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QUALITY BY DESIGN IN PHARMACEUTICAL- A REVIEW

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ABSTRACT:

The current approach to pharmaceutical quality is known as "Quality by Design." To ensure that product quality is integrated in design, contemporary pharmaceutical regulatory laws have emphasised the critical importance of integrating quality by design (QbD) ideas for complete process understanding. In order to ensure pharmaceutical quality, this paper will describe pharmaceutical quality by design and how it might be used. Quality should be considered when designing products rather than testing them. When applying QbD principles to the product design and development process, it is necessary to establish the target product quality profile (TPQP), the targeted product performance profile (TPP), and the critical quality ascribed (CQA). Based on this, we may design a method and product formulation that meet the product's specifications. This leads to the identification of the cause and impact of variability, as well as CQAs for raw material Critical Material Attributes (CMA) and Critical Process Parameters (CPP). To comply with laws and implement fresh ideas such as design space, ICH guidelines (such as Q8 pharmaceutical development, Q9 quality risk management, and FDA's Process Analytical Technology (PAT)—QbD is required.

KEYWORDS: Quality by design, Target product profile, Target product quality profile, Critical quality attributes, Process analytical technology

INTRODUCTION:

Quality by Design (QbD) is a proactive, science-driven approach to pharmaceutical development that ensures medications satisfy the highest quality, safety, and efficacy criteria. QbD assures constant delivery of high-quality medications by integrating product and process understanding, risk assessment, and control measures, resulting in improved patient outcomes and regulatory compliance. Quality is a top objective for all regulatory authorities that monitor pharmaceutical products. Quality is all about ensuring customer satisfaction with service, product, and method. Many of these quality-related initiatives highlight the importance of firms succeeding in the global marketplace. Customers want perfect performance that is supplied on time, at a reasonable price, and of great quality. There are two ways to satisfy customers: by giving features and products that are free of defects. The primary focus of this research is on solid oral dosage forms of small molecules and how pharmaceutical quality by design can be used to ensure pharmaceutical quality. The pharmaceutical business not only invests heavily in creating, producing, and presenting new pharmaceuticals to the market, but it also ensures that these goods meet all applicable safety and efficacy criteria. An alternative strategy for medication development could increase productivity, provide regulatory relief and flexibility, and have a large positive influence on business throughout the product's life cycle. In light of the industry's current shift towards submissions based on quality by design (QbD), this article analyses the techniques used to create a market formulation, as well as the accompanying data.

The FDA's Office of Generic Drugs (OGD) has created a Question-Based Review (QbR) process to assess Abbreviated New Drug Applications (ANDAs), focusing on chemistry, manufacturing, and controls. QbR introduces a new set of quality attributes and is a practical way to apply key concepts and standards from the FDA's Pharmaceutical CGMPs for the Twenty-First Century and Quality by Design (QbD) program

DESIGN:

- The product is designed to meet the needs of patients and perform well.
- The procedure is configured to consistently meet the needs for high-quality products.
- The impact of process variables and starting raw materials on the quality of the finished product is well understood.

The detection and management of important sources of process variability

Future pharmaceuticals quality system:

- Pharmaceuticals development [Q8].
- Quality risk management [Q9].
- Pharmaceuticals quality system [Q10].

Benefits of QbD

- Quality by Design is beneficial to businesses.
- Remove failures in batches.
- Reduce deviations and expensive inquiries.
- Prevent issues with regulatory compliance.
- Investing in organizational learning is an investment in the future.
- QbD is a useful science.
- Better choices for growth.
- Staff empowerment.

Regulatory aspect [9].
Key Points and Potential Discussion Topics:
QbD as a Holistic Approach:

- Comparing Incremental and Holistic Improvement: The essay stresses the drawbacks of incremental enhancements and the necessity of a thorough, QbD-based strategy to guarantee product quality.

