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A Review on Quality by Design for Pharmaceuticals

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ABSTRACT:

Quality by Design (QbD) is a systematic and science-based approach that has gained significant importance in the pharmaceutical industry. It emphasizes the proactive design and development of products and processes to ensure consistent quality and reduce the risk of failures during manufacturing. QbD provides a comprehensive framework that integrates quality principles, risk assessment, and knowledge management throughout the product lifecycle. This explores the key concepts and principles of QbD, including the use of Quality Target Product Profile (QTPP), Critical Quality Attributes (CQAs), and Critical Process Parameters (CPPs). It highlights the importance of understanding the impact of formulation and process variables on product quality and emphasizes the role of scientific understanding and experimentation in optimizing product performance. The implementation of QbD involves the application of various tools and methodologies, such as design of experiments (DoE), risk assessment techniques, and process analytical technology (PAT). These tools enable the identification and control of potential sources of variability, facilitating the development of robust manufacturing processes and ensuring consistent product quality. Furthermore, it discusses the regulatory perspective on QbD, highlighting the regulatory initiatives and guidelines that support its implementation. It emphasizes the shift from a traditional, inspection-based approach to a more science-based, risk-based, and knowledge-driven approach to pharmaceutical development and manufacturing. Finally, QbD offers a systematic and proactive approach to ensure quality throughout the product lifecycle. By integrating scientific knowledge, risk assessment, and quality principles, QbD enables the development of robust processes, reduces manufacturing variability, and enhances patient safety by delivering high-quality pharmaceutical products. Its adoption by the pharmaceutical industry promotes innovation, efficiency, and regulatory compliance in drug development and manufacturing.

Keywords: Attributes, PAT, Product, QbD, Tools, Validation.

1. INTRODUCTION

Quality by Design (QbD) is a systematic approach used in various industries, including pharmaceuticals, biotechnology, and manufacturing, to ensure the quality and reliability of products and processes[1,2]. It is a proactive approach that focuses on building quality into the product or process right from the design stage, rather than relying on post-production testing and inspection. The key principle of Quality by Design is to understand the critical aspects of a product or process that can affect its quality and performance and then design and control those aspects to ensure desired outcomes[3]. It emphasizes the use of scientific and risk-based approaches to develop a deep understanding of the product and process, and to identify and mitigate potential sources of variability and risk. In the context of pharmaceuticals, Quality by Design is a regulatory initiative introduced by the U.S. Food and Drug Administration (FDA) as part of its initiative to enhance pharmaceutical manufacturing quality and innovation[4,5]. The goal is to shift from a traditional, inspection-based approach to a science- and risk-based approach that ensures product quality through robust design, thorough understanding, and effective control of critical variables.

1.1. Quality by Design (QbD) {ICH Q8(R1)} is a systematic approach to pharmaceutical development that focuses on ensuring product quality by design rather than relying on end-product testing alone. QbD principles can be applied to various aspects of pharmaceutical development, including both formulation development (in pharmaceutics) and analytical method development[6,7]. Here are some specific applications of QbD in these areas:

a. Formulation Development:

Design Space: QbD encourages the identification and understanding of critical formulation and process parameters that affect product quality. By establishing a design space, which is a multidimensional space defining the acceptable ranges for these parameters, formulation scientists can optimize formulations and processes to ensure consistent product quality[8].

Risk Assessment: QbD emphasizes the identification and assessment of risks associated with formulation and process variables. Risk assessment tools, such as Failure Mode and Effects Analysis (FMEA) and Fishbone diagrams, can be used to identify potential risks and develop strategies to mitigate them[9].

Real-Time Release Testing (RTRT): QbD facilitates the implementation of RTRT, where critical quality attributes (CQAs) are monitored during manufacturing to ensure product quality. This reduces the reliance on end-product testing and enables timely adjustments to the process if deviations from the desired quality are observed[10].

b. Analytical Method Development:

Method Understanding: QbD encourages a thorough understanding of the analytical method and its relationship to the product's CQAs. This involves identifying critical method parameters and their impact on method performance[11].

