ejpmr, 2025, 12(8), 403-409

SJIF Impact Factor 7.065

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN (O): 2394-3211

ISSN (P): 3051-2573

PROCESS VALIDATION OF PHARMACEUTICAL DOSAGE FORMS: A SCIENTIFIC REVIEW

Siddhi Sartape[1*], Pushpanjali Shinde[1], Shrikrishna Baokar[2] and Rajendra Patil[3]

[1]Department of Pharmaceutical Quality Assurance, Delonix Society's Baramati Collage of Pharmacy, Barhanpur, Tal- Baramati, Dist- Pune, Maharashtra, India 413102.

[2]Department of Pharmaceutical Analysis, Delonix Society's Baramati Collage of Pharmacy, Barhanpur, Tal- Baramati, Dist- Pune, Maharashtra, India 413102.

[3]Department of Pharmaceutical Chemistry, Delonix Society's Baramati Collage of Pharmacy, Barhanpur, Tal- Baramati, Dist- Pune, Maharastra, India 413102.

***Corresponding Author: Siddhi Sartape**

Department of Pharmaceutical Quality Assurance, Delonix Society's Baramati Collage of Pharmacy, Barhanpur, Tal- Baramati, Dist- Pune, Maharashtra, India 413102.

Article Received on 19/06/2025 **Article Revised on 09/07/2025** **Article Accepted on 29/07/2025**

ABSTRACT

Ensuring product quality is a fundamental requirement in pharmaceutical manufacturing. Process validation plays a crucial role in building a robust production system capable of consistently delivering drug products that meet predetermined specifications and safety standards. Validation is not merely an end-stage quality check; it is a lifecycle activity that begins at the process design stage and continues through routine manufacturing. Process validation involves comprehensive documentation and scientific evidence to confirm that a manufacturing process operates within defined parameters and produces high-quality drug substances and products. This review outlines the principles and regulatory expectations surrounding pharmaceutical process validation, including types such as prospective, retrospective, concurrent, and revalidation. Additionally, validation approaches for solid oral dosage forms (e.g., tablets), semisolid forms (ointments and creams), and aerosol formulations are discussed, with emphasis on critical process parameters, quality attributes, and control strategies. In accordance with Good Manufacturing Practices (GMP) and regulatory guidelines from the FDA, EMA, and WHO, process validation supports product integrity, enhances manufacturing efficiency, and minimizes risks of batch failure and product recalls. This article serves as a comprehensive guide to the scientific, practical, and regulatory aspects of process validation across pharmaceutical dosage forms.

INTRODUCTION

The pharmaceutical industry is tasked with producing medications that are not only effective but also safe, consistent, and high in quality. To achieve this, manufacturers must ensure that their production processes are well understood, controlled, and capable of consistently yielding products that meet predefined quality attributes. One of the key tools to achieve this assurance is process validation.

Process validation is defined by the United States Food and Drug Administration (USFDA) 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".[1] Rather than relying solely on end-product testing, modern validation emphasizes quality by design (QbD)—embedding quality into each step of the process.

Historically, the concept of validation was introduced in the mid-1970s by FDA officials Ted Byers and Bud Loftus to ensure that pharmaceutical products meet safety and efficacy requirements. Today, process validation is a mandatory regulatory requirement under Current Good Manufacturing Practices (cGMP**)** and a central part of the Quality Management System (QMS).

Process validation ensures that variability in raw materials, equipment, environment, and personnel is minimized and controlled. This leads to greater product consistency and reduced risk of manufacturing failures or product recalls. Solid dosage forms like tablets and capsules, semisolid forms such as ointments and creams, and specialized systems like aerosols each require tailored validation strategies based on their unique formulation and processing characteristics.

In summary, the objective of process validation is to provide documented assurance that the manufacturing process will consistently produce products meeting their intended quality specifications. It encompasses risk assessment, critical process parameter (CPP) identification, and ongoing monitoring to maintain process control throughout the product lifecycle.

