

A Review on QbD Approach in Analytical Method Development and Validation

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ABSTRACT

Quality by Design (QbD) is a cutting-edge pharmaceutical development that enhances analytical method robustness by emphasizing a thorough understanding of processes, risk management, and continuous improvement. Unlike traditional methods that often focus on end-product testing, QbD integrates quality into the development stages through a structured process. This involves defining the analytical target profile, identifying critical quality attributes, and employing the design of experiments to optimize method parameters. The implementation of QbD begins with a comprehensive understanding of the analytical objectives, leading to the identification of method variables that impact quality. Using risk assessment tools such as failure mode and effects analysis, developers can pinpoint potential risks and focus on areas of highest concern. Design of Experiments (DoE) plays a crucial role in this approach by exploring the interaction between variables and establishing a robust design space. Organizations can decrease variability, comply with regulations, and perform better methods when they adopt QbD concepts. This systematic approach not only minimizes the risk of method failures but also ensures consistent product quality, leading to increased patient safety and satisfaction. Furthermore, QbD facilitates faster development cycles and cost efficiencies by reducing the need for post-launch troubleshooting and modifications. This abstract provides a comprehensive overview of the role and significance of QbD in analytical method development, highlighting its components, benefits, and impact on the pharmaceutical industry.

Keywords: Quality by design, Analytical target profile, Critical quality attributes, design of experiments.

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INTRODUCTION

When it comes to pharmaceuticals, quality is everything. The efficacy, safety, and integrity of pharmaceutical goods directly impact patient health and safety. A crucial framework for guaranteeing that pharmaceutical goods continuously fulfill these high criteria is QbD. QbD is a cutting-edge methodology that places an emphasis on incorporating quality into processes and products from the outset as opposed to depending exclusively on testing completed items. Originally developed in the pharmaceutical industry, QbD is now being adopted across various sectors, including biotechnology, chemical manufacturing, and food production, for its systematic and scientific approach to quality assurance.^{1,2}

Benefits of Quality by Design

Implementing QbD offers numerous benefits, making it an attractive approach for organizations committed to quality and innovation:

Improved Product Quality

Quality by Design guarantees that the product is made with quality in mind from the beginning, which leads to more consistency and fewer defects. By understanding the factors that impact quality, manufacturers can produce products that consistently meet customer expectations.

Reduced Costs and Waste

By optimizing processes and reducing variability, QbD minimizes waste and reduces production costs. This efficiency translates into cost savings for manufacturers and more competitive pricing for consumers.

Enhanced Regulatory Compliance

Regulatory agencies, such as the FDA and EMA, endorse QbD principles, as they provide a transparent, scientific approach to quality assurance. Implementing QbD helps organizations meet regulatory requirements more efficiently, reducing the risk of compliance issues.

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Faster Time to Market

QbD's systematic approach accelerates product development by reducing the need for extensive testing and rework. This speed to market provides a competitive advantage, allowing companies to capture market share and respond to consumer demands quickly.

Continuous Improvement

Quality by design encourages organizations to continuously assess and improve their processes.

This proactive approach ensures that products remain competitive and aligned with evolving market and regulatory requirements.

Risk Mitigation

By identifying and managing risks early in the product lifecycle, QbD reduces the likelihood of failures and recalls. This risk mitigation not only protects the brand's reputation but also ensures the safety and satisfaction of consumers.³⁻⁵

Key Principles of QbD

Quality by design is based on several key principles that guide its implementation:

Gaining an understanding of the product and process

QbD necessitates a deep comprehension of the product as well as the procedures that go into producing it.

This involves identifying the desired quality attributes and the factors that can affect them.

Building quality into the product

The focus is on designing processes that inherently ensure quality, minimizing the need for extensive testing and quality checks after production.

Risk management

QbD involves identifying and managing risks throughout the product lifecycle. This proactive approach helps to anticipate and mitigate potential issues before they impact the product's quality.

Design of experiments (DoE)

Process optimization is made possible by investigating the connections between process factors and product qualities through structured experiments.