Design of Experiments (DoE): DoE is a key tool in QbD for method development. It allows for a systematic exploration of the parameter space to understand the effects of method variables on critical method attributes (CMAs). This helps in optimizing the method and establishing the design space[12].

1.2. Method Validation: QbD promotes a science-based approach to method validation[13]. By understanding the method's performance characteristics and its relationship to product quality, validation can be focused on the critical aspects of the method, reducing unnecessary testing.

Real-time process monitoring and control: Employing advanced process analytical technologies (FDA PAT Guidelines, Sep. 2004) and automation to continuously monitor and control key process parameters, enabling proactive adjustments and interventions to maintain product quality and Continuous improvement and lifecycle management: Emphasizing the need for ongoing monitoring, analysis, and optimization of the product and process throughout its lifecycle, incorporating feedback and lessons learned to drive continuous improvement[14].

In both pharmaceutics and analytical method development, QbD aims to enhance process understanding, optimize performance, and ensure consistent product quality. It fosters a proactive approach to quality assurance throughout the product lifecycle, resulting in more robust and reliable pharmaceutical products and analytical methods. By applying Quality by Design principles, companies can enhance product quality, reduce variability, increase process efficiency, and improve overall customer satisfaction. It promotes a proactive and systematic approach to quality, resulting in more robust and reliable products and processes[15].

Benefits of QbD[16]:

- QbD offers a good business
- Eliminates batch failures
- Minimize deviations and costly investigations
- Empowerment of technical staff
- Increase manufacturing efficacy, reduce cost and project rejections.
- Ensure consistent information
- Efficient, agile and flexible system.

2. STEPS INVOLVED IN QUALITY BY DESIGN PRODUCTS[17]:

1. Development of new molecular entity
   - Preclinical study
   - Nonclinical study
   - Clinical study
   - Scale up
   - Submission for market approval
2. Manufacturing
   - Design space
   - Process Analytical Technology
   - Real Time Quality control
3. Control Strategy
   - Risk based decision
   - Continuous improvement
   - Product performance

The Quality by Design (QbD) approach is a systematic and proactive strategy to ensure quality in the development and manufacturing of pharmaceutical products.

2.1. Structure for a QbD startup plan, seven steps[18]:

1. Define the Target Product Profile (TPP):
    - Clearly articulate the desired quality attributes of the product.
    - Identify the intended use, patient population, dosage form, route of administration, and other relevant characteristics.
2. Identify Critical Quality Attributes (CQAs):
    - Determine the key quality characteristics that are critical to the safety and efficacy of the product.
    - Define specifications and acceptance criteria for each CQA.
3. Establish a Design Space:
    - Develop a comprehensive understanding of how formulation and process parameters affect product quality.
    - Conduct experiments and gather data to define a multidimensional design space within which the product will consistently meet its quality attributes.
4. Design and Conduct Experiments:
    - Utilize experimental design techniques to explore the effects of various factors on product quality.
    - Conduct risk assessments and design experiments to optimize the formulation and manufacturing process.
5. Develop a Control Strategy:
    - Define the critical process parameters (CPPs) and critical material attributes (CMAs) that impact CQAs.
    - Establish appropriate control limits and ranges for CPPs and CMAs.
    - Define the sampling plan, testing methods, and acceptance criteria.
6. Process Validation:
    - Execute process validation studies to demonstrate the manufacturing process's capability to consistently produce the desired quality product.
    - Utilize statistical tools and data analysis to ensure process robustness and control.
7. Continued Process Verification and Improvement:
    - Implement ongoing monitoring and analysis of manufacturing data to ensure the process remains in control.
    - Identify opportunities for process optimization, continual improvement, and risk mitigation.
    - Implement change management processes to evaluate and implement process changes.

3. QUALITY BY DESIGN (QBD) IN PHARMACEUTICALS

Even though the pharmaceutical industry has focus on quality, it has failed to keep up with other industries in terms of manufacturing efficiency and productivity.

