

# Process Validation in the Pharmaceutical Manufacturing Industry

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**Abstract:** *Process validation is a crucial component of the pharmaceutical manufacturing industry, ensuring that a process consistently produces a product meeting its predetermined specifications and quality attributes. This paper provides a comprehensive analysis of process validation, exploring its significance, stages, and elements. Additionally, it delves into the current statistical and regulatory perspectives, post-process qualification, and strategies for continued process verification and stability. The paper also outlines qualification strategies, including the assessment of Active Pharmaceutical Ingredients (APIs) and equipment matrices, and emphasizes the importance of a robust risk assessment strategy in process validation.*

**Keywords:** Process validation, pharmaceutical

## 1. Introduction

The pharmaceutical manufacturing process is bound by stringent regulatory standards to ensure the safety, efficacy, and quality of medicinal products on a consistent basis. One of the most critical aspects of process overview within this industry is process validation, which ensures that each step in the manufacturing process is designed, conducted, and controlled so that the product yielded consistently meets its quality specifications. Although various leading regulatory agencies like the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) provide respective guidance on process validation, this concept is not merely restricted to a regulatory requirement but, in fact, it is a scientific approach that provides confidence in the robustness of the manufacturing process.

According to the FDA, process validation is defined as the collection and evaluation of data and documented evidence to establish scientific evidence that a process is capable of consistently producing a product that meets its predetermined specifications and quality attributes. This involves a series of activities conducted during the lifecycle of a product, from process design through to commercial production [1]. The EMA definition is also along the same lines with the result of process validation being documented evidence of a parameterized operation producing a medicinal product with predetermined specifications and quality attributes on a reproducible, consistent basis [2]. This research article examines the various stages and elements of process validation, qualification strategy, the regulatory perspective, strategies for risk assessment, and future trends in this context.

## Stages of Process Validation

The process validation lifecycle can be divided into three main stages of process design, process qualification, and continued process verification. Each stage has its specific objectives, methodologies, and documentation requirements, contributing to the overall assurance of product quality. The first stage of process design is arguably the most critical stage in the process validation lifecycle and focuses on developing a detailed understanding of the pharmaceutical manufacturing process based on scientific principles and understanding of the product nuances. This stage also involves defining the process parameters and the control strategy. It is during this phase that the critical quality attributes (CQAs) of the final product are identified which are essentially physical, chemical, biological, or microbiological properties or characteristics that need to be controlled within predefined limits to ensure the desired product quality. Identifying CQAs is the foundation of process validation as they guide the development of control strategies and the identification of critical process parameters (CPPs). These parameters must be controlled within specific ranges to ensure that the process yields a product of consistent quality. The identification and control of CPPs are essential for maintaining the validated state of the process. CPPs and CQAs combined lay the foundation for control strategy which is a planned set of controls, derived from current product and process understanding, that ensures process performance and product quality. The control strategy is a critical element of process validation, ensuring that all aspects of the process are controlled to prevent variability that could impact product quality. The control strategy will be implemented during the product's commercial production process and will be subsequently reflected in the planned master production and control records. Techniques such as Design of Experiments (DoE) are often employed to systematically optimize these parameters, ensuring the process is robust and capable of delivering the desired product quality.

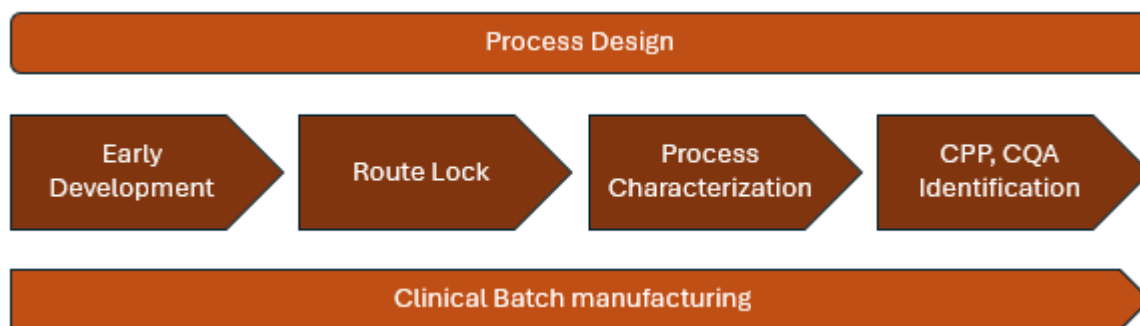


Figure 1: Process design stage overview in process validation

The second stage of process qualification is where the process design is evaluated to determine if it is capable of reproducible commercial manufacturing. This stage plays a pivotal role in bridging the gap between process design/development and full-scale commercial production ensuring that all the elements as required by the manufacturing process are properly installed, operational, and capable of performing. Thus, qualification of facilities, utilities, and equipment, as well as the performance of the process itself are important parts of this stage. This is accomplished through few key activities

