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A COMPREHENSIVE STUDY ON PHARMA INDUSTRY QUALITY BY DESIGN

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ABSTRACT

The concept of Quality by Design reflects the current regulatory viewpoints on pharmaceutical products globally. Improvement of performance is necessary for the pharmaceutical industry. It is necessary to introduce new technologies that can reduce costs and improve product quality at the same time. Quality by design (QbD) is the most effective approach to guaranteeing quality in every pharmaceutical product. The main objective of QbD is to ensure a top-quality product by combining current understanding with latest evaluations during the development phase. Both the FDA and ICH are strongly supporting the implementation of QbD. Quality by Design (QbD) in the pharmaceutical sector centers on understanding how materials and process parameters affect the quality of final products. This review examines key components of Quality by Design (QbD) like Target product quality profile, Critical quality attributes, Risk assessment, Design space, and Control strategy to understand how dosage forms function within the specified design space. QbD also deals with tools like DoE, Quality risk management, and process analytical technology. These criticisms highlight the importance of QbD in promoting a scientific mindset in the creation of pharmaceutical products.

Keywords: Quality by Design, Critical Quality Attributes, Target product quality profile, Risk assessment, Design space.

INTRODUCTION

Optimization involves creating a viable solution quickly while minimizing the use of resources such as manpower and productivity expenses. The conventional method of optimization focuses on optimizing one variable at a time, making it a time-consuming process. Additionally, achieving ideal formulation development is challenging with this approach. Practical experience in industry has demonstrated that process operating parameters have a substantial impact on the quality and standards of tableting. Process optimization involves a range of tasks aimed at cutting costs through the removal of unnecessary experimental stages, enhancing yields, and decreasing cycle times. It requires examining and adjusting the production procedure in order to enhance its efficiency and effectiveness. Typically, this involves pinpointing the Critical Process Parameters (CPPs) that impact the product's quality and quantity [1, 2].

Quality by Design (QbD) is an advancement from Quality by Testing (QbT) that focuses on all stages of the pharmaceutical system, providing flexibility in operations to enhance the value of medicines for the customer rather than just cutting costs. QbD principles support the development of formulations and process designs by analyzing processes to identify and understand sources of variability to enhance product quality. Pharmaceutical QbD is a methodical, science-driven, comprehensive, and forward-thinking approach to pharmaceutical development.

QbD is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management. Quality target product profile (QTPP) provides initial quality of the product which is implemented in the first step of QbD. And then critical quality attributes (CQA) provides attributes that can affect the quality of the product. Then risk assessment for formulation attribute that was reduced in formulation development studies followed Optimization of the formulation by changing the concentration of the release retarding polymer has been carried out [3].

1. Quality Target Product Profile

Quality Target Product Profile (QTTP) is a term that is a natural extension of Target Product Profile (TPP) for product quality.

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Critical Quality Attributes

The product characteristics that are identified as having an impact on QTPP are defined critical quality attributes. These include the physical, chemical, biological or microbiological properties characteristics or that have been demonstrated to ensure the desired product quality, if within an appropriate limit, range or distribution.

Risk Assessment

Several applications in the CMC pilot include risk assessment, especially for the drug product by linking input and process variables to CQAs. Tools used in Risk Assesment included the Ishikawa or Fish Bone Diagram, Failure mode effect analysis (FMEA), and pareto analysis [5].

Design Space

Design space as defined by the FDA (FDA May 2006) is the multidimensional combination and interaction of Input Variables (eg: Material attributes) and process parameters that have been demonstrated to provide assurance of Product Quality. By means of Design of Experiments (DoE), the relationship among different independent variables and the system performance can be found [6].

Control Strategy

A planned set of controls, derived from current product and process understanding that ensures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug-product materials and components, facility and equipment operating conditions, in process controls, finished-product specifications, and the associated methods and frequency of monitoring and control [7].

Life Cycle Management

Once the product is approved, CQAs need to be monitored continuously to ensure that the process is performing within the defined acceptable variability that served as the basis for the filed design space, Use of sophisticated statistical techniques for regress analysis of complex data sets and analytical tools for Online Analysis could form the basis of real time process monitoring.

Process Analytical Technology (PAT)

PAT can be defined as a system for designing, analyzing and controlling manufacturing through timely measurements (i.e. during processing) of Critical Quality and performance attributes of raw and in process materials and processes, with the goal of ensuring final product quality.

Critical Process Parameters (CPP)

Critical Process Parameters (CPPs) are the key manufacturing steps and parameters that significantly impact the critical quality attributes (CQAs) of a drug substance. Controlling these CPPs within defined ranges ensures consistent production of a safe and efficacious drug product.

