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A review: Quality by design apporoach used development of pharamaceutical

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Abstract
Quality by Design (QbD) has emerged as a modern and systematic framework for developing pharmaceutical products with robust and reproducible quality. It represents a key component of contemporary pharmaceutical quality strategies, emphasizing the proactive design of processes rather than relying solely on end-product testing. Although QbD offers an effective pathway for embedding quality throughout product development, its adoption remains challenging for industries where manufacturing practices are traditionally rigid despite natural variations in processes and raw materials. This review highlights the fundamental principles of QbD, outlining its major components, including identification of critical process parameters and critical quality attributes across different stages of production. The benefits, opportunities, and sequential steps involved in implementing QbD in pharmaceutical development are discussed in detail. Ultimately, the goal of pharmaceutical development is to create products and processes capable of consistently achieving the desired therapeutic performance. As quality must be incorporated during design-not inspected afterward-this paper explains how QbD can streamline development and support timely delivery of high-quality pharmaceutical products.

Keywords: Pharmaceutical product, QbD, quality, design

Introduction
The concept of Quality by Design (QbD) was formally introduced in the ICH Q8 guideline, which emphasizes that product quality cannot be assured merely through final testing; rather, quality must be intentionally incorporated during the design and development stages. As defined by ICH Q8, QbD is a structured and science-based approach to pharmaceutical development that starts with clearly defined objectives and relies on a thorough understanding of both product and process variables, along with effective process control supported by quality risk management. A central element of QbD is gaining insight into how formulation components and processing conditions influence the critical characteristics of the final product. By understanding these relationships, pharmaceutical scientists can optimize key parameters and establish mechanisms for real-time monitoring during manufacturing. This review explores the application of QbD principles to pharmaceutical development, with a particular focus on solid oral dosage forms of small-molecule drugs [1, 2].

To facilitate the implementation of QbD in generic drug development, the U.S. Food and Drug Administration's Office of Generic Drugs (OGD) introduced the Question-based Review (QbR) framework for evaluating the Chemistry, Manufacturing, and Controls (CMC) sections of Abbreviated New Drug Applications (ANDAs). Qbd provides a structured method for identifying and assessing critical quality attributes, translating the core concepts of the FDA's "Pharmaceutical cGMPs for the 21st Century" and QbD initiatives into practical regulatory expectations. In recent years, pharmaceutical industries worldwide have increasingly adopted QbD through various harmonized guidelines-such as ICH Q8, Q9, and Q10-as well as regulatory programs including Process Analytical Technology (PAT) and modern cGMP initiatives. Collectively, these efforts promote a science-driven, risk-based, and proactive approach to pharmaceutical quality, reinforcing QbD as an essential foundation for contemporary drug development and manufacturing [3, 4].

Figure 1 depicts the sequential stages involved in the life cycle of a pharmaceutical process, beginning with defining the process, followed by designing, characterizing, validating, and

finally, continuously monitoring and controlling it. The loop that connects the "monitor and control" stage back to the "define" stage signifies that any improvements identified during routine monitoring or any modifications introduced to enhance process robustness and performance lead to a reassessment or redefinition of the process. Once such changes are proposed, the process re-enters the same developmental cycle shown in Figure 1, ensuring systematic and controlled enhancement over time [5].

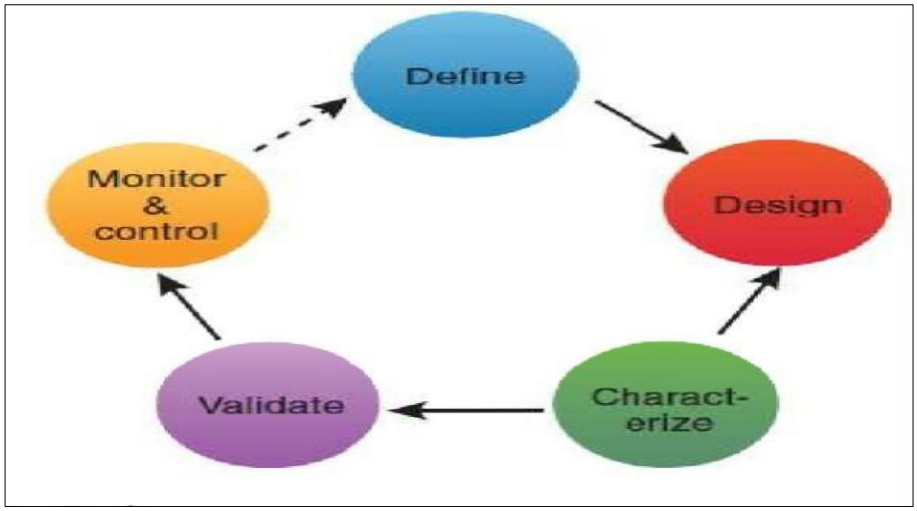


Fig 1: The steps in development of pharmaceutical product.