Current scenario in the Pharmaceutical Industry:

- Cost of revalidation
- Off-line analysis for in-process - need based
- Product specifications as primary means of control
- Unpredictable Scaleup issues
- Inability to understand failures

Systematic approach to development:

- That begins with predefined objectives

- Emphasizes products and process understanding
- Process control

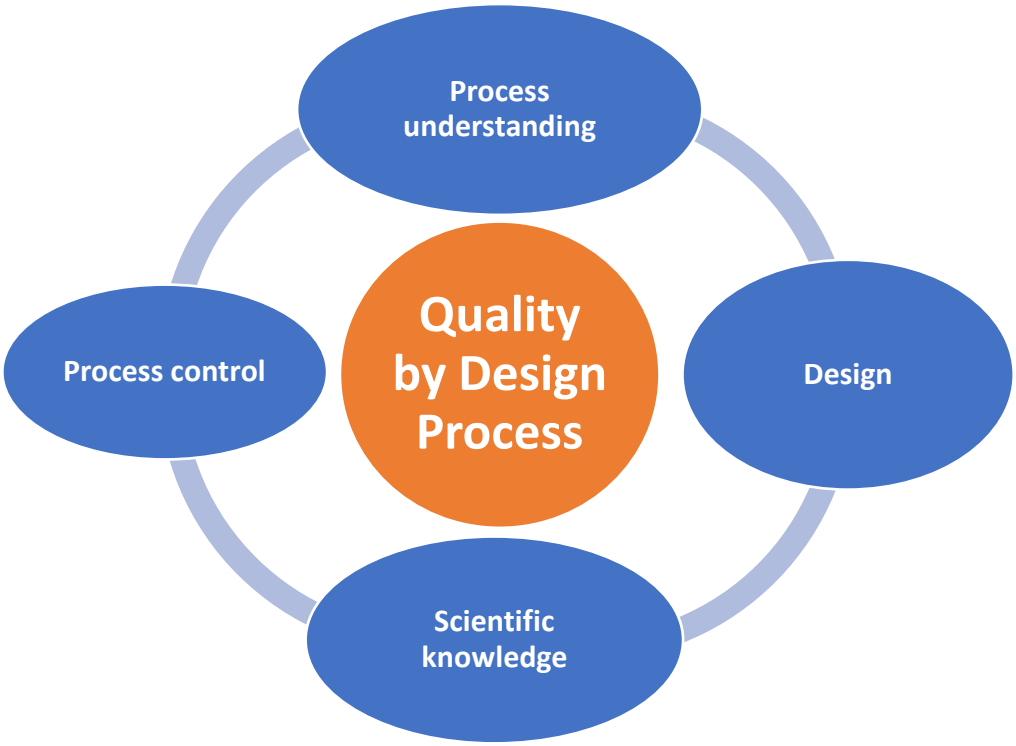

Figure 1: Quality by Design: Principles to develop successful products

3.1. Quality Target Product Profile[19]

Quality Target Product Profile (QTPP) is an important concept in Quality by Design (QbD) that helps define the desired characteristics and quality attributes of a pharmaceutical product. It serves as a guide for product development and quality control throughout the product lifecycle. The QTPP is a comprehensive description of the product that includes both the intended use and the quality attributes required to ensure its safety, efficacy, and overall quality. Here are the key elements of a QTPP in QbD:

1. Identification and Description of the Product:
    - Generic name and/or brand name of the product.
    - Dosage form (e.g., tablet, capsule, injection, etc.).
    - Strength or concentration of active ingredients.
    - Route of administration.
    - Container closure system.

2. Intended Use and Therapeutic Purpose:
    - The target patient population or disease indication.
    - The desired clinical effect or therapeutic purpose.
    - Any specific patient needs or characteristics to consider.

3. Critical Quality Attributes (CQAs):
    - Physical attributes (e.g., appearance, shape, size, etc.).
    - Chemical attributes (e.g., purity, stability, impurities, etc.).
    - Biological attributes (e.g., potency, activity, etc.).
    - Performance attributes (e.g., dissolution, disintegration, etc.).