TYPES OF VALIDATION

In pharmaceutical manufacturing, various types of validation are employed based on the stage of product development, process understanding, and regulatory requirements. Each validation type serves a specific purpose in establishing, maintaining, and verifying process performance. The major types of validation include:

Analytical Method Validation

Analytical method validation ensures that the testing methods used for evaluating drug quality are reliable, reproducible, and appropriate for their intended purpose. Key parameters assessed during method validation include:

- **Accuracy** – closeness to the true value
- **Precision** – repeatability and reproducibility
- **Specificity** – ability to distinguish analyte from other substances
- **Limit of Detection (LOD) and Limit of Quantification (LOQ)**
- **Linearity and Range**
- **Robustness** – ability to remain unaffected by small changes in method conditions
  Validation of analytical methods must be conducted in accordance with ICH Q2 (R1) guidelines.[2]

Equipment Qualification

Equipment validation, also referred to as equipment qualification, confirms that manufacturing equipment is installed, operated, and performs as intended. It comprises four stages:

- **Design Qualification (DQ):** Ensures design meets user requirements
- **Installation Qualification (IQ):** Confirms proper installation per specifications
- **Operational Qualification (OQ):** Verifies performance under defined conditions
- **Performance Qualification (PQ):** Confirms consistent output under normal conditions

These stages form a foundational step in process validation by ensuring that the equipment functions reliably throughout production.[3]

Process Validation

Process validation provides documented evidence that a manufacturing process consistently produces a product meeting its specifications and quality attributes. It can be categorized into:

- **Prospective Validation:** Conducted before commercial distribution. It uses pre-validated protocols on pilot or commercial-scale batches.
- **Concurrent Validation:** Carried out during routine production, with full documentation and monitoring of actual manufacturing batches.
- **Retrospective Validation:** Uses historical data from previously manufactured batches to demonstrate consistent quality.
- **Revalidation:** Required when there are significant changes in the process, equipment, or formulation, or after a prolonged gap in production.[4]

PROCESS VALIDATION OF TABLETS

Tablets are the most widely used oral solid dosage form due to their ease of administration, accuracy in dosing, and long shelf life. Validating the tablet manufacturing process is critical to ensuring uniformity in content, weight, hardness, and dissolution characteristics.

A typical tablet production process includes the following steps: weighing, blending, granulation, drying, compression, and coating. Validation ensures that each of these steps contributes to consistent product quality.

Blending and Mixing

Uniform distribution of active pharmaceutical ingredients (APIs) and excipients is essential. Improper blending can lead to content non-uniformity, affecting dosage accuracy and therapeutic efficacy.

Critical parameters to validate include

- **Blending method:** Diffusion (tumble), convection (high-shear), or pneumatic (fluid-bed)
- **Blending time and speed:** Longer mixing may improve homogeneity but can damage granules or lead to over-lubrication
- **Batch size and load:** Equipment must not be overfilled or underloaded
- **Uniformity of content:** Must meet pharmacopeial limits (typically 85–115% of label claim)[5]

Granulation (Wet or Dry)

Wet granulation is commonly used to improve powder flow and compressibility. The binder solution must be carefully controlled:

- **Binder concentration:** Must be optimized to avoid overwetting or under-binding
- **Granule size distribution:** Affects flow, compressibility, and dissolution
- **Drying:** Moisture content must be controlled to prevent degradation or poor compression[6]

Dry granulation or direct compression methods may be employed for moisture-sensitive APIs, requiring validation of powder flow, compressibility, and lubricant mixing.

Compression

This step converts granules into tablets. Key parameters include:

- **Compression force:** Affects tablet hardness and friability
- **Tablet weight variation:** Indicates consistency of die fill

- **Tooling and machine speed:** Must be validated to ensure minimal weight variation and mechanical integrity
- **In-process checks:** For weight, thickness, hardness, and disintegration must be defined and documented[7]

Coating

Coating enhances product appearance, protects from environmental factors, and may modify drug release.