QbD prioritises a thorough understanding of the production process in order to identify crucial parameters and build effective control measure

QbD Implementation Steps:

- Quality Target Product Profile (QTPP): Specifies the desired features and performance of the product.
- Critical Quality Attributes (CQAs): Identifies the key qualities of the product that directly affect its quality.
- Risk Assessment: Looks at potential risks in the manufacturing process and determines critical points to control.
- Design Space: Defines the operating parameters within which the product consistently meets quality attributes.
- Control Strategy: Establishes the necessary controls to maintain product quality and consistency.
- Product Lifecycle Management: Ensures ongoing monitoring and control of the product throughout its lifecycle.

Potential Discussion Topics:

- Discuss the difficulties connected with implementing QbD, such as the requirement for specialised expertise, data-driven decision-making, and cultural change inside organisations.
- QbD and Regulatory Expectations: Learn about the changing regulatory expectations for QbD, as well as the role of regulatory authorities in supporting its use.
- Case Studies: effective QbD Implementation: Examine real-world examples of effective QbD implementations and the benefits they yield.
- Future Trends in QbD: Discuss new trends in QbD, such as the incorporation of sophisticated technology like artificial intelligence and machine learning.
- QbD and Continuous Improvement: Learn about how QbD may be used to drive continuous improvement in manufacturing processes and product quality.

Opportunities

- Effective, flexible, and nimble system.
- Improve production efficiency, reduce costs, and minimize rejections and waste.
- Build a scientific understanding for every product.
- Improved communication of scientific issues with industry.
- Assure accuracy of the data.

Primary objective:

The main goals of Quality by Design (QbD) are to carefully identify and control key quality attributes (CQAs) and process factors (CPPs). This approach involves three steps. First, screening studies are conducted to narrow down the list of factors that have a big impact on product quality. Second, characterisation studies are intended to determine the association between these important parameters and CQAs. Finally, robustness testing is carried out to determine the influence of fluctuations in important elements on product quality, ensuring that the process is adaptable to real-world manufacturing settings

STEPS INVOLVED IN QUALITY BY DESIGN PRODUCTS:

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

Seven steps of Quality by Design start up plan:

1. Hire a quality expert independent of the design stage.
2. Check your organization and processes with the expert perform a gap analysis.
3. Organize a basic design quality workshop with all your stuff personal
4. Review the expert's report and recommendation.
5. Write an implementation plan, timelines and estimated costs.
6. Allocate (or outsource) resources.
7. Retain the independent expert as a "project insurance" advisor.

Quality by Design (QbD) in the Pharmaceutical Industry [10,11].

Although the pharmaceutical industry has focused on quality, it has traditionally struggled with efficiency and productivity compared to other industries. However, this is changing with the introduction of Quality by Design (QbD).

Current Challenges in the Pharmaceutical Industry

- Several difficulties hamper the industry's efficiency and productivity. The high cost of revalidation Frequent revalidations caused by changes in methods or formulas can be costly and time-consuming.
- Relying on off-line analysis can limit real-time process monitoring and control, potentially leading to quality issues.
- Relying solely on product specifications can disguise process issues and impede continual improvement.
- Unpredictable Scale-Up Issues: Transitioning from small-scale to large-scale manufacturing can be tough and cause unanticipated issues.

QbD: Systematic Approach to Development

QbD provides a systematic strategy to addressing these difficulties while also increasing pharmaceutical manufacturing efficiency and productivity. The following are the key principles of QbD.

- Clear objectives are created from the start of the development process.
- Understanding the product's critical quality attributes (CQAs) and process parameters (CPPs) is vital.
- Implementing robust process control measures ensures constant product quality. This includes the use of real-time process monitoring and control methods.

Used of PAT:

The system you've described is most likely a Quality Management System (QMS) designed specifically for industrial processes. It is consistent with the ideas of statistical process control (SPC) and total quality management (TQM).

Key Components of Such a QMS:

Quality Planning:

- Defining quality goals and objectives.

- Identifying critical quality characteristics (CQCs).
- Developing process flow diagrams and control charts.

