

Quality by Design Approaches in Pharmaceutical Development and Solid Dosage Forms Production: A Narrative Overview

Salevendula Sreelekh¹, K Vinod Kumar¹, Nawaz Mahammed¹, T Reshma^{2}, G Usha Sree¹, S Shakir Basha¹, M Bhuvaneshwari¹*

¹Department of Pharmaceutical Analysis, Raghavendra Institute of Pharmaceutical Education and Research, K.R. Palli Cross, Anantapur, Chiyvedu, Andhra Pradesh, India.

²Department of Pharmaceutical Quality Assurance, Raghavendra Institute of Pharmaceutical Education and Research, K.R. Palli Cross, Anantapur, Chiyvedu, Andhra Pradesh, India.

ABSTRACT

Quality by Design (QbD) is an essential approach to pharmaceutical development and manufacturing that has garnered significant attention in recent years. Quality in services, products, and procedures equates to customer satisfaction. Consequently, it facilitates a transition in the pharmaceutical sector and the Food and Drug Administration (FDA) toward a more scientific, risk-based, comprehensive, and proactive drug development strategy. The pharmaceutical industry is actively seeking new solutions to ensure product quality and efficiency. This paper provides a comprehensive overview of QbD principles and their application in the pharmaceutical industry. The benefits of implementing QbD principles are discussed, encompassing increased efficiency, reduced costs, and improved product quality, safety, and efficacy. As the pharmaceutical industry continues to evolve, QbD will remain a crucial aspect of drug development and manufacturing. This article aims to provide pharmaceutical professionals with a comprehensive understanding of the QbD approach.

Keywords: Quality by Design (QbD), Pharmaceutical Development, Solid Dosage forms, Drug manufacturing, Risk-based approach.

1. INTRODUCTION:

Quality by Design (QbD) is defined by the International Conference on Harmonisation of technical requirements (ICH) for registration of pharmaceuticals for human use as "a systematic approach to pharmaceutical development that begins with established objectives and stresses product and process understanding and process control, based on strong science and quality risk management"(1). Along with safety and efficacy, quality is a primary need for a substance to be considered for drug qualification and approval (2). Recent efforts have focused

on constructing "quality," as opposed to merely testing it, to guarantee the reliability of pharmaceutical products and systems. Originally proposed by Juran and Godfrey in 1998 (4) , QbD integrates quality into processes using optimisation strategies to understand and control system variables, an approach gaining momentum in the auto industry and recently endorsed by the FDA for pharmaceuticals (3-5).

QbD prioritizes the creation of an optimal process and a thorough understanding of performance for the desired product result. This approach hinges on continuous improvement based on process insights, aiming for a 'desired state' of 'regulatory flexibility'. It emphasizes scientific knowledge development, superior design, performance demonstration, and integrates Quality Risk

*Corresponding author: T Reshma

shaikreshmat614@gmail.com

Received: 13/2/2023 Accepted: 10/9/2023.

DOI: <https://doi.org/10.35516/jjps.v16i4.908>

Management (QRM), Design of Experiments (DoE), and Process Analytical Technology (PAT) for continuous learning and lifecycle management (6).

Janet Woodcock, Director of the Centre for Drug Evaluation and Research, defined a high-quality pharmaceutical in 2004 as one that consistently delivers the claimed therapeutic benefit to the user (7), and therefore, is free of contamination. In this context, 'quality' is a metric for assessing 'excellence in manufacturing,' characterized by a lack of flaws, deficiencies, and substantial variances. Notably, QbD for generic pharmaceuticals is discussed. A fundamental principle of QbD, as stated in the ICH Q8 guidance, is that "quality cannot be tested into products; it should be built in by design" (8). This study focuses on the use of QbD in ensuring pharmaceutical quality for solid oral dosage forms of small molecules. In the drug development process, the pharmaceutical industry must demonstrate the safety and efficacy of the new drug in accordance with government regulations. The adoption of a novel drug development strategy can potentially bring about significant financial and operational benefits across the entire product life cycle.

Given the recent industry shift toward QbD-based submissions, this article explores the procedures for developing a market formulation and the necessary supporting data. It outlines the steps that should be taken at the beginning of drug development, pre-manufacturing, and market entry attempts. The paper provides a foundation for manufacturing facility needs and outlines the types of data required to address regulatory matters. It also introduces advanced tools that complement the QbD approach. In this study, we present a streamlined, universal method for identifying essential metrics, material attributes, environmental factors, and quality characteristics (9). The paper also explains the risk-based distinctions controlling the assignment of criticality, which is crucial for ensuring uniformity and facilitating the incorporation of QbD concepts into the design of

pharmaceutical production processes. The paper's goal is to provide an approach and technical mechanism for developing and deploying a control strategy—a predetermined group of controls based on current knowledge of the product and the manufacturing process designed to guarantee the reliability of both. Control strategy creation is a methodical procedure that requires collaboration among professionals from various fields to bridge the gap between drug research and manufacturing. The actual application of the early Control Strategy is not the focus of this study, but rather the methodologies and principles that went into its creation. Within the context of the product quality lifecycle, this article details the development of the Design Space (10, 11). Over the established design space for materials, process parameters, environmental, and other factors, precise and reliable predictions of product quality attributes are possible. In this paper, we will examine the more technical aspects of creating a Design Space (12).