- Microbiological attributes (e.g., sterility, endotoxin levels, etc.).
- Any other relevant attributes specific to the product.

4. Acceptance Criteria:

- Specifications and limits for each critical quality attribute.
- Allowable ranges or limits for non-critical quality attributes.
- Any other specific requirements or criteria for acceptance.

5. Manufacturing Process:

- Description of the manufacturing process, including steps, equipment, and materials.
- Process parameters and controls for critical steps.
- Process capability requirements.

6. Stability:

- Stability requirements for the product over its intended shelf life.
- Any specific storage or handling conditions.

7. Regulatory and Legal Requirements:

- Compliance with applicable regulatory guidelines and requirements.
- Legal requirements for the product, such as labeling, packaging, etc.

It's important to note that the QTPP is not a fixed document and can be updated or refined as more knowledge is gained during the product development and lifecycle management phases. It serves as a foundation for risk assessment, design of experiments, and the development of a control strategy in QbD.

3.2. Critical Quality Attributes

Quality by Design (QbD) is a systematic approach to pharmaceutical development that focuses on understanding and controlling the critical quality attributes (CQAs) of a product throughout its lifecycle. CQAs are the physical, chemical, biological, or microbiological characteristics that are critical to ensuring the safety, efficacy, and overall quality of a pharmaceutical product. They can vary depending on the type of product and its intended use. Here are some examples of critical quality attributes in QbD:

- Identity
- Purity
- Potency
- Stability
- Dissolution
- Particle Size
- Content Uniformity
- Microbiological Attributes

These are just a few examples of critical quality attributes in QbD. The specific CQAs for a product will depend on factors such as its dosage form, route of administration, intended use, and regulatory requirements. The identification, understanding, and control of these critical quality attributes are fundamental to QbD principles and the development of high-quality pharmaceutical products.

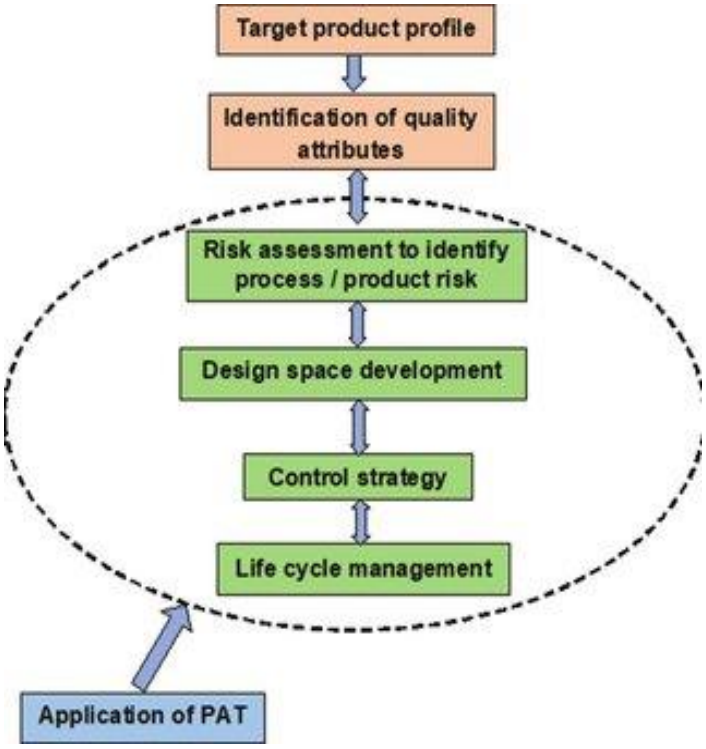

Figure 2: Decision tree to decide CQAs

4. PRODUCT QUALITY BY END PRODUCT TESTING VS QBD

Product quality can be ensured through various approaches, including end product testing and Quality by Design (QbD) methodologies. Let's explore each approach in more detail:

4.1. End Product Testing:

End product testing involves evaluating the quality of a product by conducting tests on the final manufactured item. This approach typically involves sampling a representative number of finished products and subjecting them to various tests and analyses. The goal is to verify if the product meets the specified quality standards and regulatory requirements. Some advantages and considerations of end product testing are:

Advantages:

- Simplicity: End product testing is a well-established and straightforward method to assess product quality.
- Regulatory Compliance: It allows for compliance with regulatory requirements by demonstrating that the product meets the predetermined specifications.
- Real-World Performance: End product testing reflects the quality of the actual product that reaches the market.