- Installation Qualification (IQ) to ensure that equipment, systems and utilities are installed according to the manufacturer's specifications and regulatory requirements. This phase typically covers installation, calibration, verification and documentation aspects of the concerned equipment.
- Operational Qualification (OQ) to verify that the equipment operates according to predetermined specifications across all anticipated operating ranges. Through functional testing, process simulation, challenge testing and associated documentation, this phase helps identify and mitigate any potential issues before full scale production takes over.
- Performance Qualification (PQ) to demonstrate that the process produces output that meets all acceptance criteria under simulated or actual production conditions. Successful PQ culminates the process qualification stage and serves as the basis for transitioning to full scale commercial production.

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) highlights the need for thorough process qualification as part of Good Manufacturing Practices (GMP) through its guidelines (ICH Q7) [3].

The final stage of the process validation is continued process verification (CPV), is an ongoing process that ensures the validated state is maintained throughout the product lifecycle. This stage is critical for ensuring continuous improvement and maintaining compliance with regulatory standards. A manufacturer must instill systems for detecting unplanned departures from the designed process and establish programs to collect and analyze product and process data about the performance of the process to allow for this detection. The data collected should include relevant process trends, quality of inbound materials and respective components, work in progress materials, and finished products. CPV involves routine monitoring of the process, using statistical process control (SPC), process capability analysis, trend analysis and

other quality control tools to detect and correct deviations from established norms. The data collected during CPV is used to assess process capability, identify opportunities for improvement, and ensure compliance with regulatory requirements.

#### Qualification Strategy

A well-defined qualification strategy is essential for successful process validation. This strategy involves the qualification of various elements, including the Active Pharmaceutical Ingredient (API), equipment, and facilities. Each element plays a critical role in ensuring the overall quality of the product. Many organizations may consider these elements as pre-requisites to the process validation exercise and include these in an overall drug product master validation plan which is essentially a document defining all validation activities needed to complete validation for a product. For multi-step drug substances synthesis, this document defines the facilities and their respective timeframes for setup, all validation protocols, homogeneity protocols for final product and stability study requirements.

API qualification is a key component of the qualification strategy. It involves the thorough evaluation of the API to ensure that it meets the required specifications for purity, potency, and stability. The qualification process includes assessing the API's physical and chemical properties, as well as its potential impact on the final product's quality. Equipment qualification is another critical element of the validation strategy. It involves ensuring that all equipment used in the manufacturing process is capable of operating within specified parameters and producing products that meet quality specifications. Manufacturers may use tools such as an equipment matrix which is a comprehensive list of all equipment used in the manufacturing process, along with their qualification status. It is an essential tool for managing the qualification process and ensuring that all equipment is properly qualified before use in commercial manufacturing. There are typically two categories of equipment in a pharmaceutical manufacturing process – major equipment such as reactors, centrifuges, pressure filters, ovens, mills etc. which is in the scope of equipment qualification and minor equipment such as pipe fittings, valves, drums, totes, pumps etc. which are usually out of scope. Lastly, the qualification process may also consider documented cleaning validation processes with respect to cleaning of equipment to prevent product contamination.

### Regulatory Oversight

Regulatory agencies emphasize a lifecycle approach to process validation, which begins with process design and continues through process qualification and ongoing verification. The FDA's guidance on process validation, for example, outlines the importance of understanding the sources of variability, controlling that variability, and ensuring that the process remains in a state of control throughout the product lifecycle.

The regulatory perspective also emphasizes the importance of risk management in process validation. Risk assessments are used to identify potential sources of variability and to prioritize efforts to control those risks. This approach aligns with the principles of Quality by Design (QbD), which focus on building quality into the process from the outset, rather than relying solely on end-product testing.

There have been many multiple instances in the last decade of FDA warning letters being issued to pharmaceutical companies with regards to failure of installing adequate process validation procedures, to investigate process deviations, implement corrective actions, or to include a scientific justification for the chosen process parameters.

