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Review Article

Review On Quality by Design (Qbd) In Pharmaceutical Development

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ABSTRACT

Quality by Design (QbD) represents a contemporary approach to ensuring the quality of pharmaceuticals. This paper explores the principles of Pharmaceutical Quality by Design and its application in maintaining pharmaceutical quality. It outlines the key components of QbD, identifies process parameters and quality attributes for each unit operation, and discusses the benefits, opportunities, and steps involved in implementing QbD in pharmaceutical products. The primary goal of pharmaceutical development is to create a quality product and manufacturing process that consistently delivers the desired performance. Quality should be integrated into products through design rather than tested in afterward. This includes defining the Quality Target Product Profile (QTPP), identifying Critical Quality Attributes (CQA), and understanding the impact of Critical Material Attributes (CMA) and Critical Process Parameters (CPP) on CQAs. The paper also contrasts traditional end-product testing with the QbD approach. The foundation of QbD is rooted in ICH Guidelines, specifically Q8 for pharmaceutical development, Q9 for quality risk management, and Q10 for pharmaceutical quality systems. Additionally, it discusses the application of QbD in the development and manufacturing of pharmaceuticals. [1]

INTRODUCTION

The objective of pharmaceutical development is to design a quality product and its manufacturing process to reliably deliver the intended performance. Insights gained from development studies and manufacturing experiences provide the scientific basis for establishing design space, specifications, and manufacturing controls. It is crucial to understand that quality cannot merely be tested into products; it must be built in from the

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outset. Changes in formulation and manufacturing processes during development and lifecycle management should be viewed as opportunities to enhance knowledge and refine the design space. Similarly, insights from unexpected experimental results can be valuable. The design space proposed by the applicant is subject to regulatory assessment and approval, and any movement outside this space is considered a change, typically requiring a regulatory post-approval change process. [3]

Definition of Quality by Design (QbD) :

According to the ICH Q8 (R1) guideline, QbD is a systematic approach to development that starts with predefined objectives and emphasizes understanding product and process dynamics, alongside process control, grounded in sound science and quality risk management. The FDA's Process Analytical Technology (PAT) guidelines define QbD as a system for designing, analyzing, and controlling manufacturing through timely measurements of critical quality and performance attributes of materials and processes that impact product safety and quality. [4]

History of QbD :

The concept of QbD was pioneered by quality expert Joseph M. Juran. In 1986, W. Edwards Deming elaborated on the idea of quality by design, using disease as an analogy. In 2002, the FDA launched an initiative titled "cGMP for the 21st Century: A Risk-Based Approach," aimed at modernizing pharmaceutical quality regulation and establishing a framework focused on QbD, risk management, and quality systems. QbD necessitates an understanding of how product and process variables affect quality. This new approach was further solidified by the publication of two key ICH guidelines: Q8 on pharmaceutical development and Q9 on quality risk management. [5]

Advantages of QbD :

The advantages of QbD include:

- Enhanced assurance of product quality
- Cost savings and increased efficiency for the industry
- Reduction or elimination of potential compliance issues
- Opportunities for continuous improvement
- Facilitation of innovation
- Increased likelihood of first-cycle approvals
- Improved process capability and reduced product variability and defects
- Elimination of batch failures
- Empowerment of technical staff
- Greater understanding of processes
- Better product design with fewer complications

Fundamental Aspects of QbD :

QbD requires comprehensive knowledge of how formulation development and processes influence product quality. It involves understanding sources of variability and their effects on the final product, allowing for better control of these variables. When QbD principles are effectively implemented, the need for extensive final product testing can be minimized or even eliminated. [6]

Objectives of Qbd :

The primary objective of QbD is to achieve high-quality products. Additional objectives include: [7]

- Attaining positive performance testing outcomes
- Ensuring a comprehensive integration of product and process knowledge acquired during development [8]

Foundation of Qbd :

The foundation of QbD is built on ICH guidelines Q8 for pharmaceutical development, Q9 for quality risk management, and Q10 for quality systems. [9]

Design Principles :

- Products are designed to meet patient needs and performance requirements.
- Processes are structured to consistently achieve product quality attributes.
- The impact of raw materials and process parameters on product quality is well understood. [10]
- Critical sources of process variability are identified and controlled.
- Processes are continuously monitored and updated to ensure consistent quality over time. [11]

Definition [ICH Q8(R1)] :

QbD is defined as a systematic approach to development that begins with predefined objectives and emphasizes understanding product and process dynamics, alongside process control, based on sound science and quality risk management. [12]

Benefits of Quality by Design (QbD)

1. Business Advantages :

- Enhances overall business performance.
- Reduces batch failures.
- Minimizes deviations and costly investigations.
- Prevents regulatory compliance issues.
- Fosters organizational learning, positioning the company for future success.