Considerations:

- Time and Cost: Testing each finished product can be time-consuming and costly, especially if the product has a long manufacturing cycle.
- Limited Insight: Testing only the final product provides limited insights into the underlying factors that contribute to quality issues. It does not identify specific process parameters that may affect the product's quality.
- Reactive Approach: End product testing is a reactive approach that identifies quality issues after production, which may lead to waste and delays.

4.2. Quality by Design (QbD):

QbD is a systematic and proactive approach to product development that aims to ensure quality throughout the manufacturing process. It involves understanding the impact of various factors on product quality, designing robust processes, and controlling critical parameters. QbD emphasizes the following key principles:

- Design Space: QbD defines a design space, which encompasses the ranges of input variables (such as raw materials, process parameters) that will lead to a product meeting the desired quality attributes.
- Risk Assessment: QbD involves a systematic risk assessment to identify critical quality attributes and critical process parameters that have a significant impact on product quality.
- Process Understanding and Control: QbD focuses on developing a deep understanding of the product and its manufacturing process to control critical quality attributes and process parameters.
- Continuous Improvement: QbD promotes continuous improvement by monitoring and analyzing process data, identifying trends, and implementing corrective and preventive actions.

Advantages of QbD:

- Proactive Approach: QbD is a proactive approach that considers quality from the early stages of product development, reducing the likelihood of quality issues later on.
- Process Optimization: QbD helps optimize processes by identifying critical parameters and establishing ranges that lead to consistent and high-quality products.
- Reduced Variability: By understanding and controlling critical parameters, QbD can reduce product variability and improve batch-to-batch consistency.

Considerations:

- Upfront Investment: Implementing QbD requires an upfront investment of time, resources, and expertise to conduct thorough process characterization and risk assessments.
- Regulatory Support: QbD is increasingly supported by regulatory agencies as an effective approach to ensure product quality. However, it may require additional documentation and data to demonstrate compliance.

In summary, end product testing provides a snapshot of the final product's quality and ensures compliance with specifications. On the other hand, QbD is a proactive approach that focuses on process understanding, optimization, and control to consistently produce high-quality products. QbD offers the potential for better process understanding, reduced variability, and continuous improvement throughout the product lifecycle.

5. ICH Q8, Q9, Q10 GUIDELINES: THE FOUNDATION OF QbD[20,21,22]:

The ICH (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) guidelines, specifically ICH Q8, Q9, and Q10, form the foundation of Quality by Design (QbD) principles in the pharmaceutical industry and each guideline and their contributions to QbD:

5.1. ICH Q8 Pharmaceutical Development:

ICH Q8 provides guidance on pharmaceutical development and emphasizes the need for a systematic approach to product development. It promotes the concept of QbD by encouraging a thorough understanding of the product and the identification of critical quality attributes (CQAs) that are essential for ensuring product quality. Key elements of ICH Q8 include:

- Quality Target Product Profile (QTPP): Defining the desired quality and performance characteristics of the product.
- Critical Quality Attributes (CQAs): Identifying the product attributes that are critical to ensuring quality and safety.
- Risk Assessment: Conducting a risk assessment to understand the potential impact of variables on product quality.
- Design Space: Establishing a design space that defines the acceptable ranges of input variables for maintaining product quality.
- Control Strategy: Developing a control strategy that includes appropriate testing, monitoring, and control measures to ensure product quality.