1.1. Product and Process understanding and QbD:

Effective management of product variability is essential for maintaining consistent product quality. Three principles can guide this endeavor. First, a product's variance is regulated more by its production process than by the product itself. It is feasible to reduce product variability by managing and regulating raw materials, production parameters, and environmental conditions. Second, regulating inputs that affect product quality, such as raw materials and processing parameters, within a specific range of permissible fluctuation can enable precise and trustworthy predictions of product quality features. Finally, while adhering to quality risk management concepts, product performance must be understood across material attributes, manufacturing process alternatives, and process factors. By identifying and justifying important sources of variability, a quality risk management plan may be designed to successfully manage product variability and ensure consistent product quality (13-15).

1.2. Management of the Product life cycle and Iterative Improvement:

Numerous opportunities arise during a product's lifecycle to enhance its quality, providing manufacturers with a great deal of leeway in how they choose to do so. To maintain the highest standards of quality, it is common

practice to track how well a procedure is working. Regular production yields a variety of new data and knowledge that may be utilized to refine processes (16). For consistency's sake, businesses often stick with tried-and-true techniques, such as the frozen method for handling their styles, as shown in Figure 1 (17).

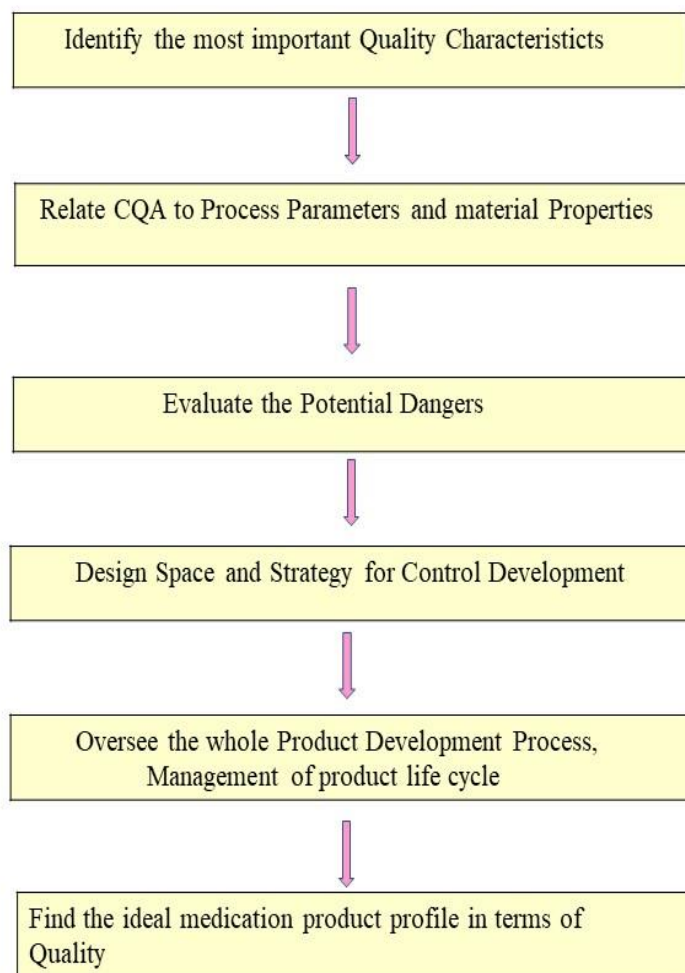


Figure 1: Management of QbD

1.3. Components of an Effective Method:

An effective method, often referred to as a mechanical method, delivers the intended satisfactory results. The selection of clear procedures and test parameters, i.e., components, is crucial for implementing such an effective

method (16).

The components of effective method include:

- Controls for the Procedures and
- Controls for the Actual Processing of the Procedures
- Batch-release testing

- Characterisation
- Comparability tests
- Tests for Consistency
- QbD's approach to risk management emphasises the

use of CQAs

1.4. Elements of QbD:

The elements of QbD are as shown in Figure 2 (18).

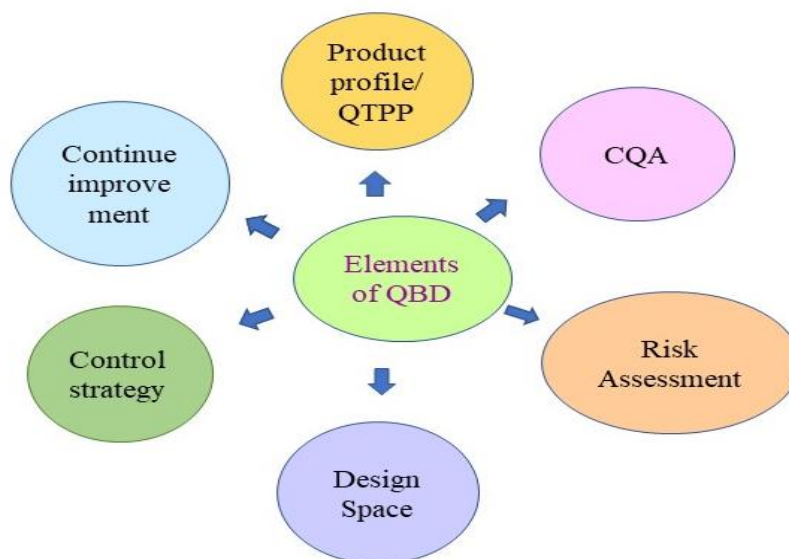


Figure 2: Elements of QbD

These Elements of a Quality-based Design strategy include:

- The TPP can be improved now that links between quality, safety, and efficacy are possible. The norms of the product are established as a baseline for further development and planning.
- Features of Critical Importance Attributes are a type of property that must fall inside certain bounds, ranges, or distributions (19).
- In Risk assessment, critical process parameters and material attributes are compared to critical quality attributes. Risk assessment instruments, such as the FMEA and the bone diagram, will be used to establish the CPPs (20). The planned methods of risk management are detailed in ICH Q9.
- The use of experiment style allows for the establishment and representation of a crucial link between CQAs and

CPPs in a stylistic domain (DOEs).