Pharmaceutical Quality by Design [6]

According to the ICH Q8 guideline, quality refers to the capability of a drug substance or drug product to fulfill its intended purpose, encompassing attributes such as identity, potency, and purity. The guideline further explains that Quality by Design (QbD) represents a structured development approach that starts with clearly defined goals and focuses on achieving a deep understanding of the product and process. It also emphasizes establishing effective process controls grounded in scientific principles and guided by quality risk management.

Pharmaceutical Quality = f (Drug substance, excipients, manufacturing, and packaging)

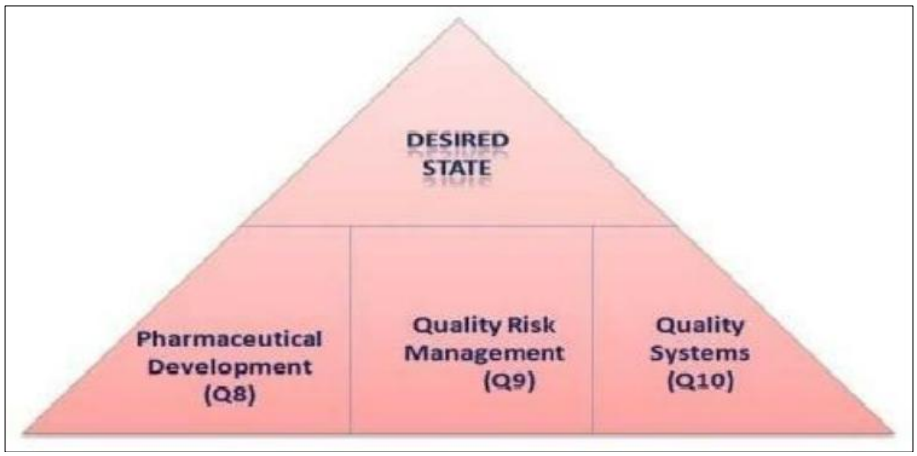


Fig 2: The Foundation of Quality by Design

Elements of Quality by Design [7]

1. Quality (QTPP and CQA)

The Quality Target Product Profile (QTPP) outlines the intended quality characteristics of the final pharmaceutical product, ensuring both safety and therapeutic effectiveness. It defines the essential critical quality attributes (CQAs) of the output materials-such as uniformity, impurity levels, particle size, appearance, and other measurable traits-each of which must fall within a justified range or limit.

2. Product Understanding (CMA)

Comprehensive knowledge of the product is crucial to confirm that it can reliably meet patient needs and maintain its performance throughout its entire shelf life. This understanding requires identifying and controlling all critical material attributes (CMAs) of the raw materials, ensuring they fall within acceptable ranges to consistently achieve the defined QTPP.

3. Process Understanding (CPP)

A detailed understanding of the manufacturing process involves recognizing the critical process parameters (CPPs)-those operational variables that significantly affect product quality. Establishing the relationships among CMAs, CPPs, and CQAs, as well as understanding the principles of scale-up, is essential. These key parameters must be continually monitored and controlled to ensure that the manufacturing

process consistently delivers a product aligned with the QTPP.

4. Control Strategy

QbD prioritizes real-time, in-process control mechanisms rather than traditional reliance on final product testing. Operating the manufacturing system under statistical control, within the boundaries of material and process conditions defined by the design space (DS), reduces the need for extensive regulatory intervention. An integrated quality management system can support the effective execution of this control strategy.

5. Continuous Improvement

Embedding quality within both the design and manufacturing phases enables companies to modify processes and materials within the approved design space, even after regulatory approval. Robust quality control tools facilitate real-time adjustments, helping organizations optimize performance, enhance efficiency, and strengthen product reliability over time.

Key aspect of quality by design include

1) The Target Product Quality Profile (TPQP): "TPQP has been defined as a prospective and dynamic summary of the quality characteristics of a drug product that ideally will be achieved to ensure that the desired quality, and thus the safety and efficacy, of a drug product is realized". This includes "dosage formed route of administration, dosage form strength(s), therapeutic moiety release or delivery and pharmacokinetic characteristics (e.g., dissolution and aerodynamic performance) appropriate to the drug product dosage form being developed and drug product-quality criteria (e.g. sterility and purity) appropriate for the intended marketed product." [8].

TPP forms the basis for product design in the following way [9].

- Dosage form
- Route of administration
- Strength, maximum and minimum
- Therapeutic effects
- product quality
- Pharmaceutical elegance.