Quality Assurance:

- Establishing quality standards and procedures.
- Implementing quality control measures.
- Conducting regular audits and inspections.

Quality Control:

- Monitoring and measuring process variables.
- Analyzing data to identify trends and potential problems.
- Taking corrective actions to prevent defects.

Quality Improvement:

- Continuously seeking ways to improve processes and products.
- Implementing lean manufacturing and Six Sigma methodologies.
- Using data-driven decision-making to optimize performance.

Specific Techniques and Tools:

Statistical Process Control (SPC): Process monitoring and control are carried out using statistical approaches.
Control Charts: Visual tools for measuring process performance and detecting irregularities. Process Capability Analysis: determining a process's ability to satisfy standards.
Root Cause Analysis: Determine the root causes of quality issues.
Corrective and Preventive Action (CAPA): Implementing strategies for addressing and preventing quality issues.
Manufacturers can improve product quality, minimise defects, and increase overall operational efficiency by efficiently adopting such a QMS.

Quality by Design (QbD): A Paradigm Shift in Pharmaceutical Development and Manufacturing: [10,12,13]

Quality by Design (QbD) is a proactive, science-based approach to drug development and production. Unlike traditional methods, which frequently rely on trial and error and extensive testing, QbD focusses on a systematic understanding of how product and process variables affect product quality. This strategy results in more efficient, robust, and dependable production processes.

Applications of QbD in Pharmaceutical Development and Manufacturing: Product Design:

- Critical Quality Attributes (CQAs): Identifying the key quality factors that need to be monitored to ensure the product is of high quality.
- Target Product Profile (TPP): Defining the essential quality features the final product must have.
- Critical Process Parameters (CPPs): Identifying the process factors that significantly affect the quality characteristics of the product.

Process Design:

1. Design of Experiments (DoE): Understanding the relationship between process factors and product quality using statistical analysis.
2. Process Analytical Technology (PAT): Implementing real-time monitoring and control approaches to ensure process consistency.
3. Risk Assessment: Detecting and managing possible threats to product quality and patient safety.

Life Cycle Management:

- Continuous Improvement: Creating a culture of continuous improvement in order to optimise processes and products.
- Change Control refers to the regulated implementation of changes to a product or process.
- Post-Approval adjustments: Making it easier to make adjustments after approval.

QBD in CMC Review Offices: A Comprehensive Overview. [14]

The use of Quality by Design (QbD) principles has greatly affected how pharmaceutical products are reviewed by regulators. Regulatory agencies, like the FDA, have accepted this approach, which focuses on science and managing risks in drug development and manufacturing.

Office of New Drug Quality Assessment (ONDQA)

- Science Based Assessment: The ONDQA uses QbD to carry out a more scientific and risk-focused evaluation of drug applications.
- Restructured Organisation: To better accord with QbD principles, the office has restructured its team, separating premarket and post market review tasks.
- CMC Pilot: The ONDQA has launched a CMC Pilot initiative to gain expertise with QbD-based applications and improve review processes.
- Application Review: The office has reviewed numerous applications submitted using QbD principles, learning valuable lessons and improving its review efficiency.

- Information Evaluation: ONDQA is concerned with assessing the quality and relevance of information presented in QbD-based applications.
- PMP Implementation: The office is aggressively implementing the Pharmaceutical Quality System (PQS) to guarantee QbD principles are followed.

Office of Generic Drugs (OGD)

- QbR Framework: OGD uses the QbR (Quality by Review) approach to govern its review of generic medicine applications. This framework contains critical scientific and regulatory review questions for evaluating product quality and manufacturing hazards.
- Product Quality Assessment: OGD determines whether a generic product is good quality and meets all regulatory requirements.
- Risk Assessment: The office assesses the risk associated with producing and designing a generic product.
- QbR Adoption: As of June 2007, OGD had received 416 applications for QbR, indicating widespread industrial acceptance.
- Question Effectiveness: OGD has effectively ensured that QbR questions address important concerns with QbD and product quality.