- Long-term planning for the organization: the sooner a problem is isolated and resolved after an unexpected occurrence, the better (21).
- Quality management and maintenance of the product's lifespan (22) and Quality management systems for QbD goods at every step of their lifespan can be established, maintained, and improved using the ICH-Q10 standard.

1.5. Target Product Profile (TPP):

The TPP details the required format of a drug's label and packaging for use in research and development.

1.5.1. Target quality product profile (TQPP):

This is a description of the product's intended application, targeted audience, administrative route, and other essential features and quality design. For a further discussion of product quality, the term TQPP may be a natural progression

from the word TPP. To understand and track information that cannot be orally transmitted from one generation to the next, the QTPP is necessary. To do this, it is necessary to define the qualities an ideal drug should possess while also considering the risks associated with using that drug (23). Quantity, purity, potency, instrumentation closing system, and individuality are all aspects of TQPP that can be produced in any quantities.

1.5.2. Considerable Quality Attributes (CQA):

There are many contexts in which CQA can be used to guarantee the reliability of a product's quality, security, effectiveness, and stability (Certificates of Conformity, or CQA for short). The quality of the result can be defined, measured, and tracked to ensure it stays within acceptable bounds. Quality characteristics consist of clinically safe and effective performance, as well as parameter boundaries nearing failure. Productivity in production is a hallmark of quality (24). The criticality risk could increase if the APT manufacturing process becomes more complex.

1.5.3. Considerable Material Attributes (CMA):

If a genuine change in a parameter makes it impossible for a product to meet a QTPP, then the product must fail. When selecting which characteristics are most significant, it is useful to consider one's level of flexibility and the specificity of each input material. Ranges of CMAs that are considered safe for use in the pharmaceutical industry include active pharmaceutical ingredients, inactive pharmaceutical ingredients, and excipients (24).

1.5.4. Critical Process Parameters (CPP):

It refers to all observable variables involved in the execution of a given procedure step that must be controlled to guarantee the desired result. One could think of each thing in this read as a parameter to a certain method (25). So, here is how it would go down: Prior to or throughout processes that significantly affect the final product's visual appeal, purity, and/or yield, relevant parameters are analyzed for their potential effects as shown in figure 3 (24).

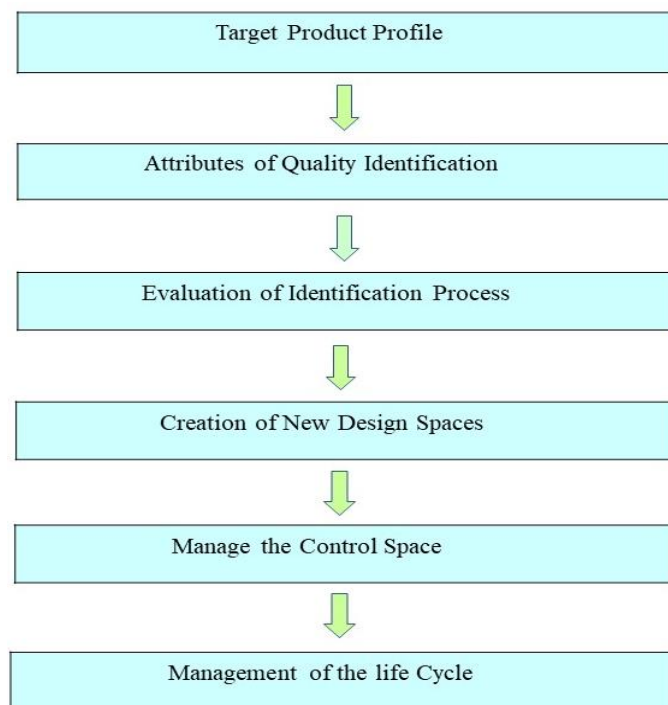


Figure 3: Important Aspects of QbD

1.6. Methods of regulation:

A comprehensive approach to producing high-quality products involves the integration of raw material specifications, process controls, and final product testing. This strategy provides a wealth of data on the substance and process under investigation. PAT serves as a versatile tool within this approach, adapting well to the context in which it is applied (18).

2. DESIGN OF EXPERTS (DOE):

The DOE is a versatile statistical tool leveraged in the design, development, and optimization of various systems, processes, and products. Its wide range of applications includes experimental design, variable screening, transfer function determination, design optimization, and robust design creation (26). In essence, DOE serves as a flexible tool for identifying influential inputs on outcomes in various contexts(27).