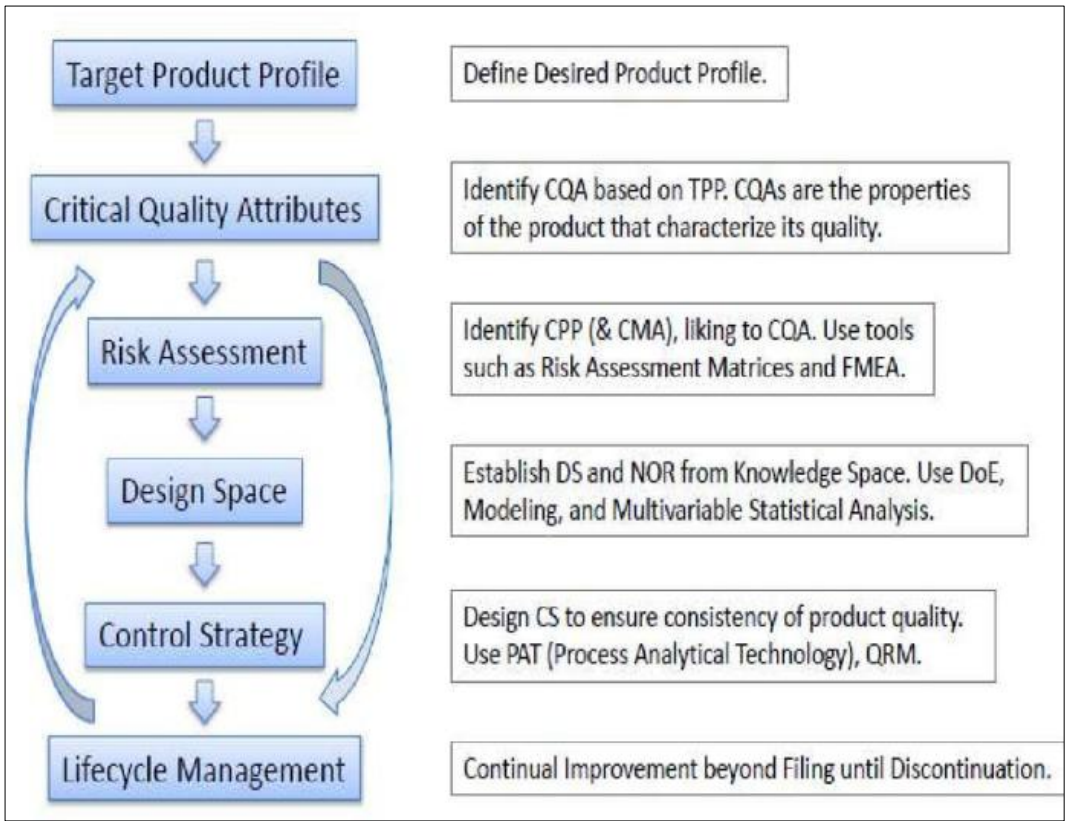


Fig 3: Elements of Pharmaceutical Development in QbD

2). Critical Quality Attribute

After defining the Target Product Quality Profile (TPQP), the next essential step is to determine the Critical Quality Attributes. CQAs are described as the physical, chemical, biological, or microbiological characteristics that must be maintained within specified limits, ranges, or distributions to assure the final product's quality. Their identification is primarily guided by risk assessment principles outlined in ICH Q9. Moreover, understanding CQAs relies heavily on existing product knowledge, which includes data gathered from laboratory studies, nonclinical investigations, and clinical evaluations related to each specific quality attribute. This accumulated experience plays a crucial role in accurately assessing potential risks associated with the product [10].