Factors Contributing to the Successful Adoption of Quality by Design (QbD) [15,16]

The successful use of Quality by Design (QbD) principles has been influenced by several important factors:

Regulatory Flexibility and Harmonization:

- Regulatory Flexibility: Regulatory authorities have embraced QbD and are increasingly willing to consider flexible approaches to drug development and production. This versatility enables more inventive and efficient operations.
- Common Dossier Acceptance: The harmonization of regulatory standards across areas has simplified the drug clearance procedure. A standard dossier format, accepted by numerous regulatory authorities, decreases the administrative load for pharmaceutical businesses.
- Post-Approval adjustments: QbD allows businesses to make specific post-approval adjustments within a predefined design space without requiring complete regulatory re- approval. This adaptability enables quick reactions to market needs and technology improvements.
- Intellectual Property Protection: Strong intellectual property laws and regulations protect the inventions and private knowledge created by QbD. This encourages businesses to invest in research and development and implement QbD concepts.
- Governments and regulatory bodies have played a critical role in the broad adoption of QbD by creating a legislative environment that encourages innovation, efficiency, and intellectual property protection.

Office of Biotechnology Products (OBP)

- Complex Products: OBP evaluates applications for sophisticated biotech goods, which frequently necessitate a more nuanced approach to quality assurance.
- QbD Integration: OBP has already included several features of 16QbD into its evaluation processes.
- Application Acceptance: The office is preparing to accept submissions that completely adhere to QbD standards.
- Biotech Pilot: OBP has launched a pilot study to get firsthand expertise with QbD-based biotech product applications.

Overall Impact of QBD

The use of QbD has greatly enhanced the quality, efficiency, and predictability of drug development and manufacturing operations. QbD has contributed to pharmaceutical product safety and efficacy by emphasising science-based methodologies, risk management, and process understanding. As regulatory agencies continue to improve their QbD review processes, the sector should anticipate to see further progress in drug development and production.

Quality by design (QbD) and well understood product and processes [17].

- All the main causes of variation are identified and understood.
- The method helps manage and reduce variability.
- Product quality can be predicted accurately and reliably within the defined range of materials, process parameters, environmental conditions, and other factors.
- To gain a deeper understanding of how the product performs across different material properties, manufacturing options, and process parameters, while applying quality risk management principles.

Quality Target Product Profile (QTPP):

A QTPP is a thorough document that describes the desirable properties of a medicinal product. It provides a road map for the full drug development process, from early-stage research to commercialisation. The QTPP focusses on three main aspects.

1. Quality: Quality considerations include the physical and chemical qualities of the medicine, as well as production techniques and stability.
2. Safety: The QTPP discusses potential dangers and harmful consequences of the drug's use.
3. Efficacy: It specifies the drug's therapeutic benefits and how effectively it works in treating a certain medical problem.

Pharmaceutical businesses may make educated decisions throughout the drug development process by establishing a well-defined QTPP, guaranteeing that the final product fulfils high quality, safety, and effectiveness criteria.

***Critical quality attributes (CQA)* [18].**

After identifying the Quality Target Product Profile (QTPP), the next step is to determine the corresponding Critical Quality Attributes (CQAs). A CQA is a property—whether physical, chemical, biological, or microbiological—that must stay within certain limits to ensure the product meets the desired quality. CQAs are specific qualities of a drug product that can be affected by changes in how it's made or prepared. However, not every quality characteristic is considered a CQA. For example, the strength and dose form of a medicine are typically fixed and do not alter during development, so they are not CQAs. However, these alterations can influence the drug's potency (assay), consistency (content uniformity), ability to dissolve (dissolution), and absorption (permeation flux), making them CQAs. CQAs are identified by applying existing information and identifying potential quality issues.

Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs)* [19,20,21]. *Understanding CMAs and CPPs

Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs) are important concepts in Quality by Design (QbD). They help ensure product quality and consistency by identifying and controlling the factors that strongly affect the product's characteristics.