2. Scientific Benefits :

- Facilitates better decision-making during product development.

Opportunities with QbD :

- Establishes an efficient, agile, and flexible system.
- Increases manufacturing efficiency while lowering costs and reducing waste and project rejections. [13]
- Builds a comprehensive scientific knowledge base for all products.
- Improves interactions with the industry on scientific matters.
- Ensures consistent and reliable information dissemination.

Steps Involved in QbD Product Development :

1. Development of New Molecular Entities :

- Conduct preclinical and nonclinical studies.
- Perform clinical studies.
- Scale up production.
- Submit for market approval.

2. Manufacturing:

- Define the design space.
- Implement process analytical technology.
- Establish real-time quality control measures.

3. Control Strategy :

- Make risk-based decisions.
- Focus on continuous improvement.
- Monitor product performance.

Seven Steps for Implementing a QbD Startup Plan :

1. Hire an independent QbD expert.
2. Conduct an organizational audit and gap analysis with the expert.

3. Organize a basic QbD workshop for all personnel.
4. Review the expert's findings and recommendations.
5. Draft an implementation plan, including timelines and estimated costs.
6. Allocate necessary resources or consider contracting out.

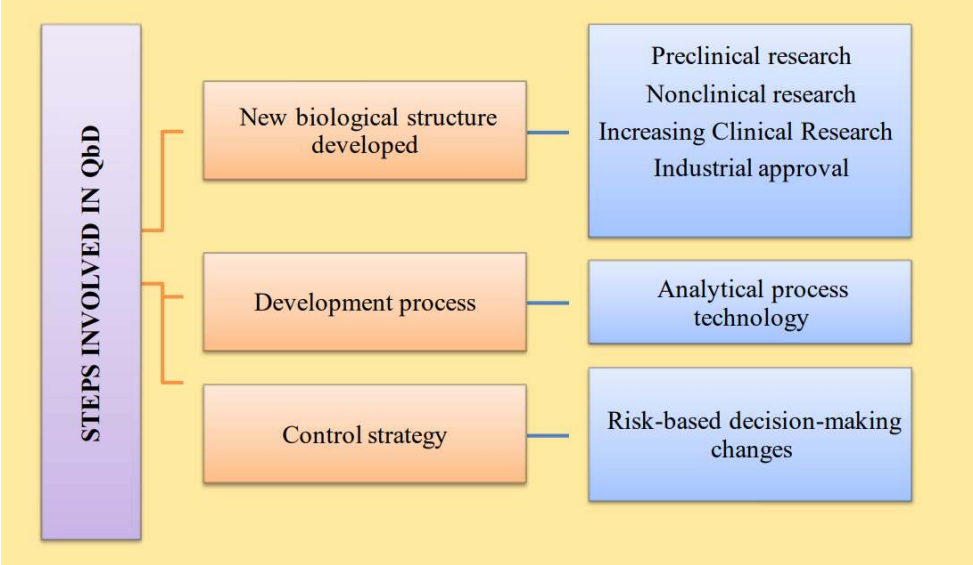

Fig 1 : Steps Invloved In Qbd

Understanding QbD in Pharmaceuticals :

Despite a strong focus on quality, the pharmaceutical industry has lagged behind other sectors in manufacturing efficiency and productivity. Current challenges include: [14]

High costs of revalidation.

Offline analysis for in-process needs.

Reliance on product specifications for control.

Unpredictable scale-up challenges.

Difficulty in understanding failures.