Continual improvement

To improve product quality and efficiency, QbD is a continual process that involves monitoring, assessing, and refining processes.^{6,7}

Parts of Quality by Design

To guarantee its efficacy, Quality by Design is made up of a number of crucial parts, including:

QTPP, or quality target product profile

The expected quality features of the product are specified in the Quality Target Product Profile (QTPP). It includes information on efficacy, safety, purity, and stability. The QTPP is the first step in creating a dependable and efficient manufacturing process.



Figure 1: Key principles of QbD

Critical Quality Attributes (CQAs)

Critical quality attributes, or CQAs, are those aspects of the product's physical, chemical, biological, or microbiological makeup that must be controlled to ensure that it meets QTPP standards. Maintaining product quality requires managing and identifying CQAs.

Critical material attributes (CMAs) and critical process parameters (CPPs)

- CPPs, are aspects of the manufacturing process that have the potential to impact CQAs. These consist of elements, including mixing speed, pH, and temperature.
- Particle size and moisture content are examples of CMAs, which are characteristics of raw materials that might affect the final product's quality.

The design area

Changes to the process parameters can be made inside the multidimensional Design Space without lowering the quality of the finished output. High levels of quality are consistently guaranteed when working in this profession.

Control strategy

A control strategy outlines the measures needed to maintain product quality. It includes monitoring systems, specifications, and operational controls to ensure processes remain within the design space.

Evaluation of risk

A key component of QbD is risk assessment, which entails locating and assessing possible hazards to quality. To rank hazards and create mitigation plans, tools like fishbone diagrams and FMEA are employed.

Advantages of Quality by Design (QbD)

QbD is a methodical and proactive approach to the development and production of pharmaceuticals. By integrating quality into the design of processes and products, QbD offers numerous advantages that extend beyond mere compliance with regulatory standards. These advantages include enhanced product quality, cost savings, improved efficiency, and better risk management. Let's explore these benefits in detail.

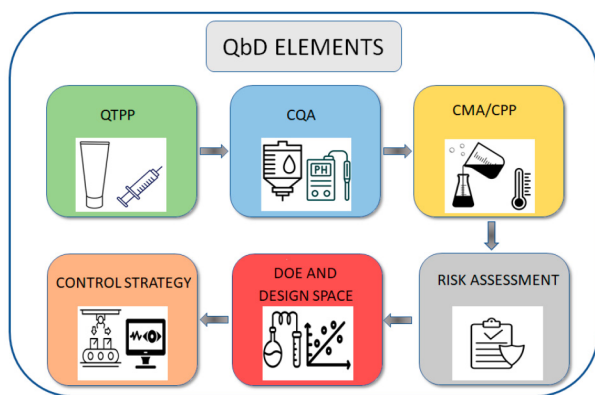


Figure 2: Elements of QbD

Improved Product Quality

Enhanced Consistency and Reliability

- *Built-in quality*

QbD ensures that quality is integrated into the product from the initial stages of development. By focusing on understanding the factors that influence quality, manufacturers can design processes that consistently produce high-quality products.

- *Reduced variability*

By means of a thorough comprehension of process parameters and their influence on CQAs, QbD reduces variability in the end product. This produces results that are more dependable and consistent.⁸⁻¹⁰

Better Control Over CQAs

- *Identifying CQAs*

QbD assists in identifying the essential quality features that need to be managed to guarantee the safety and effectiveness of products.

- *Monitoring and control*

Continuous monitoring of CQAs ensures that they remain within specified limits, leading to improved product performance and patient safety.

Cost Efficiency and Resource Optimization

Reduced waste and rework

- *Process optimization*

By optimizing processes through Design of Experiments (DoE) and other QbD tools, manufacturers can reduce waste, rework, and scrap.

- *Cost savings*

Efficient processes lead to significant cost savings in terms of raw materials, labor, and energy consumption.

Streamlined development process

- *Faster time to market*

QbD accelerates the development process by reducing the need for trial-and-error approaches, allowing companies to bring products to market more quickly.

- *Resource efficiency*

Focused experimentation and risk-based approaches ensure that resources are used effectively, maximizing return on investment.