Critical Material Attributes (CMAs)

Critical Material Attributes (CMAs) are properties of raw materials that, if not controlled, can significantly affect the quality of the final product. These are natural characteristics of the materials that can influence the product's key features.

Examples of CMAs:

- Purity: The concentration of contaminants in a raw material.
- Particle Size: The particle size distribution within a powder.
- Moisture Content: The quantity of water in a material.
- Assay: Critical Process Parameters (CPPs) include the concentration of the active component.

The Role of CMAs and CPPs in QbD

CMAs and CPPs play a crucial role in QbD by:

- Ensuring product quality: Manufacturers can reduce variability and ensure that products fulfil quality standards on a consistent basis by managing CMAs and CPPs.
- Improving process efficiency: Manufacturers may optimize operations and decrease waste by knowing how CMAs and CPPs affect them.
- Facilitating regulatory compliance: CMAs and CPPs can contribute to regulatory compliance by providing a scientific foundation for regulatory filings.

ICH Q8, Q9, and Q10: The Cornerstones of QbD [22,23,24,25].

ICH Guidelines Q8, Q9, and Q10 form the basis for Quality by Design (QbD), a structured approach to drug development. These guidelines provide a framework for analysing, designing, developing, and producing high-quality pharmaceutical products.

Key Concepts and Alignments:

- QbD and ICH Q8, Q9, Q10:
- Aligned Concepts: The QbD principles are strongly related to the notions expressed in these ICH guidelines.
- Design Space: The design space, an important notion in QbD, specifies the operating conditions that a process must adhere to in order to continuously produce quality goods.
- Process Robustness: QbD emphasizes the creation of resilient processes that are less vulnerable to variation.
- Design of Experiments (DOE): DOE is a sophisticated statistical method used in QbD to determine the effect of process factors on product quality.
- Quality Management: QbD encourages a proactive quality management approach that concentrates on prevention rather than detection.[26,27,28]

REFERENCE:

1. Amit S. Patil, Anil M. Pethe, "Quality by Design (QbD): A new concept for development of quality pharmaceuticals", Vol.14, Issue 2, April-June 2013, page no. 13-14
2. Bhadra, R. M., 1, Luhar, S. V., 2, & Narkhede, S. B., 3. (2019). A brief review on Quality by Design [QbD] a Systematic Approach [Journal-article]. JOURNAL FOR INNOVATIVE DEVELOPMENT IN PHARMACEUTICAL AND TECHNICAL SCIENCE, 2(6), 31–33.
3. Gayatri P. Gage, Mithun Rudrapal et.al, "REVIEW ON QUALITY BY DESIGN (QbD)", AJPER April – June. 2020, Vol 9, Issue 2 (37-49)
4. Mogal V., Dusane, J., Borase, P., Thakare, P., Kshirsagar, S., & Department of Pharmaceutics, MET's Institute of Pharmacy, Bhujbal Knowledge City, Adgaon, Nashik 422003, Maharashtra, India. (2016). A review on quality by design. In PHARMACEUTICAL AND BIOLOGICAL EVALUATIONS (Vol. 3, Issue 3, pp. 313–319) [Review Article].

