and parameters which will be investigated or monitored during the validation activity, and the reasons for their inclusion;
vi. List of the equipment/facilities to be used (including measuring/monitoring/recording equipment) together with the calibration status;
vii. List of analytical methods and method validation, as appropriate.
viii. Proposed in-process controls with acceptance criteria and the reason(s) why each in-process control is selected;
ix. Additional testing to be carried out with acceptance criteria;
x. Sampling plan and the rationale behind it;
xi. Methods for recording and evaluating results;
xii. Process for release and certification of batches (if applicable).

b. Continuous process verification approach

Approach objectives:

- Enable ongoing monitoring and adaptation for product quality maintenance.

Validation batches:

- Number of batches required for assurance varies by manufacturer.

Protocol Preparation:

- Scientifically define the method for verification and control strategy.
- Regularly evaluate critical attributes and parameters using tools like Process Analytical Technology (PAT) and Multivariate Statistical Process Control (MSPC)

c. Hybrid approach

- Blend traditional and continuous approaches for optimal results.
- Utilize substantial product and process knowledge for enhanced validation.
- Applicable for validation activities after changes or during ongoing process verification.

5. Ongoing Process Verification during Lifecycle

The ongoing process verification (also known as continued process verification) is the documented evidence that the process remains in a state of control during commercial manufacture. It applies to all process validation approaches.

- Manufacturers must continuously monitor and assess product quality and process trends.
- The frequency and extent of verification should adapt over time as process understanding and performance evolve.
- Verification is done under approved protocols, using statistics where appropriate.
- It supports the product's validated status, addresses incremental changes, and may require enhanced sampling or other actions as needed.

6. Phases of Process Validation according to FDA

There are three phases of process validation according to the FDA:

Stage 1 - Process Design

- Building and capturing process knowledge and understanding: This involves documenting the process steps, identifying critical process parameters (CPPs), and establishing critical quality attributes (CQAs).
- Establishing a strategy for process control: This involves developing a control strategy to ensure that the CPPs are maintained within acceptable ranges and that the CQAs of the product are met.

Stage 2 - Process Qualification

- Design of a facility and qualification of utilities and equipment: This involves ensuring that the facility and equipment are designed to meet the requirements of the process and that they are capable of consistently producing a quality product.
- Process performance qualification (PPQ): This involves conducting a series of production runs under simulated commercial conditions to assess the process's ability to meet predetermined quality standards.

Stage 3 - Continued Process Verification

- Ongoing assurance that the process remains in a state of control: This involves monitoring process performance data, conducting periodic audits, and implementing process improvements as needed

7. Validation Master Plan (VMP)

A Validation Master Plan (VMP) is a document that outlines the strategy for qualification and validation activities in the pharmaceutical industry. It contains the following key information:

i. Policy: The overarching policies and principles for qualification and validation.
ii. Organizational Structure: Roles and responsibilities of personnel involved.
iii. Facilities and Equipment: Overview of facilities, equipment, and their qualification status.
iv. Change Control and Deviation Management: Procedures for handling changes and deviations.
v. Acceptance Criteria Guidance: Guidance on developing criteria for qualification and validation.
vi. References: Refers to relevant existing documents.
vii. Strategy: Outlines the overall approach to qualification and validation, including requalification plans if needed.

The VMP ensures consistency, compliance, and quality in the validation process.

8. Conclusion

In conclusion, process validation is crucial for ensuring the safety, effectiveness, and consistency of pharmaceutical products, meeting global regulatory standards. The high number of drug recalls, surpassing 1,000 annually, highlights the industry's imperative for ongoing improvement and stringent regulations to elevate product safety and quality.

References

- cGMP-Process validation : General Guidelines and practices. 2011
- GMP-Annex 15 : Qualification and Validation
- FDA Data dashboard - Drug Recalls: https://datadashboard.fda.gov/ora/cd/recalls.htm