### Approaches towards process validation

There are several approaches to process validation, each suited to different stages of production, types of products, and regulatory requirements. The most common and simplified approach, called prospective validation, involves completion of validation before the commercial production of the drug. Prospective validation typically includes the development of a comprehensive validation plan, defining critical process parameters (CPPs), and performing a series of validation runs under conditions that mimic the intended commercial production. This ensures that the process is well-understood and capable of consistently producing a product that meets specifications before full-scale manufacturing begins. A pharmaceutical company might use prospective validation when developing a new tablet formulation, ensuring that all processing steps, such as mixing, granulation, and compression, are optimized and validated before commercial production. In other scenarios, where the time to market of a drug such as a seasonal flu vaccine may be critical and data from replicate production runs is unavailable because of a limited number of batches, a concurrent validation approach may be employed. Validation is performed when the product is being manufactured and distributed, with the validation data being collected concurrently thus allowing the manufacturer to meet the market demand while still ensuring that the process is being validated. However, the risk is higher since the product is already being distributed while validation data is being collected. For a long-established manufacturing process such as those for an over-the-counter drug, the manufacturer may employ a retrospective validation technique. This approach is based on the review and analysis of historical data from previous batches that were manufactured under the same process conditions. It is used when new CQAs or CPPs have been identified or changes to in-process acceptance criteria and controls are applicable to a process which has been in commercial production for some time. The parametric release approach relies on process validation and real-time monitoring to release products based

on the satisfactory completion of process parameters rather than end-product testing. This is especially useful in sterile manufacturing environments, such as terminally sterilized products, where critical parameters like time, temperature, and pressure are closely monitored and the manufacturer has the option to rely on validated sterilization processes rather than testing each batch for sterility.

## 2. Current Statistical and Regulatory Perspective on Process Validation

The approach to process validation has evolved significantly, with a growing emphasis on statistical methods and regulatory expectations. Regulatory agencies such as FDA and the EMA have provided guidelines that highlight the importance of a lifecycle approach to process validation, which integrates science, risk management, and quality assurance.

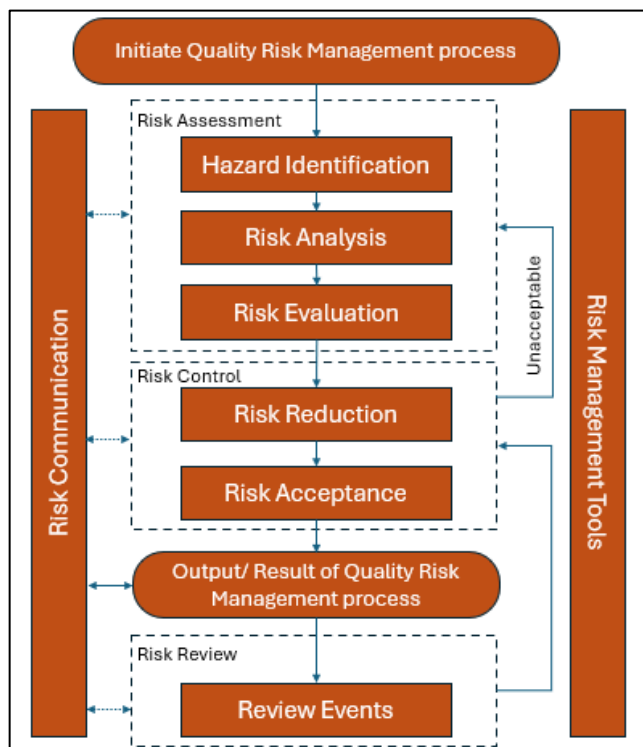
### Statistical Methods

Statistical methods are integral to modern process validation as they provide scientific tools needed to analyze data, assess process capability, and monitor ongoing process performance. These methods help ensure that the process is robust and capable of consistently producing products that meet quality specifications. Design of Experiments (DoE) employed during the process design stage of process validation is used to establish the relationships between factors affecting a process and the output of that process. It can be used to evaluate the impact of different formulation components and process parameters on the quality attributes of a drug product. The validation team can gain a far more comprehensive understanding of the process with fewer experiments as compared to traditional one-factor-at-a-time methods by systematically varying multiple factors at once. Statistical Process Control (SPC) involves the use of control charts to track process performance and detect any variations in the process during manufacturing. Tools such as X-bar, R charts help the validation team ensure that a process remains in control during routine production and any loss of control is detected immediately before they result in out-of-specification products. Manufacturers also employ process capability analysis to assess whether a process is capable of producing products that meet specification limits consistently. After a process has been validated, metrics such as the capability index ( $C_p$ ) and the performance index ( $C_{pk}$ ) measure the potential capability of a process and process centering respectively assess whether the process is capable of consistently producing the product units with a specific characteristic within the established limits. Analysis of Variance (ANOVA) is used to determine if there are statistically significant differences between different batches or to assess the effect of different process parameters. For example, a manufacturer might use the ANOVA method to compare the dissolution rates of tablets produced under different mixing times to determine if there are significant differences. Another perspective is to consider the probabilistic approach to understanding and managing variability in process performance which may be particularly useful in the risk assessment stage of process validation. In pharmaceutical manufacturing, Monte Carlo simulations can be used to predict the probability of different outcomes, such

as the likelihood that a batch will fail to meet specifications under varying conditions.