Validation aspects include

- Spray rate and atomization pressure
- Coating solution uniformity and viscosity
- Pan rotation speed and temperature
- Weight gain consistency

Uniform coating ensures batch-to-batch consistency and avoids defects like peeling, mottling, or cracking.[8]

PROCESS VALIDATION OF OINTMENTS AND CREAMS

Ointments and creams represent key semisolid dosage forms widely used for topical application. They serve local or systemic delivery functions and must possess consistent texture, spreadability, drug content uniformity, and stability. Unlike solid oral forms, semisolids involve unique rheological and emulsification considerations during manufacturing. Therefore, validation of these dosage forms requires careful control of formulation and processing parameters to ensure consistent product quality.

Process validation for ointments and creams involves identifying and controlling critical process parameters (CPPs) and critical quality attributes (CQAs) such as viscosity, homogeneity, pH, emulsion stability, and API content uniformity.

Key Steps in Manufacturing and Parameters to Validate

Step	Parameters to Validate
Phase Preparation	Temperature, mixing speed, sequence of addition
Emulsification	Emulsification time, shear rate, phase ratios
Homogenization	Pressure, cycle count (for globule size control)
Cooling	Cooling rate, target temperature
API Addition (post-emulsification)	Mixing time, content uniformity
Filling & Packing	Fill volume, weight variation, container closure integrity

Critical Manufacturing Parameters

- **Temperature Control**

Temperature plays a crucial role in emulsification, solubilization, and physical stability. High temperature may degrade thermo labile APIs, whereas insufficient heating can result in incomplete emulsification or phase separation.

- **Recommended practice:** Maintain oil and aqueous phases within ±2°C before mixing.
- **Validation point:** Batch records must capture peak and equilibrium temperatures for each phase.[9]
- **Mixing Speed and Duration**
  Shear rate directly impacts viscosity, particle dispersion, and homogeneity. Over-shearing may break emulsions or degrade polymeric thickeners, while under-mixing may lead to phase separation or poor drug distribution.
- **Validation point:** Determine minimum and maximum mixing durations to achieve target viscosity without degradation.[10]

Addition of Polymers and Gums

Polymers such as Carbomers, Xanthan gum, or Hydroxy propyl methyl cellulose (HPMC) are common rheology modifiers. These agents must be properly dispersed and hydrated to ensure consistency.

- **Best practices**
  - Add polymers slowly using high-shear mixers or inline homogenizers
  - Avoid lump formation or incomplete hydration
  - Validate dispersion time and shear rate required for complete solubilization.[11]

Emulsification Parameters

Stability of oil-in-water (O/W) or water-in-oil (W/O) emulsions depends on controlled emulsification.

- **Control strategy**
  - Validate emulsifier concentration and order of addition
  - Monitor phase inversion temperature (PIT)
  - Use droplet size analysis to verify emulsion stability.[12]

Quality Attributes to Monitor

CQA	Purpose
pH	Ensures skin compatibility and formulation stability
Viscosity	Indicates texture, spreadability, and consistency
Homogeneity	Confirms even API distribution
API Assay	Verifies potency and uniformity
Microbial Limit	Ensures safety in non-sterile products
Emulsion Type Confirmation	Verifies formulation integrity
Globule Size	Affects texture and release profile

Common Challenges and Control Strategies

Challenge	Control Strategy
Phase separation	Optimize emulsification parameters (shear, time, temp)
API sedimentation	Use proper homogenization and polymer stabilizers
Microbial contamination	Use validated preservatives and hygienic equipment

Life Cycle Approach to Validation (as per FDA & ICH)

Following the FDA's Process Validation Guidelines (2011) and ICH Q8–Q10**,** validation of creams and ointments is executed across three key stages:

1. **Process Design (Stage 1)**
   - Develop formulation and identify CPPs & CQAs
   - Conduct risk assessment and scale-up trials
   - Select appropriate mixing, heating, and cooling strategies