5.2. ICH Q9 Quality Risk Management:

ICH Q9 provides guidance on quality risk management, which is an integral part of QbD. It encourages a systematic and proactive approach to identify, assess, control, and communicate risks throughout the product lifecycle. Key elements of ICH Q9 include:

- Risk Assessment: Identifying and evaluating risks to product quality, patient safety, and regulatory compliance.
- Risk Control: Developing strategies and implementing controls to mitigate identified risks.

- Risk Communication: Ensuring effective communication of risks and risk management decisions within the organization and to relevant stakeholders.
- Risk Review: Continuously monitoring and reviewing risks and risk control measures to ensure their effectiveness.

5.3. ICH Q10 Pharmaceutical Quality System:

ICH Q10 focuses on establishing and maintaining a pharmaceutical quality system (PQS) that ensures the consistent production of high-quality products. It provides a framework for implementing an effective quality management system and integrating QbD principles into daily operations. Key elements of ICH Q10 include:

- Quality Management: Implementing a robust quality management system that emphasizes a culture of quality and continuous improvement.
- Lifecycle Approach: Adopting a lifecycle approach to product development, manufacturing, and post-approval changes.
- Change Management: Applying a systematic approach to managing changes and assessing their impact on product quality.
- Knowledge Management: Promoting the capture, retention, and sharing of knowledge throughout the organization to support decision-making and improve processes.

Together, these three ICH guidelines (Q8, Q9, and Q10) provide a framework for the implementation of QbD principles in the pharmaceutical industry. They emphasize the importance of understanding product quality attributes, managing risks, and maintaining an effective quality management system throughout the product lifecycle. By following these guidelines, pharmaceutical companies can enhance product quality, reduce variability, and ensure patient safety.

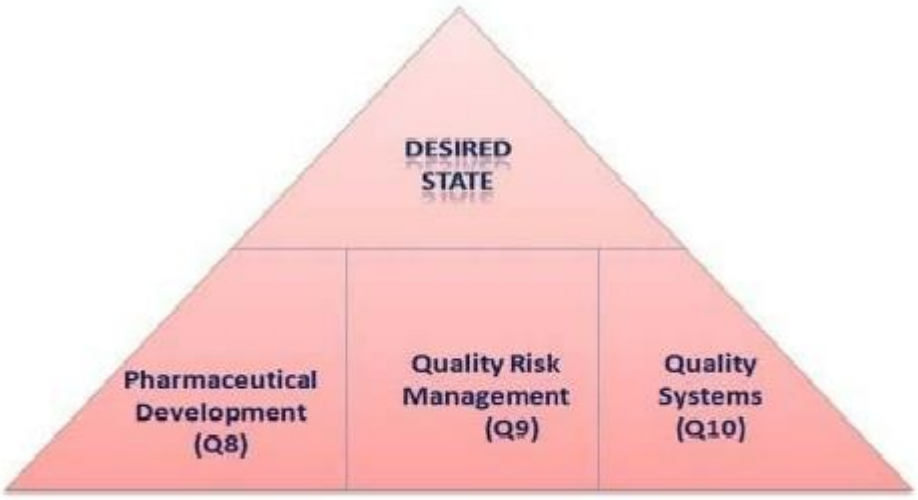

Figure 3: The Foundation of QbD

6. APPLICATIONS OF QUALITY BY DESIGN[23,24]:

Quality by Design (QbD) is a systematic approach to product development that focuses on building quality into the product from the outset, rather than relying on post-production testing and inspection. It is widely used in various industries, including pharmaceuticals, biotechnology, food and beverages, chemicals, and manufacturing. Here are some applications of Quality by Design:

1. Pharmaceutical Industry: QbD is extensively applied in the pharmaceutical industry to ensure the quality, safety, and efficacy of drug products. It involves designing and controlling the formulation and manufacturing processes to consistently produce high-quality pharmaceuticals. QbD principles are used to define the critical quality attributes (CQAs) of the drug product, establish the critical process parameters (CPPs), and conduct risk assessments to optimize the formulation and manufacturing processes.