Enhanced Regulatory Compliance

Alignment with regulatory expectations

- *Regulatory support*

Regulatory agencies such as the FDA and EMA advocate for QbD, as it provides a scientific and risk-based framework for product development.

- *Simplified approvals*

Implementing QbD can simplify regulatory submissions and approvals by providing clear documentation and rationale for design choices.

Reduced risk of non-compliance

- *Proactive risk management*

QbD's emphasis on risk assessment and management reduces the likelihood of compliance issues, such as product recalls or quality defects.

- *Continuous monitoring*

Ongoing monitoring ensures that processes remain compliant with regulatory standards, minimizing the risk of deviations.

Risk Management and Mitigation

Proactive identification of risks

- *Early detection*

QbD involves early identification and assessment of risks throughout the product lifecycle, enabling proactive management of potential issues.

- *Prioritization of risks*

Tools like FMEA help prioritize risks based on their impact, guiding targeted mitigation strategies.

Enhanced process robustness

- *Robust processes*

Understanding the connection between process variables and product quality enables QbD to assist in the development of reliable, less variable processes.

- *Resilience to changes*

Robust processes can better withstand changes in raw materials, environmental conditions, or equipment, maintaining product quality.

Continuous Improvement and Innovation

Culture of continuous improvement

- *Data-driven decisions*

QbD fosters a culture of continuous improvement, where data-driven decisions lead to ongoing enhancements in product quality and process efficiency.

- *Feedback loops*

Continuous monitoring and feedback loops enable real-time adjustments, leading to iterative improvements.

Encouragement of innovation

- *Innovative solutions*

QbD encourages innovative solutions to quality challenges by promoting a deep understanding of processes and their interactions.

- *Adaptability*

The flexibility inherent in QbD allows companies to adapt quickly to new technologies or market demands, fostering innovation.

Patient-Centric Benefits

Improved patient safety and efficacy

- *Consistent product performance*

QbD ensures that products consistently meet quality standards, enhancing patient safety and therapeutic efficacy.

- *Fewer adverse events*

By minimizing variability and ensuring quality, QbD reduces the risk of adverse events related to product defects.

Enhanced patient confidence

- *Trust in quality*

When QbD concepts are used to product development, patients can feel more confident in the dependability and quality of the final product, which improves brand loyalty and reputation.

Environmental and Sustainability Benefits

Reduced environmental impact

- *Efficient resource use*

Optimized processes lead to more efficient use of resources, reducing waste and environmental impact.

- *Sustainability goals*

QbD aligns with sustainability goals by minimizing the carbon footprint and promoting responsible manufacturing practices.

Contribution to sustainable development

- *Long-term viability*

By focusing on quality and efficiency, QbD contributes to the long-term viability of manufacturing processes, supporting sustainable development initiatives.

Regulatory Aspects of QbD

Alignment with Global Regulatory Expectations

Key Regulatory Agencies and Guidelines

- *U.S. Food and Drug Administration (FDA):*

- **Guidelines:** FDA has been a strong advocate for QbD, incorporating its principles into the Process Analytical Technology Guidance and ICH Q8(R2) Pharmaceutical Development guidelines.

- **Objective:** The FDA aims to enhance product quality through scientific understanding and risk management, encouraging the industry to adopt QbD.

- *European Medicines Agency (EMA):*

- **Guidelines:** EMA's Guideline on the Use of QbD in Drug Development promotes QbD principles to ensure robust and reliable pharmaceutical processes.
- **Objective:** EMA supports the use of QbD to achieve consistent product quality and regulatory compliance.

- *International council for Harmonisation (ICH):*

- **Guidelines:** The ICH has developed several guidelines that incorporate QbD, including:
 - **ICH Q8(R2):** Pharmaceutical development.
 - **ICH Q9:** Quality risk management.
 - **ICH Q10:** Pharmaceutical quality system.
- **Objective:** ICH guidelines aim to harmonize regulatory expectations across regions, promoting a unified approach to pharmaceutical quality.