2.1. Software for the DOE:

Utilizing efficient statistical software, DOE may be rapidly conceived of and studied. There are paid and open-source statistical programs available for this task (28). There are a variety of popular commercial bundles, like programs that will be employed to carry out DOE are:

- Minitab
- SAS
- SPSS
- Prisma
- Statistica
- Statgraphics

2.2. Benefits of DOE:

Experimental design, or DOE, aims to elucidate the relationship between an independent variable and a dependent variable by gauging the effects of changing the independent variable. This approach requires modulating the independent variable while controlling or minimizing confounding factors. Offering superior control over these factors compared to other methodologies, experimental design enables the replication of results under the same

conditions, fostering trust and confidence in the findings. Consistency in outcomes enhances the reliability and validity of the study. With meticulously designed and executed experiments, researchers can robustly examine causal relationships and draw substantive conclusions (29).

2.3. Methods of DOE:

2.3.1. Design Space:

The multidimensional interplay of input variables, including material attributes and process parameters, within the design space guarantees quality. Post-approval modifications are complex and require relocation outside the designated design space. These modifications are subject to regulatory inspection and approval (30). The researcher's individual style may influence the relationship between Y and F, which is a function of the method parameters and quality/material attributes.

2.3.2. Process Analytical Technology (PAT):

It is a state-of-the-art tool for designing, analyzing, and controlling the manufacturing of pharmaceuticals by monitoring critical quality and performance attributes of raw and in-process Materials & processes in real time (i.e., on line, off line, in line) to guarantee the final product meets specifications (31). The idea behind PAT is to minimize potential for harm during the production of a medicine.

2.3.2.1. PAT Implementation at Various Stages:

These are the four stages for the implementation of PAT(32).

- The first step is the collection of data about the manufacturing process.
- Data evaluation of process parameters constitutes the scale-up phase.
- The process understanding phase is temporary.
- Actual Process monitoring and control is the final, permanent Step.

2.3.2.2. Advantages of PAT in Terms of Quality:

To obtain Quality PAT technology is incorporated (18). It had advantages which are listed below:

- For the purpose of incorporating quality into

manufacturing processes

- Effects and variables in the preparation process that influence the final product quality are correlated. There are many factors to consider, such as the surrounding environment, manufacturing methods, and the raw materials.
- Creates a reliable plan for minimizing any damage to the process.
- PAT is used to enhance the manufacturing process all through the product's lifespan.

2.3.2.3. Benefits of PAT:

PAT provides numerous benefits in product manufacturing, including reduced rework, accurate process control, increased safety through automation, and

quicker validation processes. These advantages help to reduce errors and improve the overall quality and efficiency of the product manufacturing process (18).

2.3.3. High Quality Risk Management:

The FDA defines risk management as "a strategic safety program designed to lower product risk by using one or more actions or technologies," which is a pretty good definition of what quality risk management is. It is a methodical procedure used to monitor and analyze potential threats to a drug's quality at every stage of development as per the ICH for Q9 guideline (33).

The process of risk management is performed for risk assessment as shown in Figure 4.

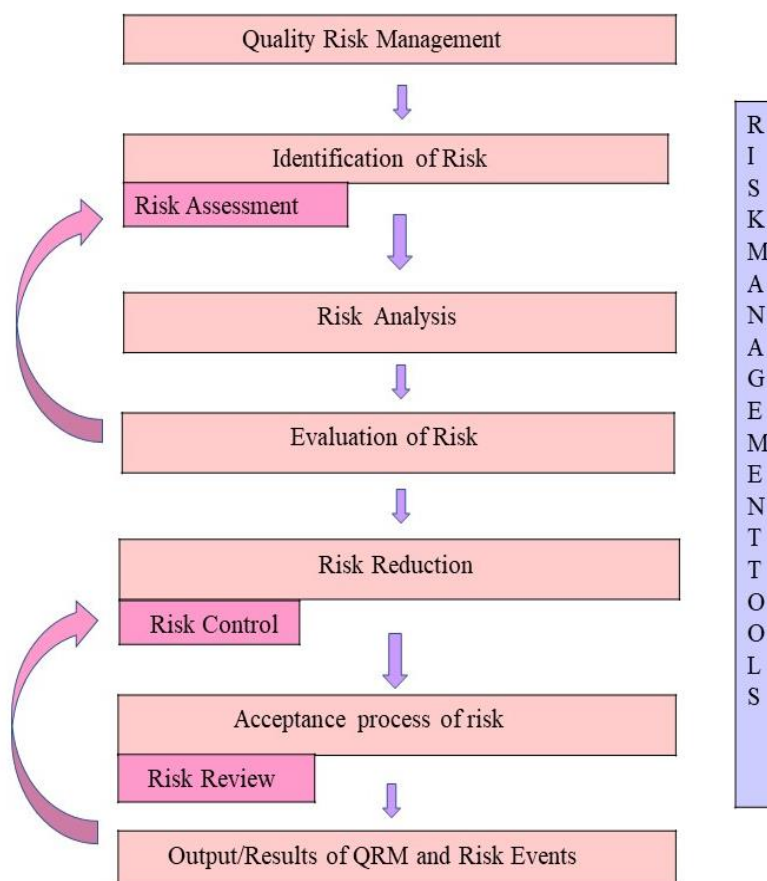


Figure 4: Process of Risk Assessment (17)

2.3.3.1. Probability and Risk analysis:

The term "risk" encompasses not just the potential for harm but also the degree of such harm. The overall quality of a method or procedure can be enhanced through careful consideration of the hazards involved. The purpose of a risk analysis is to determine which factors have the greatest bearing on the final product's quality. When the FDA, commerce, research and development (R&D), prototypes, and numerous manufacturing sites are involved, a risk assessment can facilitate better communication among them all (34).