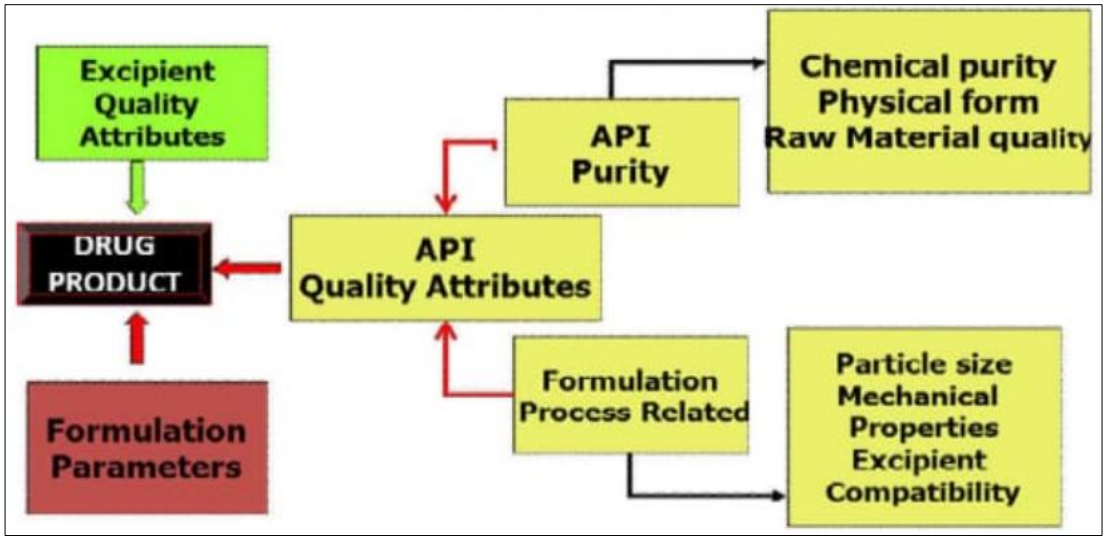


Fig 4: Role of (CQA)

3). Critical Process Parameter

CPPs are described as the process variables whose fluctuations can influence a Critical Quality Attribute (CQA). Therefore, these parameters must be carefully monitored or controlled to ensure the manufacturing process consistently delivers the intended product quality. Process robustness refers to the capability of a process to maintain acceptable performance and product quality even when there is natural variability in input materials or operating conditions. To verify that a process is reproducible and consistently reliable, an evaluation of process capability is required. Process capability represents the statistical measurement of the natural variability of a process for a specific attribute. The six sigma approach is widely recognized as the standard method for determining process capability. The process capability index is calculated by dividing the defined tolerance range for a characteristic by the actual process capability [11, 12].

4). Risk Assessment

Quality risk management involves a structured and systematic approach to identifying, analyzing, controlling, communicating, and continuously reviewing risks that could impact the quality of a pharmaceutical product throughout its lifecycle. The preliminary list of variables that may influence CQAs is often broad; however, this list can be refined, ranked, and narrowed down through Quality Risk Assessment (QRA) techniques [13].

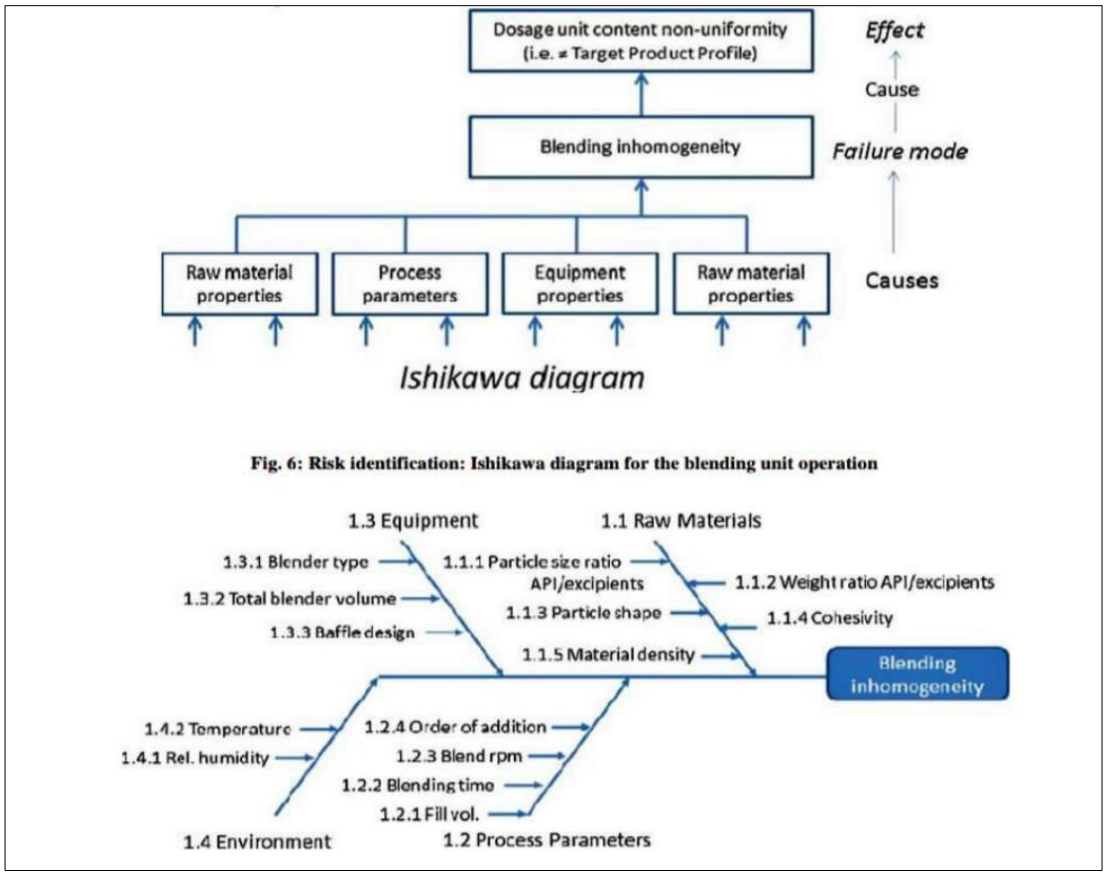


Fig. 6: Risk identification: Ishikawa diagram for the blending unit operation

5). Design Space

According to ICH Q8(R2), the design space refers to a multidimensional range created by the interaction of input variables-such as material attributes-and process parameters that have been scientifically proven to ensure consistent product quality. Operating within this established design space is not regarded as a process change. However, any movement outside the approved design space is considered a modification and typically requires submission of a regulatory post-approval change request [14].