Critical Material Attributes (CMAs)

Identifying Critical Material Attributes (CMAs) in drug substance manufacture is crucial for ensuring consistent quality and minimizing risks [9].

Design of Experiments (DOE)

DOE allows for the creation of statistical models that can elucidate how factors impact Critical Quality Attributes (CQAs) and the correlation between input/output parameters. The ideal mixes of ingredients can be discovered to produce tablets with specific Critical Quality Attributes that align with the Quality Target Product Profile. Design of Experiments (DOE) is highly effective because it yields a set amount of information with much less effort compared to the traditional method of focusing on one variable at a time. Besides revealing the main effects, the application of DOE also offers a deeper understanding of variable interactions, which are crucial for optimizing a formulation or process. A key aspect of DOE is the arbitrary sequence in which the experiments are conducted. This stops premature decisions from being made without taking into account all the data, and it also guarantees that errors made during experimentation are randomly distributed.

The Department of Energy assesses the impacts of concurrent adjustments in circumstances, yet they may not uncover the fundamental mechanisms causing the observed effect. Depending on how they are designed, they could just offer the necessary "empirical feedback" for optimizing a process, for instance. These designs are very cost-effective and offer the necessary information with minimal experimental work [10, 11].

Statistical Data

Data is essential for conducting a statistical evaluation. Data should be accurately and thoroughly collected, however there will always be some level of uncertainty in terms of their precision, as experimental techniques have their constraints. Data must be collected on multiple items in order to be able to utilize them for a statistical evaluation. There needs to be enough data collected in order to apply statistical analysis. The amount of data needed depends on the statistical method used [8].

MATERIALS AND METHODS

As per the ICH Q8 guideline, QbD represents a structured method for pharmaceutical development that starts with set goals and focuses on understanding products and processes, alongside process control rooted in solid scientific principles and effective quality risk management. As QbD suggests a more structured approach to development, it may encompass a blend of existing knowledge, design of experiments (DOE), quality risk management, and knowledge management (ICH Q10)

during the entire product life cycle. When a systematic approach is implemented, enhancements occur in the desired quality of the product and assist regulators in comprehending a company's strategy more effectively.

The FDA guidance documents Q8, Q9, and Q10 provide a structured framework for implementing Quality by Design (QbD) principles in pharmaceutical development and manufacturing.

Q8 (Pharmaceutical Development): This guidance emphasizes the importance of designing quality into products from the outset. It outlines the need for a thorough understanding of the product and its manufacturing process. Key elements include:

- Quality Target Product Profile (QTPP): Defines the desired quality characteristics of the product.
- Critical Quality Attributes (CQAs): Identifies the physical, chemical, biological, or microbiological properties that must be controlled to ensure product quality.
- Control Strategy: A plan that describes the controls necessary to ensure that CQAs are consistently met throughout the product lifecycle.

Q9 (Quality Risk Management): This document focuses on the integration of risk management into the QbD framework. It provides guidance on:

- Risk Assessment: Identifying and evaluating risks associated with product quality.
- Risk Control: Implementing measures to mitigate identified risks.
- Risk Communication: Sharing risk information among stakeholders to ensure informed decision-making [12].

Q10(Pharmaceutical Quality System): This guidance outlines a quality system that supports the implementation of QbD principles. Key components include:

- Lifecycle Approach: Emphasizes the importance of continuous improvement and adaptation of the quality system throughout the product lifecycle.
- Quality Culture: Encourages organizations to foster a culture of quality, where all employees are engaged in maintaining and improving product quality.
- Documentation and Change Management: Stresses the need for proper documentation and management of changes to ensure that quality is maintained.

Integration of Q8, Q9, and Q10: Together, these documents provide a comprehensive approach to pharmaceutical development, emphasizing the importance of understanding and controlling processes to ensure product quality. They encourage a proactive stance on quality, enabling organizations to anticipate and mitigate risks while fostering a culture of continuous improvement [13].

METHODOLOGY

Step 1: Defining the Objectives

- To understand the manufacturing process and production processes.
- To optimize tablet formulation and manufacturing processes using QbD principles.
- To analyze the impact of critical parameters on the quality of the final product.
- To analyze for risks or deviations observed in the manufacturing process.

Step 2: Gather Existing Data

Collect detailed records from the BMR.

Step 3: Identify Critical Quality Attributes (CQAs) and Critical Process Parameters (CPPs)

- **CQA Identification**: Based on the quality control tests, the CQAs and CPPs that are essential for ensuring product quality.