5. Nadpara, N. P., Thumar R. V., Kalola V. N., Patel P. B., & Department of Quality Assurance,S. J. Thakkar Pharmacy College, Opp. Drivein cinema, Avadh Road, Rajkot, Gujarat, India.(2012). QUALITY BY DESIGN (QBD): A COMPLETE REVIEW. In Int. J. Pharm Sci. Rev. Res. (Vol. 17, Issue 2, pp. 20–28) [Journal-article].
6. Abhay Dilip Bhoir, Dr. Nitin C. Mohire, "A Review on Quality by Design", Volume 5, Issue 6, November-December 2023, page no. 1 to 13
7. Gupta, N. V. (2015). A Review on quality by design approach (QBD) for Pharmaceuticals. International Journal of Drug Development and Research, 52–60. https://www.researchgate.net/publication/280737251
8. Rushali R. kadam, Dr. M. P. Patil et.al, A Review on; Quality by Design (QbD)", Asian J. Res. Pharm. Sci. 2017; Vol. 7: Issue 4Looby M, Ibarra N, Pierce JJ, Buckley K, O'Donovan E, Heenan M, et.al application of quality by design principles to the development and technology transfer of a major process improvements for the manufacture of a recombination protein. Biotechnology progress.2011;27(6): 1718-29.
9. Yu LX, Pharmaceutical quality by design: Product and process development, understanding and control. pharmaceutical research 25,2008,781-791
10. Munson J, Gujral B, Stanfield CF, A review of process analytical technology (PAT) in the U.S. Pharmaceutical industry. Current pharmaceutical analysis,2,2006,405-414
11. food and drug administration, office of genetic drugs white paper on question – based review:
12. Leuenberger H, Puchkov M, Krausbauer E, Betz G manufacturing pharmaceuticals granules, is the granulation end – point a myth, powder technology,189,2009,141-148.
13. Nasr M. Risk-based CMC review paradigm, Advisory committee for pharmaceutical science meeting, 2004.
14. Woodcock J, The concept of pharmaceutical Quality. American pharmaceuticals review,2004,1-3.
15. Food and Drug Administration, Office of Generic Drugs White Paper on Question-based Review
16. Nadpara, N. P. Thumar, et.al & Department of Quality Assurance, S. J. Thakkar Pharmacy College, Opp. Drivein cinema, Avadh Road, Rajkot, Gujarat, India. (2012). QUALITY BY DESIGN (QBD): A COMPLETE REVIEW. In Int. J. Pharm. Sci. Rev. Res. (Vol. 17, Issue 2, pp. 20–28) [Journal-article].
17. Jain S. Quality by Design (QbD): A Compressive understanding implementation and challenges of in pharmaceutical development. Int J of Pharm Pharma Sci. 2014; 6:29-35.
18. [5]Ranga S, Jaimini M, Sharma SK, Chauhan BS, Kumar A. A review on design of experiment. International Journal of Research and Reviews in Pharmacy and Applied science. 2013;3(6):86782.
19. Roy S (2012) "Quality by Design-Holistic concept of building quality in pharmaceuticals". Int. J Pham Biomed Res 3:100-108.
20. Sangshetti J.N, Chitlange S.S, Zaheer Z, Quality by Design in Pharmaceuticals, 1st edition, August 2015.
21. Sangshetti J.N, Deshpande M, Arote R, Zaheer Z, Shinde DB. Quality by design approach: Regulatory need. Arab J Chem, 2014.
22. Q9. Quality Risk Management. ICH Harmonized Tripartite guidelines. International conference Harmonization of technical requirements for registration of pharmaceuticals for humanuse2006
23. Q10: Pharmaceutical Quality System, ICH Tripartite guidelines. International conference on harmonization of technical requirements of pharmaceuticals for human use ,2007
24. Q8 (R1): Pharmaceutical Development, Revision 1, ICH harmonized tripartite guidelines, international conference on harmonization of technical requirements for registration of pharmaceuticals for human use,2007
25. food and drug administration, office of genetic drugs white paper on question – based review:
26. Statistical Optimization of Pharmaceutical Formulations by P.K. Shiromani President Shirman Pharmaceutical Consulting.
27. Drakulich, A. Critical challenges to implementing QbD: A Q&A with FDA.pharm.technol.2009;33:90-94.
28. Lawrence X. Yu (2006) Director of science. "Implementation of Quality by Design", Question based review.
29. Delasko J.M, Cocchetto D, Burke L.B, Target product profile: Beginning drug development with the end in mind, Jan/Feb2005; issue1.
30. Chang RK, Raw A, Lionberger R, Yu L. Generic development of Topical dermatologic products, part II: quality by design for Topical semisolid products. AAPS J. 2013; 15(3)