- *Importance of regulatory alignment*

- **Global Consistency:** Alignment with regulatory guidelines ensures that pharmaceutical products meet consistent quality standards worldwide, facilitating international market access.
- **Regulatory Compliance:** Compliance with QbD guidelines reduces the risk of regulatory issues, such as product recalls or penalties, enhancing brand reputation.

In order to guarantee that the methods used for analysis are reliable, accurate, and effective, analytical method development is an essential component of the chemical and pharmaceutical industries. In this process, QbD has emerged as a crucial framework that offers a methodical approach to method development.¹¹⁻¹³

Role of QbD in Analytical Method Development:

Analytical method development is the process of creating procedures to accurately measure compounds or properties. QbD in analytical method development involves designing methods that are reliable, reproducible, and suitable for their intended purpose.

Benefits of Using QbD in Analytical Method Development

Improved understanding of methods

QbD helps in understanding the relationship between method variables and method performance.

Enhanced method robustness

By understanding the method's critical variables, QbD enhances robustness and reliability.

Reduction of variability

Systematic experimentation under QbD reduces variability and increases consistency.

Efficiency in development

QbD can reduce the time and cost of method development by

identifying optimal conditions faster.

Steps in QbD for Analytical Method Development

Steps involved in implementing QbD in analytical method development:

1. Define the analytical target profile (ATP)

The analytical target profile (ATP) outlines the requirements of the method. It includes:

Purpose of the method: What is being measured, and why?

Performance criteria: Accuracy, precision, sensitivity, specificity, etc.

2. Conduct risk assessment

Risk assessment identifies potential variables that could affect the method's performance. Prioritizing risks can be done with the aid of instruments like failure mode and effects analysis (FMEA).

3. Identify CQAs and critical method parameters (CMPs)

CQAs: Characteristics of the method that must be controlled to ensure quality (e.g., retention time, resolution).

CMPs: Variables that can affect CQAs (e.g., pH, temperature, flow rate).

4. DoE

DoE is a structured approach to experimentation. It involves: Selecting variables: Based on the risk assessment, select variables to study.

- Creating an experimental matrix: Plan experiments systematically to explore interactions between variables.
- Analyzing data: Use statistical methods to determine the impact of variables on CQAs.

5. Develop and optimize the method

Use insights from DoE to develop and optimize the method. Focus on:

- Robustness: Ensure the method performs consistently under different conditions.
- Accuracy and Precision: Validate the method's accuracy and precision.

6. Validate the Method

Validation ensures that the method meets the ATP. Key validation parameters include:

- Linearity: The method should produce results that are directly proportional to the concentration of analytes.
- Accuracy: The closeness of measured values to the true value.
- Precision: Reproducibility of findings in the same circumstances.
- Specificity: Ability to measure analytes in the presence of other components.
- Sensitivity: Detection and quantification limits.

7. Continuous monitoring and improvement

Once the method is validated and in use, continuous monitoring is essential. Collect data to ensure ongoing compliance with

the ATP and make improvements as necessary.

Tools and Techniques in QbD for Analytical Method Development:

• Statistical software

Statistical software is vital for QbD, facilitating data analysis and DoE. Examples include:

JMP: Offers powerful visualization and analysis tools.

Minitab: Widely used for statistical analysis in various industries.

Design-Expert: Specializes in the design of experiments and optimization.

• Risk assessment tools

Fishbone Diagram: Identifies potential causes of variability.

Failure mode and effects analysis: Risks are systematically assessed together with their effects using FMEA.

Risk ranking and filtering: Prioritizes risks based on severity and probability.

• Process analytical technology (PAT)

PAT involves using real-time data to monitor and control processes, ensuring compliance with quality standards.

Challenges and Considerations

Complexity and cost

Implementing QbD can be complex and costly initially, requiring investment in training and tools.

Regulatory requirements

Increasingly, regulatory bodies are expecting submissions to adhere to QbD standards, which calls for extensive documentation and rationale.

Change management

Transitioning to QbD requires a cultural shift within organizations, emphasizing proactive quality management.

Applications of QbD in analytical method development

QbD is a systematic approach that emphasizes understanding and controlling processes to ensure quality. In analytical method development, QbD offers a framework that enhances the robustness, accuracy, and efficiency of analytical methods. By applying QbD principles, organizations can develop methods that are better suited to their intended purposes, comply with regulatory expectations, and deliver consistent results.