Step 4: Optimize the Process and Implement Corrective Measures

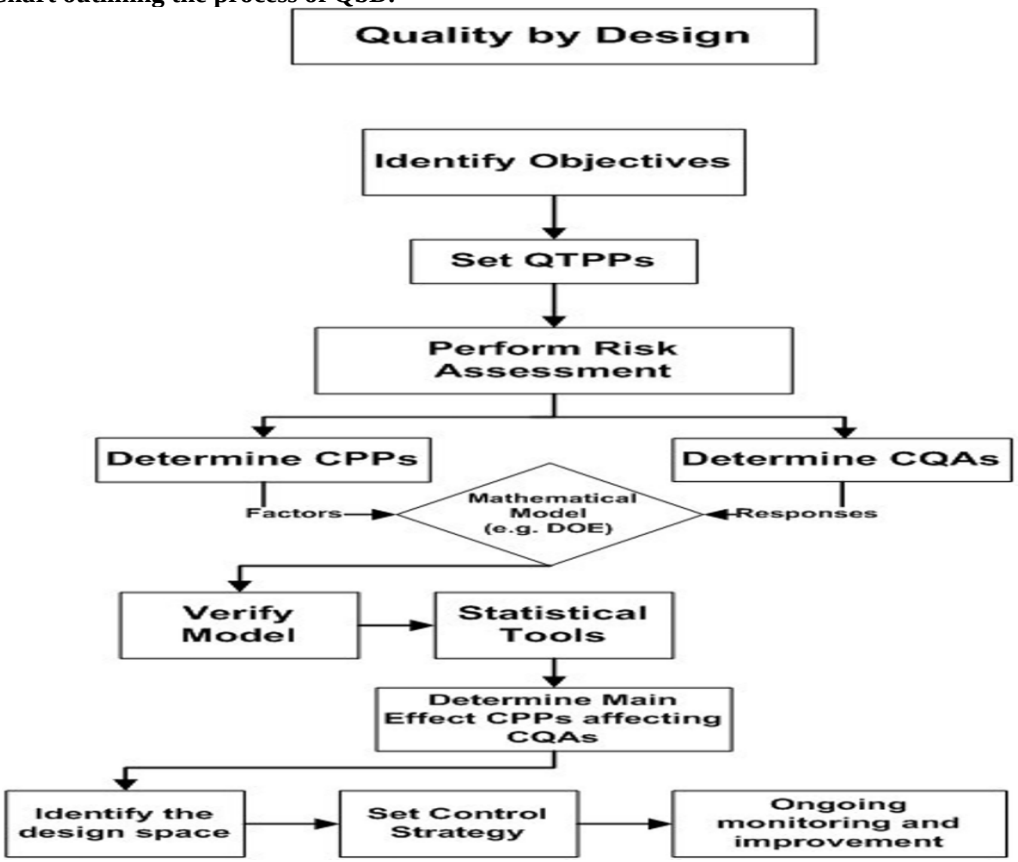
- **Optimization**: Based on the data analysis, the optimal settings were identified for the CPPs that yield the desired CQAs. This may involve:
- Adjusting process parameters to improve tablet quality.
- Establishing a design space where the process can operate effectively.[8]
- **Corrective Actions**: Based on the findings from the case studies, corrective measures were implemented for any identified issues. The effectiveness of these measures were documented for the purpose of improving the product quality.

Step 5: Verification and Documentation

- **Verification**: Verification is a thorough review of data by the second subject matter expert to cross verify any shortcomings. Verify that the optimized process meets regulatory requirements and internal quality standards.
- **Documentation**: Compile all findings, methodologies, and results into a comprehensive project report or book.

Diagram 1: Elements of QbD encompasses the following points:

Figure 1: Flow Chart outlining the process of QbD.



CONCLUSION

Quality by Design (QbD) is a crucial factor in quality enhancement in pharmaceutical products. The QbD approach aims to create a reliable method that ensures the final product's quality and efficacy while minimizing variations between batches and reducing errors. QbD is a promising scientific method for quality assurance in the pharmaceutical sector, providing a framework for successful product commercialization. QbD can be used in the development and assessment of analytical techniques, analyzing all possible factors and essential analytical responses to determine their relationships. Key analytical factors are recognized in a method that aligns with ICH Q8 and Q9. A repository like this facilitates ongoing enhancement and change management of the method throughout its lifecycle. A QbD strategy grounded in a risk-evaluated change control process should be adopted, with risk assessments conducted whenever a method is modified and equivalency assessments conducted if a change is recognized as moving the method beyond its design space. [14, 15]. We the authors had taken part in a review study on QbD technique in production process of Methylcobalmin Pregablin (Sustained Release Dosage Form) in pharmaceutical industry.

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