2. **Process Qualification (Stage 2)**
   - Conduct Installation Qualification (IQ)**,** Operational Qualification (OQ)**,** and Performance Qualification (PQ)
   - Validate 3 consecutive commercial-scale batches
   - Monitor parameters such as temperature, viscosity, API uniformity, and microbial quality

3. **Continued Process Verification (Stage 3)**
   - Implement trending of process data (e.g., pH, viscosity)
   - Periodic review of deviations, out-of-specification (OOS) results, and batch performance
   - Revalidation after significant changes

PROCESS VALIDATION OF AEROSOL DOSAGE FORMS

Pharmaceutical aerosols, particularly pressurized metered-dose inhalers (pMDIs)**,** are advanced dosage forms designed to deliver medication to the respiratory tract. They are widely used in the management of asthma, chronic obstructive pulmonary disease (COPD), and other pulmonary conditions due to their ability to provide rapid, localized, and measured drug delivery. Given the complex interplay between formulation, device design, and patient handling, validating aerosol processes is crucial for ensuring product performance and consistency.

Characteristics of Aerosol Dosage Forms

pMDIs consist of:

- Active pharmaceutical ingredient (API)
- Propellant (e.g., hydro fluoro alkanes: HFA-134a, HFA-227ea)
- Co-solvents (e.g., ethanol)
- Surfactants or lubricants
- Primary container (canister), metering valve, actuator, and spacer

These components work together to deliver a consistent aerosol spray or mist upon actuation. The drug dose is suspended or dissolved in the propellant, and the metering valve ensures accurate dosing.

Process Validation Objectives for pMDIs

Validation of the manufacturing process for aerosol dosage forms ensures:

- Consistent dose delivery
- Content uniformity across actuations
- Appropriate droplet size and spray pattern
- Stability and integrity of the pressurized system

As per FDA**,** EMA, and ICH guidelines, process validation should be based on a lifecycle approach, incorporating scientific and risk-based decision-making.[13]

Critical Process Parameters (CPPs) and Quality Attributes (CQAs)

Parameter	Purpose / Impact
Propellant filling pressure	Affects spray force, dose content, and valve sealing
Crimping force of valve	Ensures leak-proof sealing and accurate metering
Actuator/orifice dimensions	Influences spray pattern and droplet size
Homogeneity of suspension	Prevents dose variability and clogging
Container closure integrity	Maintains sterility and prevents leakage
In-process temperature	Influences propellant behavior and drug solubility
API particle size	Affects deposition in lungs and bioavailability
Drug content per spray	Confirms therapeutic dose consistency

Process Steps and Validation Activities

1. Mixing / Suspension Homogeneity

- Validate that APIs and excipients are uniformly suspended or dissolved.
- Parameters: Mixing time, shear rate, and temperature.

2. Propellant Charging

- Validate pressure and fill weight of propellant.
- Filling must occur under controlled, low-temperature environments to minimize evaporation losses.

3. Valve Crimping
- Crimping pressure is critical for forming a secure seal.
- Improper crimping can cause leakage or metering failure.

4. Filling
- Validate fill weight accuracy, content uniformity, and pressure testing.
- Real-time fill weight monitoring is advised.

5. Container Closure Integrity
- Perform leak testing using methods such as water bath, helium leak detection, or vacuum decay.

6. Finished Product Testing
- Average weight per actuation
- Content per spray
- Spray pattern and plume geometry
- Droplet size distribution (via laser diffraction or cascade impaction)
- Delivered dose uniformity
- Retentive dose on actuator
- Microbial limits (for non-sterile aerosols)

5.5 Validation Testing Techniques for Aerosol Forms

Test	Purpose
Spray Pattern Imaging	Evaluates the dispersion profile from the nozzle
Plume Geometry Analysis	Assesses the shape and reach of spray (important for targeting airways)
Andersen Cascade Impactor (ACI)	Determines aerodynamic particle size distribution
Dose Uniformity	Ensures consistency across canisters and actuations
Valve Delivery Rate	Measures API delivered per actuation
Flammability Test	Required for hydrocarbon or alcohol-based propellants
Moisture Content	High water content can affect stability
Vapor Pressure Test	Ensures container pressure within label claim