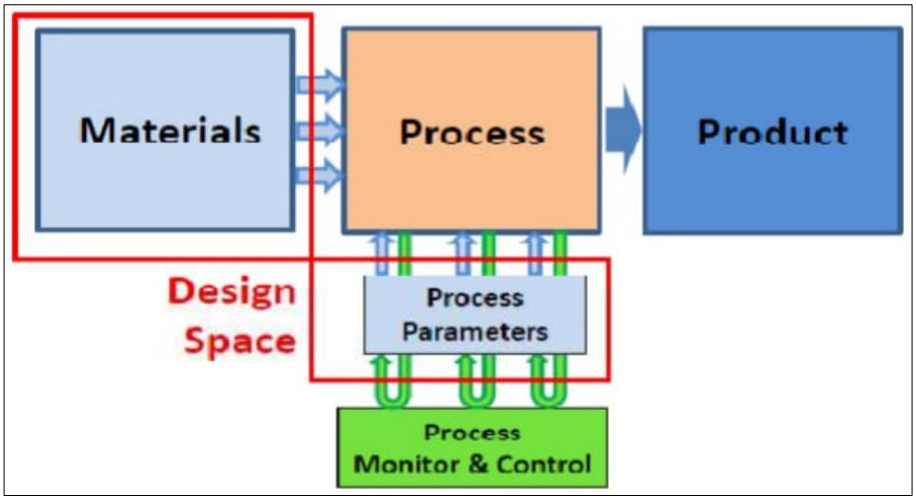


Fig 5: Design Space

6). Control Strategy

As outlined in ICH Q8(R2), a control strategy refers to the systematic approach used to assess, manage, and ensure the quality of in-process materials and the final product. This strategy is built on process data, which generally includes an appropriate combination of measured material attributes and monitored process parameters.

A comprehensive control strategy may involve several key elements, such as:

- Regulation of raw material attributes (including drug substance, excipients, and primary packaging materials) based on their known influence on process performance and product quality.
- Defined product specifications to ensure the final product meets predetermined quality standards.
- Procedural controls, which include documented methods and operational instructions.
- Facility-related controls, such as management of utilities, environmental conditions, and equipment operating parameters.
- Controls applied to critical unit operations that could affect subsequent processing steps or the quality of the end product-for example, how drying may influence degradation or how granule particle size distribution may affect dissolution [15].