A systematic approach to development is essential, starting with predefined objectives and emphasizing a thorough understanding of products and processes. [15]

Quality Target Product Profile (QTPP) :

The QTPP summarizes the drug development program, focusing on safety and efficacy. Key components include: [16]

- Description
- Clinical pharmacology
- Indications and usage
- Contraindications
- Warnings and precautions
- Adverse reactions
- Drug abuse and dependence
- Overdosage
- Dosage and administration
- How supplied
- Animal pharmacology/toxicology
- Clinical studies

The QTPP naturally extends to product quality, outlining the essential characteristics that ensure the drug product consistently delivers the promised therapeutic benefits. [17]

Critical Quality Attributes (CQAs) :

Identifying critical quality attributes is vital for defining purity, potency, and bioavailability. Key points include: [18]

Establishing a link between critical process parameters (CPPs) and CQAs.

Recognizing manufacturability as a critical attribute for business success.

Understanding that the level of criticality may vary between active pharmaceutical ingredient (API) manufacturing and drug product manufacturing. [19]

Target Product Quality Profile (TPQP) :

The TPQP serves as a strategic foundation for drug development, emphasizing "planning with the end in mind." Its applications include: [20]

Drug Substance and Excipient Properties :

Thorough characterization of the drug substance is essential for achieving the specified product quality. [21]

Formulation Design and Development : Developing sensitive in vitro dissolution methods is crucial, as not all prototypes can be tested in humans. [22]

Manufacturing Process Design and Development : Process design must align with formulation design, documenting all factors necessary for commercial manufacturing. [23]

Successful Adoption of QbD :

Regulatory flexibility for QbD submissions.

Acceptance of a common dossier by regulatory agencies worldwide.

Ability to implement post-approval changes within a predefined design space with regulatory leniency. [24]

Legal protections for intellectual property.

Consistent Quality Assurance :

The design space concept ensures that critical process parameters are identified and consistently controlled, leading to products that consistently meet desired quality standards. [25]

Continuous Improvement through Quality by Design (QbD) :

Key Elements for Continuous Improvement :

- Process Control Strategy: Focuses on managing the process effectively.
- Performance Monitoring: Emphasizes ongoing process enhancement.
- Real-Time Feedback: Provides immediate insights for adjustments.
- Knowledge Accumulation: Grows with experience and leverages new technologies to boost process efficiency. [26]

ICH Q8, Q9, Q10 Guidelines: The Foundation of QbD

The ICH guidelines—Q8 for Pharmaceutical Development, Q9 for Quality Risk Management, and Q10 for Quality Systems—serve as the cornerstone for implementing QbD principles in the pharmaceutical industry. [27]

Alignment of QbD with ICH Guidelines :

- Conceptual Alignment : QbD principles align with ICH guidelines, emphasizing the importance of design space, process robustness, and quality management. [28]

- Design Space: A multidimensional framework that illustrates the interactions between variables (e.g., raw material attributes) and process parameters, ensuring quality assurance. [29]
- Regulatory Flexibility: Once a design space is approved, regulatory requirements for post-approval changes are simplified, allowing for greater operational flexibility. [30]

Development and Utilization of Design Space :

- Science-Based Design: Enhances understanding of processes to support a scientific approach. [31]
- Integration of Processes: Aligns drug substance and drug product development to optimize manufacturing. [32]
- Effective Monitoring : Employs extensive monitoring during development to improve process understanding and control. [33]

Role of Process Analytical Technology (PAT) :

PAT is crucial in QbD, facilitating:

- Process Understanding: Used during development to gain insights into processes. [34]
- Routine Monitoring: Implemented in manufacturing to ensure product quality and reduce reliance on extensive release testing. [35]

Applications of QbD in Pharmaceutical Development :

QbD represents a systematic approach to pharmaceutical development and manufacturing, contrasting with traditional methods. [36]

QbD in CMC Review Offices :

- Science-Based Assessment : Restructured organizations focus on both premarket and postmarket evaluations. [37]
- Pilot Programs: Various applications have been submitted, yielding valuable lessons and insights for future implementations. [38]

Case Studies Demonstrating Successful QbD Implementation :

1. Case Study 1: Tablet Formulation Optimization :

Objective: Enhance quality and consistency of tablet formulations.