2. Biotechnology: QbD is employed in the development and production of biotechnology-based products, such as therapeutic proteins, vaccines, and gene therapies. By applying QbD principles, biopharmaceutical companies can enhance the understanding of their products and processes, identify critical quality attributes, and implement robust control strategies to ensure consistent quality and performance of biologics.

3. Food and Beverage Industry: QbD principles can be utilized to enhance the quality and safety of food and beverage products. By understanding the critical parameters affecting product quality, companies can design processes that minimize variability and optimize product attributes such as taste, texture, and shelf life. QbD also helps in identifying and controlling potential hazards and allergens, ensuring compliance with regulatory requirements.

4. Chemical Industry: QbD finds applications in the chemical industry for the development and production of specialty chemicals, polymers, and other chemical products. It allows for the design of chemical processes with a focus on product quality, process efficiency, and sustainability. QbD principles help in optimizing reaction conditions, identifying critical raw material attributes, and establishing appropriate control strategies to ensure consistent product quality.

5. Manufacturing: QbD principles can be extended to various manufacturing processes across different industries. By applying QbD concepts, companies can systematically design and control their manufacturing processes to produce products with desired quality attributes. This approach involves understanding the critical process parameters, establishing appropriate control strategies, and implementing continuous process monitoring and improvement methodologies.

Overall, the applications of Quality by Design span across different industries, providing a framework for designing quality into products and processes, reducing variability, enhancing process understanding, and ensuring regulatory compliance. By adopting QbD principles, companies can improve product quality, reduce costs, and enhance customer satisfaction.

7. CONCLUSION

In the pharmaceutical industry, Quality by Design (QbD) has emerged as a powerful framework for ensuring the quality, safety, and efficacy of drug products. QbD principles provide a systematic and science-based approach to pharmaceutical development and manufacturing, enabling companies to design quality into products from the beginning. Here is an overall conclusion for QbD in the pharmaceutical industry. Enhanced Product and Process Understanding by QbD promotes a deep understanding of the relationship between critical quality attributes (CQAs) and critical process parameters (CPPs) by utilizing tools such as risk assessment, design of experiments (DoE), and process analytical technology (PAT). This increased understanding enables companies to develop robust and reliable processes that consistently deliver high-quality products. Reduced Variability and Batch Failures are done by identifying and controlling critical sources of variability, QbD minimizes the risks of batch failures, product recalls, and deviations. It allows for the establishment of appropriate control strategies, process monitoring, and continuous improvement, leading to increased process robustness and product consistency. Accelerated Development and Regulatory Approval in QbD facilitates a more efficient and streamlined drug development process. The systematic approach of QbD enables companies to identify critical factors early on, optimize formulation and manufacturing processes, and address potential risks proactively. This can lead to reduced development time, faster regulatory approvals, and quicker market entry. Improved Risk Management in QbD incorporates risk assessment methodologies, such as failure mode and effects analysis (FMEA), to identify and mitigate risks throughout the product lifecycle. By addressing potential risks in a proactive manner, companies can enhance patient safety, product quality, and compliance with regulatory requirements. The cost reduction and efficiency by implementing QbD principles can lead to cost savings and increased efficiency. By reducing batch failures, rejections, and post-production testing, companies can minimize waste and improve resource utilization. Furthermore, QbD enables process optimization, which can result in higher yields, reduced production costs, and improved overall operational efficiency. Finally the compliance with regulatory expectations in QbD aligns with regulatory expectations and guidelines, such as the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q8, Q9, and Q10. By adopting QbD principles, pharmaceutical companies can demonstrate a robust understanding of their products and processes, leading to increased regulatory compliance and smoother regulatory inspections.

Overall, Quality by Design (QbD) has become an integral part of pharmaceutical development and manufacturing. By systematically designing quality into products and processes, QbD enables companies to enhance product understanding, reduce variability, accelerate development timelines, improve risk management, and achieve regulatory compliance. Implementing QbD principles in the pharmaceutical industry ultimately leads to higher quality products, increased patient safety, and improved operational efficiency.

CONFLICT OF INTEREST: None

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