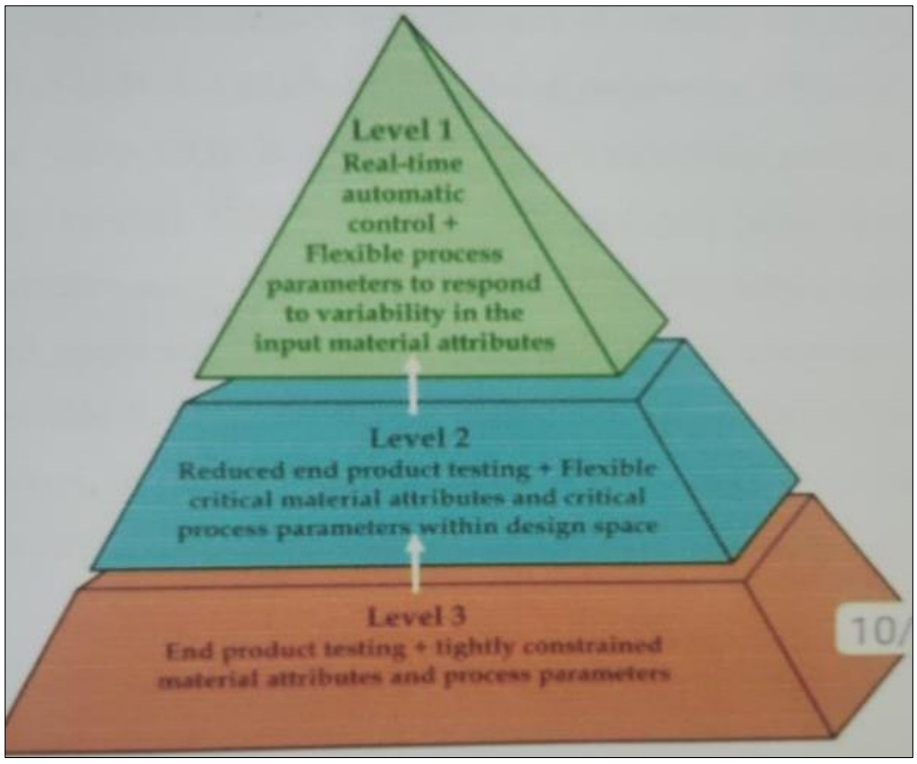


Fig 6: Control Strategy

7). Life Cycle Management

Within the Quality by Design (QbD) framework, any process modifications that remain inside the approved design space do not require regulatory review or additional approval. This allows manufacturers to implement process enhancements aimed at improving consistency and efficiency with fewer post-approval regulatory submissions. Beyond this regulatory flexibility, the deeper scientific understanding of the manufacturing process enables more accurate and informed risk assessments-aligned with ICH Q9-regarding the potential impact of process adjustments or deviations on the final product's quality [16].

Tools of Quality by Design

Design of Experiments (DOE): Design of Experiments (DOE) is a systematic and structured approach used to identify and understand the relationships between various factors and the resulting process outcomes. It is noted that applying DOE can yield benefits significantly greater-four to eight times-than the cost of conducting the experiments, and in a considerably shorter time frame. In QbD, DOE is particularly valuable because it enables the extraction of maximum scientific knowledge from a limited number of experimental runs.

When applied to pharmaceutical development, DOE considers factors such as raw material attributes (e.g., particle size) and process parameters (e.g., mixing speed or processing time), while the responses or outputs typically include critical quality attributes such as blend uniformity, tablet hardness, thickness, and friability [17, 18].

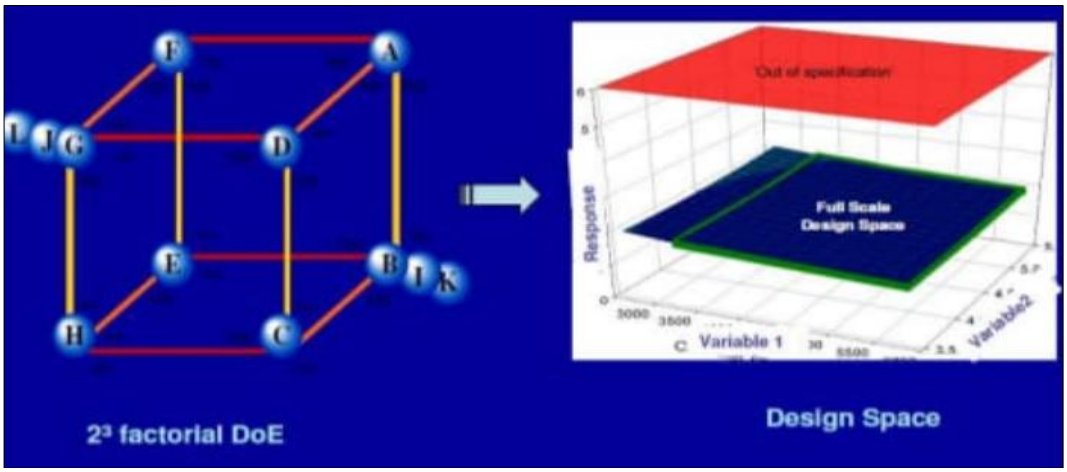


Fig 7: Design of experiment (DOE)

Process Analytical Technology (PAT)

Process Analytical Technology is described as a framework for designing, analyzing, and controlling pharmaceutical manufacturing by continuously measuring critical quality and performance attributes of raw materials and in-process components. The overarching objective of PAT is to ensure that the finished product consistently meets quality requirements.

The primary aim of PAT is to improve process understanding and strengthen process control, aligning with the principle that pharmaceutical quality should be inherently built into a product rather than tested into it. Within this context, the design space is established based on key and critical process parameters identified during process characterization, along with their acceptable operational ranges. These parameters become the central focus of PAT tools implemented on-line, in-line, or at-line [19].

From a PAT perspective, a manufacturing process is considered well understood when:

a) All critical sources of variability are clearly identified and scientifically justified.
b) The process is capable of effectively managing this variability.
c) The resulting product quality attributes can be predicted with accuracy and reliability.

Quality Benefits of PAT

Building quality into the product

- PAT helps establish clear relationships between process variables-such as environmental conditions, material attributes, and operational parameters-and their influence on product quality.
- It supports the development of a strong, science-based risk management approach by deepening process understanding.
- Through continuous monitoring and data-driven insights, PAT enables ongoing improvement of the manufacturing process across the entire product lifecycle.