Here are several ways that risk can be assessed: ICH guideline Q9 outlines a handful of approaches to risk analysis:

- Analysis of Potential Effects of Failures (APFA)
- Fault Mode, Effects, and Criticality Analysis (FMECA)
- Fault Tree Analysis (FTA)
- Hazard Analysis and Critical Control Points (HACCP)
- Hazard Operational Analysis (HOA)
- Preliminary Hazard Analysis (PHA)
- Risk Ranking and Filtering (RRF).
- Tools in the field of applied mathematics

2.3.3.2. Evaluation of Risk Methods:

➤ Failure mode effects analysis (FMEA):

In the pharmaceutical sector, FMEA is a popular method for evaluating potential dangers. It is an approach that anticipates potential problems and systematically works to address them. The term "failure mode" is used to describe any type of problem that can occur in a product, service, or manufacturing system. After identifying potential sources of malfunction, FMEA software ranks the severity of each issue and recommends solutions (19). The criticality of outcomes can be studied using this tool, and it can also provide you a clear picture of the current state of affairs.

➤ Failure Mode, Effects and Criticality Analysis (FMECA):

Extending FMEA methodology, we have FMECA.

Failure Mode, Effects, and Criticality Analysis is an expansion of FMEA that investigates the severity, frequency, and detectability of potential outcomes. In FMECA, all potential points of failure are cataloged and ranked according to their severity. It is necessary to take corrective action if the danger associated with this criticality is unacceptable. This has applications in areas where there is a high probability of error, such as manufacturing (19). In addition to contributing to control plans and other quality assurance procedures, the tool can be used to design and optimize maintenance plans for repairable systems.

➤ Fault Tree Analysis (FTA):

Assuming that a product's or process's functionality would fail, fault tree analysis (FTA) is used. The findings are graphically depicted as a tree of failure modes (19). This can be used in the investigation of a complaint or deviation to determine its cause and verify that any proposed solutions won't introduce new difficulties.

➤ Hazard Analysis and crucial control points (HACCP):

It is an organized process that ensures product quality and safety by identifying, managing, and preventing hazards associated with product design, development, and production. HACCP provides extensive documentation to demonstrate process or product awareness by specifying control and monitoring criteria. A hazard is defined as a concern for both safety and quality in a process or product (35).

3. QBD APPROACHES:

Defined objectives, the number of input elements, and interactions to be researched, as well as the statistical validity and effectiveness of each design, should all be considered when choosing the appropriate experimental design. To help clarify the practical applications of Design of Experiments (DoE), experiments can be categorized into two broad groups.

3.1. Screening:

These screening strategies are the most used because of

their low cost. These experimental layouts make it possible to examine a large variety of inputs while keeping the total number of tests to a minimum (36). However, there are some caveats that should be considered if we are to gain a more complete picture of how input factors affect response outcomes.

3.1.1. Two-level full factorial design: A two-level complete factorial design is the most effective screening design since it allows for the estimation of primary effects of input components and their interactions on output responses. The huge number of experiments required is the primary drawback of two-level full factorial designs when compared to fractionate factorial and Plackett-Burman designs (37). For a full factorial design with two levels, where k is the total number of inputs, conducting 2^k experiments is warranted.

3.1.2. Fractional factorial design:

For screening purposes, fractionate factorial designs are popular because they allow for the assessment of a high number of input elements with a minimal number of experiments.

The formula L^{F-1} is the foundation of this plan (38). A formulator with three levels and four factors will have thirty-three iterations if the corresponding equation, $L^{F-1} = 3^4 - 1 = 3^3 = 27$, is used. Picking the best process run from among these 27.

3.1.3. Plackett-Burman design:

Since the Plackett-Burman (PB) design examines the interplay between two variables, it is commonly employed to conduct PB. The PB layout can process 11 variables all at once. This layout was designed for economic efficiency (38).

Two-level fractionate factorial designs (resolution III), such as Plackett-Burman designs, permit investigation of N input components with N experiments (The value of N must be a multiple of 4).

3.2. Optimization:

Because they can simulate a wide variety of response surfaces, these optimization designs are the most used. Screening designs feature only two levels for each input

factor, which limits them to simulating a 1st order (linear) response surface. To represent a 2nd order (quadratic) response surface, optimization designs often require 3–5 levels for each input factor.

3.2.1 Three-level full factorial design:

Since a larger number of experiments are needed, a three-level complete factorial design is often employed only when a study of two or three input components is warranted (37). There should be 3^k experiments, where k is the total number of inputs being evaluated.

3.2.2. Central Composite Design (CCD):

One of the most common optimization designs is the central composite design (CCD), which requires a lot less tests than the more common three-level complete factorial designs (36).

3.2.3. Box-Behnken design:

The Box-Behnken design, a subset of the three-level fractional factorial design, facilitates the modelling of both first and second-order response surfaces. It provides a cost-efficient alternative when there's an abundance of input variables, as compared to three-level complete factorial designs. Distinctly, the Box-Behnken Design is not a component of factorial or fractional factorial; it operates independently as a quadratic layout (29). Additionally, these designs can be rotated (or near rotated) and exhibit three unique levels for each variable.