QbD Approach: Identified critical quality attributes (CQAs) and utilized design of experiments (DOE) to establish a robust design space. [39]

Outcome: Achieved a more consistent formulation with real-time monitoring, leading to improved product quality and regulatory compliance. [40]

2. Case Study 2: Biopharmaceutical Process Optimization :

Objective: Optimize monoclonal antibody production.

QbD Approach: Identified critical process parameters (CPPs) and conducted risk assessments to manage potential deviations. [41]

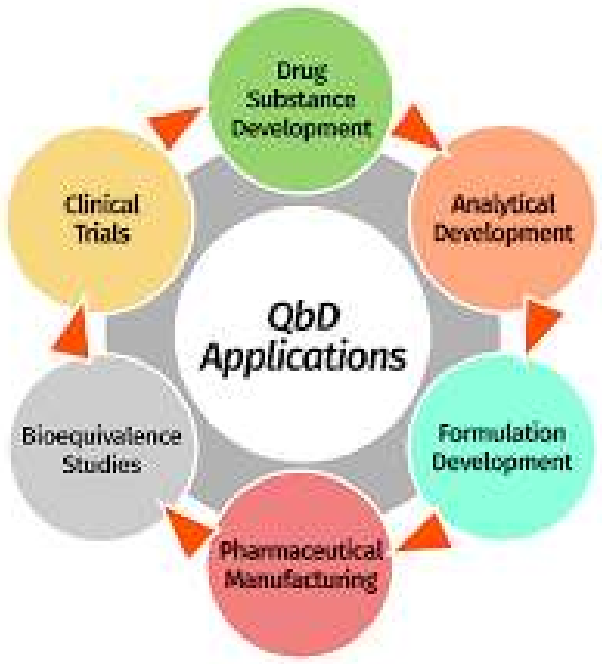

Fig 2 : QBD Applications

Benefits of Implementing QbD for the FDA :

- Enhanced Scientific Review: Improves coordination across review, compliance, and inspection processes. [42]
- Better Regulatory Submissions: Increases consistency and quality of submissions. [43]
- Flexibility in Decision-Making: Ensures decisions are based on scientific evidence rather than empirical data. [44]
- Resource Optimization: Focuses on addressing higher-risk areas effectively.

Benefits to Industry :

- Improved Product Design: Leads to fewer manufacturing issues.
- Reduced Regulatory Burden: Minimizes the need for manufacturing supplements for post-market changes. [45]
- Cost Efficiency: Potentially lowers overall manufacturing costs and waste.
- Streamlined Review Process: Facilitates quicker approvals and enhances interactions with regulatory bodies. [46]

Regulatory Landscape and QbD Expectations :

The regulatory environment has evolved to prioritize product quality, safety, and efficacy, with QbD becoming a key approach to meet these expectations. [47]

1. ICH Expectations: Guidelines emphasize understanding product and process to maintain quality. [48]
2. FDA Quality Systems Approach: Manufacturers are encouraged to integrate quality into their processes, aligning with cGMP regulations. [49]
3. Risk-Based Approach: Regulatory agencies expect thorough risk assessments to identify and mitigate potential quality risks. [50]

Integration of QbD Concepts in Regulatory Submissions :

- Submission Dossiers: Incorporating QbD elements enhances the quality of regulatory submissions. [50]
- Quality Target Product Profile (QTPP): Clearly defining CQAs and their relevance is crucial. [50]
- Design Space Inclusion: Demonstrates the flexibility of the manufacturing process while ensuring product quality. [50]

Continuous Improvement through Quality by Design (QbD) :

Key Components for Continuous Improvement :

- Process Control Strategy: Focuses on effectively managing the manufacturing process. [50]
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CONCLUSION:

The goal of a well-characterized method development effort is to create a reliable method that consistently produces data meeting predefined criteria within defined boundaries. QbD can be applied to the development and evaluation of analytical methods, studying all potential factors (inputs) and critical analytical responses (outputs) to determine their relationships. This approach parallels the process development outlined in ICH Q8 and Q9.A corporate knowledge repository is essential throughout this process to capture critical information, enabling continuous improvement and change control of methods over their lifecycle. Each method change should undergo a risk assessment to ensure performance criteria are still met, facilitating method improvements and transitions between different techniques. [50]

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