Advantages of PAT

- Reduces the overall production cycle time.
- Minimizes the likelihood of product rejection or the need for reprocessing.
- Facilitates detailed and real-time control strategies for batch or continuous release.
- Enhances efficiency in large-scale or bulk manufacturing operations.

Tools Categorized Under the PAT Framework

a. Multivariate Tools for Design, Data Acquisition, and Analysis

These involve statistical and mathematical techniques used for process modeling, experimental design, and pattern recognition. They allow for comprehensive evaluation of multiple variables simultaneously, offering insights that single-factor studies cannot provide.

Such tools help pinpoint and analyze the factors that directly influence the stability and quality of the product. By understanding how variables interact, these tools can also

help predict potential failure modes and quantify associated risks.

b. Process analyses

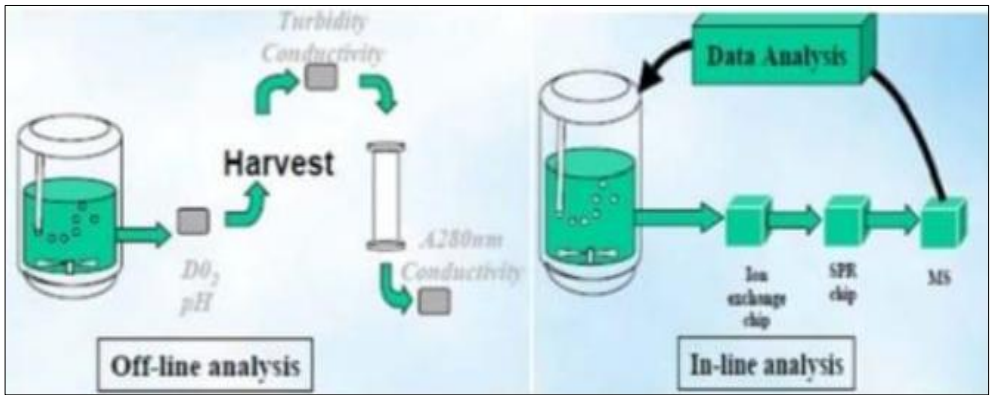
Process analysis tools are methods used to measure individual (univariate) process parameters-such as temperature, pH, or pressure-that reflect key physical, chemical, and environmental conditions within the manufacturing system. These measurements can be performed in several ways:

In-line: Measurements are conducted directly within the process stream in real time, without removing the sample from the production environment.

At-line

The sample is temporarily withdrawn from the process, tested nearby, and then either returned if it meets specifications or rejected if it falls outside acceptable limits.

On-line: The sample is diverted for testing, with the analysis still occurring within the process environment. After analysis, the sample may or may not be returned to the system depending on the method used.



c. Process control tools

Process control tools strengthen the ability to maintain consistent Critical Quality Attributes (CQAs) by monitoring and regulating the interactions between the established manufacturing process and the intended product design.

Continuous improvement and knowledge management

- A thorough understanding of the product, built by collecting and analyzing data throughout its development, supports more efficient and scientifically justified post-approval changes.
- Information gathered during development becomes more valuable when it is grounded in scientific principles, as it contributes directly to regulatory decision-making.
- These tools help establish multidimensional relationships among various factors-such as between formulation components-and aid in evaluating how existing knowledge may be applied or adapted across different conditions or scenarios.

Risk Management Methodology

Quality Risk Management is described as a structured and systematic approach used to assess, control, communicate, and continually review risks that may affect the quality of a pharmaceutical product throughout its lifecycle. Risk-assessment tools help identify and categorize parameters such as process conditions, equipment variables, and raw material attributes that could influence product quality, drawing upon existing knowledge and initial experimental data.

The initial list of potentially influential parameters is often extensive, but it can be narrowed down and ranked through additional investigative studies, such as Design of Experiments (DOE) or mechanistic modeling. Once the key parameters have been recognized, they can be examined more deeply through mathematical modeling, advanced experimental work, or mechanistic studies to build a stronger and more comprehensive understanding of the manufacturing process [20].

Benefits of QBD: [21, 22, 23, 24]

- Supports overall business efficiency.
- Reduces the likelihood of batch failures.
- Minimizes deviations and the need for costly investigations.
- Helps prevent regulatory compliance issues.
- Encourages organizational learning, creating long-term value.
- Reflects sound scientific principles.
- Enables better decision-making during product development.
- Enhances the capability and confidence of technical personnel.

Opportunities: [25, 26]

- Establishes a more efficient, adaptable, and responsive manufacturing system.
- Improves production efficiency while reducing operational costs, rejections, and waste.
- Strengthens the scientific knowledge base across all products.
- Facilitates better communication with regulatory agencies on scientific matters.
- Promotes consistency and reliability in shared information.