4. APPLICATIONS, ADVANTAGES AND DISADVANTAGES OF QBD

4.1. Applications:

4.1.1. Inclusions for FDA Submissions Should Utilize QbD

Adherence to principles is a fundamental aspect of Approval. Here are the noted applications (36):

1. Establishment of a stronger scientific foundation for evaluation.
2. Enhancement of coordination among reviews, compliance checks, and inspections.
3. Improvement in the quality of data submitted to

regulatory agencies.

4. Increased consistency across processes and outcomes.
5. Elevation of evaluation standards by establishing a Quality Management System for Chemistry Manufacturing and Controls.
6. Enhancement of decision-making flexibility.
7. Ensuring that conclusions are based on scientific evidence rather than anecdotal accounts.
8. Inclusion of various fields in the decision-making process.
9. Focused efforts toward the most critical risks.

4.1.2. Utilizing QbD with various analytical approaches (2):

QbD applicable for Analytical Methods (2).

1. Chromatographic methods like HPLC, employed in stability studies, method development, and detection of impurities in pharmaceuticals.
2. Hybrid techniques such as Liquid Chromatography-Mass Spectrometry (LC-MS).
3. Advanced methodologies including ultra-high-performance liquid chromatography (UHPLC) and capillary electrophoresis.
4. Moisture content determination *via* Karl Fischer titration.
5. Compound identification and quantification using UV or other vibrational spectroscopy techniques.
6. Genotoxic residue examination.
7. Dissolution study methodologies

4.2. Advantages of QbD implementation in Pharmaceutical Industry:

Implementing QbD principles holds several benefits across various areas, despite recognized obstacles to its practical deployment (39-42). Understanding these challenges is crucial for regulatory bodies like the MHRA, striving for broader QbD implementation.

These benefits include:

1. Improved quality control (QC) for pharmaceuticals and reduction in product variation through the

establishment of a robust approach and minimization of variabilities.

2. Enhanced financial efficiency and reduced regulatory burden due to streamlined manufacturing processes and changes within the "Analytical Design Space" not being considered method shifts.
3. Increased transparency leading to improved comprehension of drug control strategies, thereby expediting the approval, scale-up, validation, and commercialization process.
4. Mitigation of penalties, product recalls, and out-of-specification results through Quality Risk Management (QRM) and continuous improvement mechanisms.
5. Optimization of regulatory scrutiny resulting in more chances of first-cycle approval, reduction in review time for CMC, and updates to regulatory filings.
6. Enhanced probability of successful method transfers from R&D to QC, allowing for the development of novel methods throughout a product's lifecycle.

4.3. Challenges:

There is a need to use QbD to enhance the quality of pharmaceuticals; however, this is often met with resistance due to a lack of familiarity with the industry. There has never been more emphasis on the end result than on a solid scientific understanding of the manufacturing process in the pharmaceutical sector. The pharmaceutical industry strongly endorses adopting QbD. The FDA has asked that the final regulation include terminology criteria for evaluating control systems and standards for switching out analytical approaches. There are ten key barriers that prevent QbD from becoming widespread. The significance of each of these factors depends on the particular medicine at hand and the stage of its adoption process (24, 30).

International organizational barriers include:

- Cross-functional misalignment (e.g., disconnects

between R&D and manufacturing, or quality and regulatory functions).

- Uncertainty regarding QbD implementation costs and timelines.
- Incomplete understanding of CQA implications due to insufficient execution technology (e.g., data management issues).
- The challenge of ensuring suppliers and contract manufacturers align with QbD implementation.

The regulatory authority is actively involved (24, 30) with the next six difficulties:

- Ambiguity in handling QbD applications.
- Unease due to perceived unmet promises of regulatory benefits.
- Inadequate collaboration among international regulatory bodies.
- Insufficient industry support for QbD.
- Limited familiarity with the pharmaceutical process, hindering QbD implementation.
- Difficulty achieving consensus between field inspectors and the FDA on the QbD approach.
- Industry demand for more comprehensive QbD guidance.

ABBREVIATIONS:

1. QbD	:	Quality by Design
2. ICH	:	International Council for Harmonization
3. FDA	:	Food and Drug Administration
4. Q8	:	Pharmaceutical Development
5. Q9	:	Quality Risk Management
6. Q10	:	Pharmaceutical Quality System
7. TPP	:	Target Product Profile
8. QTPP	:	Quality Target Product Profile
9. CQA	:	Considerable Quality Attributes
10. CMA	:	Considerable Material Attributes
11. DOE	:	Design of Experiments
12. PAT	:	Process Analytical Technology
13. IPQC	:	In - Process Quality Control
14. FTA	:	Fault Tree Analysis

- Concern that QbD might protract regulatory approval or yield irrelevant data.

Pharmaceutical businesses believe that QbD may lengthen the time it takes to submit a regulatory approval application or provide the regulatory body with irrelevant information for decision-making.

CONCLUSION:

Quality by Design (QbD) is a vital approach to pharmaceutical development and manufacturing that aims to ensure products consistently meet required quality standards. By implementing QbD principles, pharmaceutical companies can reduce costs, increase efficiency, and enhance product quality, safety, and efficacy. QbD emphasizes a methodical and scientific approach to drug development, including the identification of critical quality attributes and critical process parameters, risk assessment, and continuous monitoring and improvement. Ultimately, QbD can help ensure that patients receive safe and effective medications that meet their healthcare needs. As the pharmaceutical industry continues to evolve, QbD will remain a crucial aspect of drug development and manufacturing.