### Risk Assessment Strategy

Risk assessment is a fundamental aspect of process validation in the pharmaceutical industry, providing a systematic approach to identifying, assessing, and controlling potential risks that could impact product quality and efficacy. It is essential that a pharmaceutical manufacturer develops a robust risk assessment strategy to ensure that the manufacturing process is designed and controlled in a way that minimizes variability and ensures consistent product quality, thus safeguarding patient safety. A possible model for quality risk management is outlined in the diagram below [4].



**Figure 2:** Overview of a typical quality risk management process [4]

The first step in the risk assessment process is risk identification which involves identifying potential sources of variability that could impact product quality, regulatory compliance, operational efficiency or patient safety. Common sources of risk include variability in raw materials, process parameters, equipment performance, and environmental conditions. EMA recommends three fundamental questions as an aid towards clearly defining risk(s) for risk assessment purposes.

- What might go wrong?
- What is the likelihood(probability) it will go wrong?
- What are the consequences (severity)?

Through application of tools and methods such as process mapping, failure mode and effects analysis (FMEA), and hazard analysis and critical control points (HACCP), manufacturers can systematically identify hazards, perform risk analysis and risk evaluation to ultimately prioritize risks and determine which risks require the most attention. The output of a risk assessment exercise is either a quantitative estimate of risk such as a 'risk score' or a qualitative

description of a range of risk such as 'high', 'medium', or 'low' [4].

Risk control involves implementing measures to mitigate or eliminate identified risks. This may include adjusting process parameters, implementing additional controls, or redesigning the process to reduce variability. The goal of risk control is to ensure that the process is robust and capable of consistently producing high-quality products. In order to perform risk control, EMA recommends relying on questions such as the following [4]:

- Is the risk above an acceptable level?
- What can be done to reduce or eliminate the risk?
- What is the appropriate balance among benefits, risks and resources?
- Are new risks introduced as a result of the identified risks being controlled?

Based on the above assessment, an organization may choose to perform risk reduction which involves focus on processes for risk mitigation or complete avoidance of risk if it exceeds an acceptable level. In other cases, a decision might be made to accept the risk within some tolerance limits.

The final step in the risk assessment process is risk review. This involves regularly reviewing the risk assessment to ensure that it remains current and relevant. As the process evolves and new risks are identified, the risk assessment should be updated to reflect these changes. The frequency of reviews is usually based upon the level/severity of the concerned risk.

During the risk management process, it is imperative that an organization performs risk communication with all impacted stakeholders such as regulators and industry, patients, internal stakeholders, logistics partners etc. regarding the existence, nature, form, probability, severity, acceptability, control measures, detectability, or other aspects of the identified risks.

### 3. Recent Trends

Recent advancements in process validation in the pharmaceutical manufacturing industry have focused on enhancing efficiency, reliability, and flexibility. Application of modern technology such as artificial intelligence (AI), machine learning (ML), data analytics and automation are set to revolutionize process validation. AI and ML enabled models have the ability to analyze vast amounts of data generated during the manufacturing process and identify underlying patterns and correlations. This enables manufacturers to gain real time monitoring and control capabilities and incorporate immediate corrections to any process deviations if the process spills outside of specified parameters. ML models can also predict equipment failures which helps in minimizing downtime and maintaining consistent product quality. Quality-by-Design (QbD) frameworks emphasize designing processes with a thorough understanding of how various factors affect product quality and the incorporation of AI and ML into these frameworks helps for a deeper understanding of how various variables affect product quality [5].

These advancements are shaping the future of process validation, making it more robust and adaptable to the evolving needs of the pharmaceutical industry.

#### 4. Conclusion

Process validation is a critical component of the pharmaceutical manufacturing industry, ensuring that processes are capable of consistently producing products that meet quality specifications. By following a structured approach to process validation, including process design, qualification, and continued verification, manufacturers can ensure the robustness of their processes and maintain compliance with regulatory requirements. The integration of statistical methods, a robust qualification strategy, and a comprehensive risk assessment approach further enhances the effectiveness of process validation. As the industry continues to evolve, the importance of process validation will only increase, as manufacturers strive to produce high-quality products that meet the needs of patients and regulatory agencies alike.

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