Applications of QbD in Analytical Method Development

Chromatographic method development

Chromatography is a key analytical technique used in various industries, including pharmaceuticals, chemicals, and food. QbD enhances chromatographic method development by:

Optimizing separation conditions

Through DoE, QbD helps identify optimal conditions for separation, such as mobile phase composition, flow rate, temperature, and pH.

• *Enhancing robustness*

QbD guarantees that the procedure is reliable and consistent under various circumstances by comprehending the influence of variables on separation performance.

• *Improving resolution and sensitivity*

QbD aids in achieving better resolution and sensitivity, critical for detecting and quantifying analytes in complex matrices.

Spectroscopic Method Development

For both qualitative and quantitative analysis, spectroscopy is frequently used. QbD improves spectroscopic method development by:

• *Defining spectral parameters*

Identifying optimal wavelength, path length, and sample preparation methods to achieve accurate and precise measurements.

• *Managing interferences*

QbD helps understand and control potential interferences from matrix components, improving method specificity.

• *Enhancing calibration and validation*

QbD ensures that calibration models are robust and validated across a wide range of concentrations and conditions.

Assay development for biopharmaceuticals

Biopharmaceuticals present unique analytical challenges due to their complexity and sensitivity. QbD aids in assay development by:

• *Defining critical attributes*

Identifying key attributes such as potency, purity, and stability that must be monitored to ensure product quality.

• *Optimizing assay conditions*

Using DoE to evaluate variables such as enzyme concentration, reaction time, and temperature, leading to optimized assay conditions.

• *Ensuring method robustness*

By understanding the impact of environmental factors and matrix effects, QbD enhances the robustness of assays for biopharmaceuticals.

Dissolution method development

Dissolution testing is critical for evaluating drug release and bioavailability. QbD improves dissolution method development by:

• *Identifying critical variables*

Determining key factors such as agitation speed, medium composition, and temperature that influence dissolution behavior.

• *Optimizing method conditions*

Using DoE to optimize dissolution parameters, ensuring consistent and reliable results.

• *Enhancing method transferability*

QbD ensures that dissolution methods are transferable across different laboratories and equipment, maintaining consistency.

Method Validation and Transfer

QbD supports method validation and transfer by:

• *Defining validation parameters*

Establishing clear criteria for accuracy, precision, linearity, specificity, and robustness.

• *Facilitating method transfer*

Ensuring that methods are transferable between laboratories and analysts through robust design and clear documentation.

• *Continuous monitoring*

Implementing monitoring systems to ensure ongoing method performance and compliance with specifications.^{14,15}

CONCLUSION

QbD transforms analytical method development by providing a structured, scientific approach that enhances method reliability, robustness, and efficiency. By focusing on understanding and controlling critical variables, QbD ensures that analytical methods meet the highest standards of quality and performance.

The applications of QbD in analytical method development span various techniques, including chromatography, spectroscopy, biopharmaceutical assays, and dissolution testing. Through systematic experimentation, risk assessment, and continuous improvement, QbD enables the development of methods that are well-suited to their intended purposes, compliant with regulatory requirements, and capable of delivering consistent results.

As industries continue to adopt QbD principles, the benefits of enhanced quality, efficiency, and innovation will drive success and competitiveness in an increasingly demanding global market.

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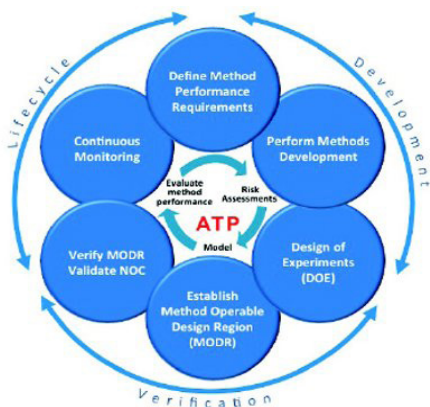


Figure 3: Applications of QbD

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