15. FMEA	:	Failure Mode Effect Analysis
16. HACCP	:	Hazard Analysis and Critical Control Points
17. QMS	:	Quality Management System
18. QRM	:	Quality Risk Management
19. RPN	:	Risk Priority Number
20. PBD	:	Placket Burman Design
21. CCD	:	Central Composite Design
22. BBD	:	Box Behnken Design
23. FFD	:	Fractional Factorial Design
24. CMC	:	Chemistry Manufacturing and Controls
25. AFPA	:	Analysis of Potential Effects and Failure
R&D	:	Research and Development

REFERENCES

- Singh J. International conference on harmonization of technical requirements for registration of pharmaceuticals for human use. *Journal of Pharmacology and Pharmacotherapeutics*. 2015; 6(3): 185-7.
- Sangshetti JN, Deshpande M, Zaheer Z, Shinde DB, Arote R. Quality by design approach: Regulatory need. *Arabian Journal of chemistry*. 2017; 10: S3412-S25.
- Bhutani H, Kurmi M, Singh S, Beg S, Singh B. Quality by design (QbD) in analytical sciences: an overview. *Quality Assurance*. 2004; 3: 39-45.
- Joseph J, Godfrey AB. Juran's quality handbook. New York: McGraw-Hill; 1998.
- Cook J, Cruaños MT, Gupta M, Riley S, Crison J. Quality-by-design: are we there yet? *AAPS PharmSciTech*. 2014; 15(1): 140-8.
- O'Connor E. Implementation of a quality risk management approach to commissioning and qualification in the biopharmaceutical industry. 2012.
- Woodcock J. The concept of pharmaceutical quality. *American Pharmaceutical Review*. 2004; 7(6): 10-5.
- Beg S, Hasnain MS, Rahman M, Swain S. Introduction to quality by design (QbD): fundamentals, principles, and applications. *Pharmaceutical quality by design: Elsevier*. 2019; p. 1-17.
- Raju C, Sivagami B. Development and Validation of a Simple and Sensitive ICP-MS Method for the Quantification of Elemental Impurities in Propafenone Hydrochloride Drug Substance. *Jordan Journal of Pharmaceutical Sciences*. 2023; 282-300.
- Food U, Administration D. Pharmaceutical cGMPs for the 21st century—A risk-based approach. Final report. 2004.
- Yu LX, Raw A, Lionberger R, Rajagopalan R, Lee LM, Holcombe F, et al. US FDA question-based review for generic drugs: A new pharmaceutical quality assessment system. *Journal of Generic Medicines*. 2007; 4(4): 239-46.
- Nadpara NP, Thumar RV, Kalola VN, Patel PB. Quality by design (QbD): A complete review. *Int J Pharm Sci Rev Res*. 2012; 17(2): 20-8.
- Lionberger RA, Lee SL, Lee L, Raw A, Yu LX. Quality by design: concepts for ANDAs. *The AAPS journal*. 2008; 10: 268-76.
- Callis JB, Illman DL, Kowalski BR. Process analytical chemistry. *Analytical Chemistry*. 1987; 59(9): 624A-37A.

15. Yu LX. Pharmaceutical quality by design: product and process development, understanding, and control. *Pharmaceutical research*. 2008; 25: 781-91.
16. Gawade A, Chemate S, Kuchekar A. Pharmaceutical Quality by Design: A new approach in product development. Research and Reviews: *Journal of Pharmacy and Pharmaceutical Sciences*. 2013; 2(3): 5-12.
17. Patel H, Parmar S, Patel B. A comprehensive review on Quality by Design (QbD) in pharmaceuticals development. 2013; 4(5).
18. Chandramouli R. Review on Quality by Design Approach (Qbd). *Current Trends in Biotechnology and Pharmacy*. 2021; 15(4): 447-54.
19. Gandhi A, Roy C. Quality by design (QbD) in pharmaceutical industry: tools, perspectives and challenges. *PharmaTutor*. 2016; 4(11): 12-20.
20. Lunney PD, Cogdill RP, Drennen JK. Innovation in pharmaceutical experimentation Part 1: review of experimental designs used in industrial pharmaceuticals research and introduction to Bayesian D-optimal experimental design. *Journal of Pharmaceutical Innovation*. 2008; 3: 188-203.
21. Kadam VR, Patil M, Pawar VV, Kshirsagar S. A review on: Quality by design (QbD). *Asian J Res Pharm Sci*. 2017; 7(4): 197-204.
22. Jain S. Quality by design (QBD): A comprehensive understanding of implementation and challenges in pharmaceuticals development. *Int J Pharm Pharm Sci*. 2014; 6(1): 29-35.
23. Drakulich A. Critical challenges to implementing QbD: A Q&A with FDA. *Pharmaceutical Technology*. 2009; 33(10).
24. Savitha S, Devi K. Quality By Design: A Review. *Journal of Drug Delivery and Therapeutics*. 2022; 12(2-S): 234-9.
25. Pokharana M, Vaishnav R, Goyal A, Shrivastava A. Stability testing guidelines of pharmaceutical products. *Journal of Drug Delivery and Therapeutics*. 2018; 8(2): 169-75.
26. Durakovic B. Design of experiments application, concepts, examples: State of the art. *Periodicals of Engineering and Natural Sciences*. 2017; 5(3).
27. Haruna F, Apeji YE, Oyi AR. Development and Characterization of a Microcrystalline Cellulose-based co-Processed Excipient using Design of Experiment Approach. *Jordan Journal of Pharmaceutical Sciences*. 2022; 15(4): 553-68.
28. Granato D, de Araújo Calado VM, Jarvis B. Observations on the use of statistical methods in food science and technology. *Food Research International*. 2014; 55: 137-49.
29. Ranga S, Jaimini M, Sharma SK, Chauhan BS, Kumar A. A review on Design of Experiments (DOE). *Int J Pharm Chem Sci*. 2014; 3(1): 216-24.
30. Jain S. Quality by design (QBD): A comprehensive understanding of implementation and challenges in pharmaceuticals development. *Int J Pharm Pharm Sci*. 2014; 6: 29-35.
31. Jadhav JB, Girawale NN, Chaudhari RA. Quality by Design (QBD) approach used in development of pharmaceuticals. *Int J Pure App Biosci*. 2014; 2(5): 214-23.
32. Purohit P, Shah K. QUALITY BY DESIGN (QBD): NEW PARAMETER FOR QUALITY IMPROVEMENT & PHARMACEUTICAL DRUG DEVELOPMENT. *Pharma Science Monitor*. 2013; 3(3).
33. Bhattacharya J, Pharm M, Phil M. Quality Risk Management—Understanding and control the risk in pharmaceutical manufacturing industry. *International Journal of Pharmaceutical Science Invention*. 2015; 4(1): 29-41.