Regulatory Guidelines

The following documents provide regulatory frameworks and testing expectations for aerosol validation:
- FDA Guidance for Industry: Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products (2002)
- ICH Q8(R2), Q9, Q10: Quality by Design, Risk Management, and Pharmaceutical Quality Systems
- WHO Technical Report Series No. 961, Annex 3: Stability and validation guidelines for inhalation products
- United States Pharmacopeia (USP) <601>, <602>, <603>: Aerosol tests and specifications

Common Challenges in MDI Validation

Challenge	Control Strategy
Dose variability	Ensure proper suspension/mixing and accurate valve crimping
Actuator clogging	Validate particle size and avoid agglomerates
Propellant evaporation	Use low-temperature environments and validated sealing systems
Batch inconsistency	Apply in-process controls and real-time monitoring
Container leakage	Perform robust closure integrity testing

REGULATORY GUIDELINES FOR PROCESS VALIDATION[14-20]

Process validation is a regulatory expectation under current Good Manufacturing Practices (cGMP) as enforced by national and international authorities. It ensures that every step of the manufacturing process—from raw material handling to final product release—is controlled, reproducible, and compliant with quality standards.

Several key regulatory agencies and guidelines frame the global expectations for pharmaceutical process validation:

United States Food and Drug Administration (FDA)

The FDA Guidance for Industry: Process Validation – General Principles and Practices (2011) defines validation as a lifecycle process comprising three stages:

1. Process Design
2. Process Qualification
3. Continued Process Verification (CPV)

It emphasizes Quality by Design (QbD), risk management, and scientific justification in validation planning.

European Medicines Agency (EMA)

The EMA guideline on process validation requires that manufacturers demonstrate process consistency and include process analytical data, control strategies, and lifecycle monitoring in marketing authorization applications.

World Health Organization (WHO)

The WHO Technical Report Series No. 1019, Annex 3, outlines general principles of validation and highlights the importance of documented evidence, validation master plans, and revalidation following process changes.[3]

International Conference on Harmonisation (ICH)

ICH guidelines relevant to process validation include:

- **ICH Q8(R2):** Pharmaceutical Development
- **ICH Q9:** Quality Risk Management
- **ICH Q10:** Pharmaceutical Quality System

These documents support risk-based, science-driven process validation across the drug development lifecycle.

Pharmacopoeial Standards

Authorities like the United States Pharmacopeia (USP), Indian Pharmacopoeia (IP), and British Pharmacopoeia (BP) offer monographs and test procedures (e.g., for uniformity of dosage, dissolution, and microbial limits) that are often incorporated into validation protocols.[5]

CONCLUSION

Process validation is a foundational element in pharmaceutical manufacturing that ensures consistent product quality, patient safety, and regulatory compliance. By scientifically demonstrating that each step of the production process consistently yields outputs within predefined specifications, validation minimizes risk, enhances efficiency, and fosters trust in the drug supply chain.

Validation is not a one-time activity but an ongoing lifecycle process that includes initial qualification, periodic review, change control, and continuous monitoring. It requires comprehensive documentation, cross-functional collaboration, and adherence to global regulatory expectations.

Whether the dosage form is **a** tablet**,** ointment**,** cream**,** or aerosol, validation must account for the unique critical parameters, formulation behaviors, and quality attributes associated with each. By integrating risk-based thinking**,** analytical rigor, and technological tools, pharmaceutical manufacturers can design, control, and optimize robust processes that meet regulatory and patient expectations alike.

Ultimately, a well-validated process leads to fewer deviations, reduced batch failures, enhanced process understanding, and improved product lifecycle management. In a landscape of evolving regulations and patient demands, process validation remains a cornerstone of pharmaceutical excellence.

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