34. Roy S. Quality by design: A holistic concept of building quality in pharmaceuticals. *International Journal of Pharmaceutical and Biomedical Research*. 2012; 3(2): 100-8.
35. de Ruijter VN, Redondo-Hasselerharm PE, Gouin T, Koelmans AA. Quality criteria for microplastic effect studies in the context of risk assessment: a critical review. *Environmental Science & Technology*. 2020; 54(19): 11692-705.
36. Fukuda IM, Pinto CFF, Moreira CdS, Saviano AM, Lourenço FR. Design of experiments (DoE) applied to pharmaceutical and analytical quality by design (QbD). *Brazilian journal of pharmaceutical sciences*. 2018; 54.
37. Kolekar YM. Understanding of DoE and its advantages in Pharmaceutical development as per QbD Approach. *Asian Journal of Pharmacy and Technology*. 2019; 9(4): 271-5.
38. Jindal K, Goswami M. SIGNIFICANCE OF DESIGN OF EXPERIMENTS (DoE) IN PHARMACEUTICAL SCIENCES: A BRIEF REVIEW.
39. Nasr M. FDA's quality initiatives—An update, 10th APIC/CEFIC. 2006.
40. Tang Y, Aaps O. Quality by design approaches to analytical methods-FDA perspective. FDA/CDER. 2011.
41. Somma R. Development knowledge can increase manufacturing capability and facilitate quality by design. *Journal of Pharmaceutical Innovation*. 2007; 2(3-4): 87-92.
42. Purohit D, Saini M, Pandey P, Tripathy S, Dureja H. Implementation of Quality by Design: A Review. *Applied Clinical Research, Clinical Trials and Regulatory Affairs*. 2019; 6(2): 99-111.

مناهج التصميم بالجودة في تطوير الأدوية وإنتاج الأشكال الصيدلانية الصلبة: نظرة عامة سردية

سالفيندولا سريليك¹، ك فينود كومار¹، نواز محمد¹، تي ريشما^{2*}، جي أوشا سري¹، شاكرا باشا¹، م يوفانييسواي¹

¹قسم تحليل الأدوية، معهد راغافندرا للتعليم والبحث الصيدلاني، تقاطع كيه آر بالي، أنانتابور، تشيبودو، أندرا براديش، الهند.

²قسم ضمان الجودة الصيدلانية، معهد راغافندرا للتعليم والبحث الصيدلاني، تقاطع كيه آر بالي، أنانتابور، تشيبودو، أندرا براديش، الهند.

ملخص

التصميم بالجودة (QbD) هو نهج أساسي في تطوير الأدوية وتصنيعها، وقد حظي باهتمام كبير في السنوات الأخيرة. الجودة في الخدمات والمنتجات والإجراءات تعني رضا العملاء. نتيجة لذلك، فهي تسهل الانتقال في القطاع الصيدلاني وإدارة الغذاء والدواء (FDA) نحو استراتيجية تطوير الأدوية التي تكون أكثر علمية، قائمة على المخاطر، شاملة، واستباقية. تسعى الصناعة الصيدلانية إلى حلول جديدة لضمان جودة المنتج وكفاءته. يقدم هذا البحث نظرة عامة شاملة على مبادئ QbD وتطبيقاتها في الصناعة الصيدلانية. يتم مناقشة فوائد تطبيق مبادئ QbD، بما في ذلك زيادة الكفاءة، وتقليل التكاليف، وتحسين جودة المنتج، والسلامة، والفعالية. مع استمرار تطور الصناعة الصيدلانية، سيظل QbD جانباً أساسياً في تطوير الأدوية وتصنيعها، ويهدف هذا المقال إلى توفير فهم شامل لمنهج QbD للعاملين في مجال الصيدلة. الكلمات الدالة: التصميم بالجودة، تطوير الأدوية، الأشكال الصيدلانية الصلبة، تصنيع الأدوية، النهج القائم على المخاطر.

* المؤلف المراسل: تي ريشما

shaikreshmat614@gmail.com

تاريخ استلام البحث: 2023/2/13 وتاريخ قبوله للنشر: 2023/9/10.