Appication of quality by design [27-31]

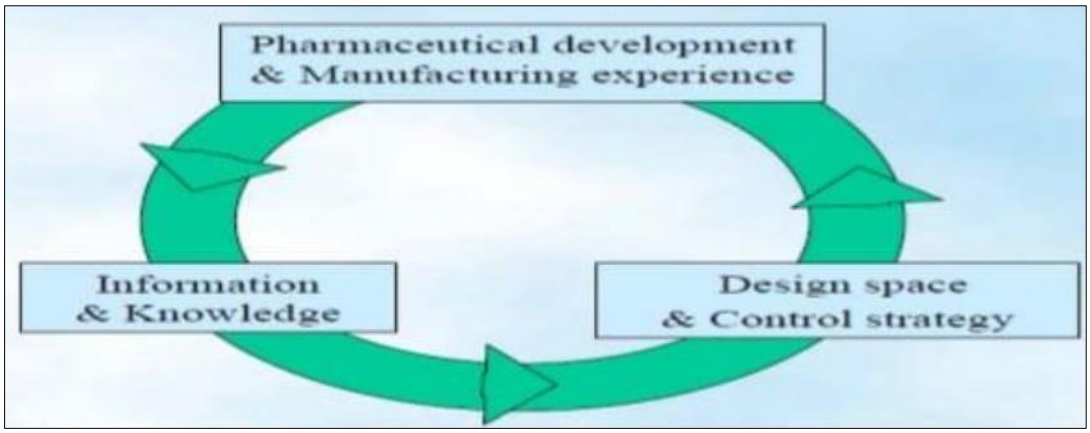
1) Benefits to Industry

- Promotes the development of well-designed products with fewer manufacturing challenges.
- Decreases the need for frequent post-marketing manufacturing supplements by relying on strong

process understanding, risk evaluation, and mitigation strategies.
- Enables the adoption of innovative technologies to enhance manufacturing efficiency without extensive regulatory oversight.
- Helps lower overall production costs by reducing waste and unnecessary reprocessing.
- Simplifies the regulatory review process, leading to fewer deficiencies and faster approvals.
- Strengthens communication with regulatory bodies, shifting discussions toward scientific rationale rather than procedural details.
- Supports continuous improvement in both product quality and manufacturing processes.

2). Pharmaceutical Development

Quality by Design principles are widely applied throughout pharmaceutical development and manufacturing, supporting robust formulation design, process optimization, and lifecycle management.



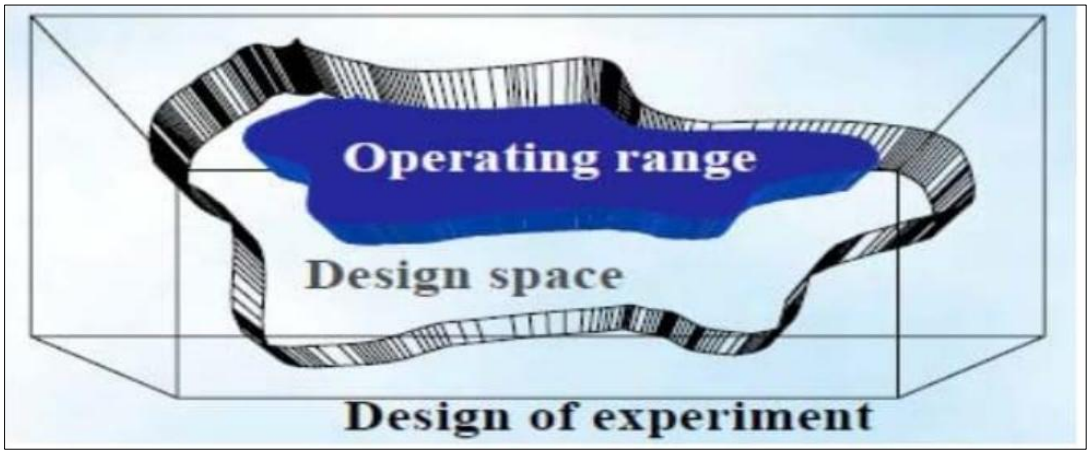
3) In process analytical technique (PAT)

PAT refers to a structured system used to design, analyze, and control manufacturing processes through real-time measurement of critical quality and performance attributes of raw materials and in-process components, ensuring the consistent quality of the final product.

4) Design Space

The design space is defined as the multidimensional range formed by the interaction of input variables and process parameters that have been proven to ensure product quality.

Key features include
- Clear linkage between process inputs (material attributes and process parameters) and CQAs.
- Proposed by the manufacturer and subject to regulatory review and approval.
- May be implemented either before or after marketing authorization.
- Can be developed for specific unit operations or extended to the entire manufacturing process.
- Operating within the approved design space is not considered a regulatory change.

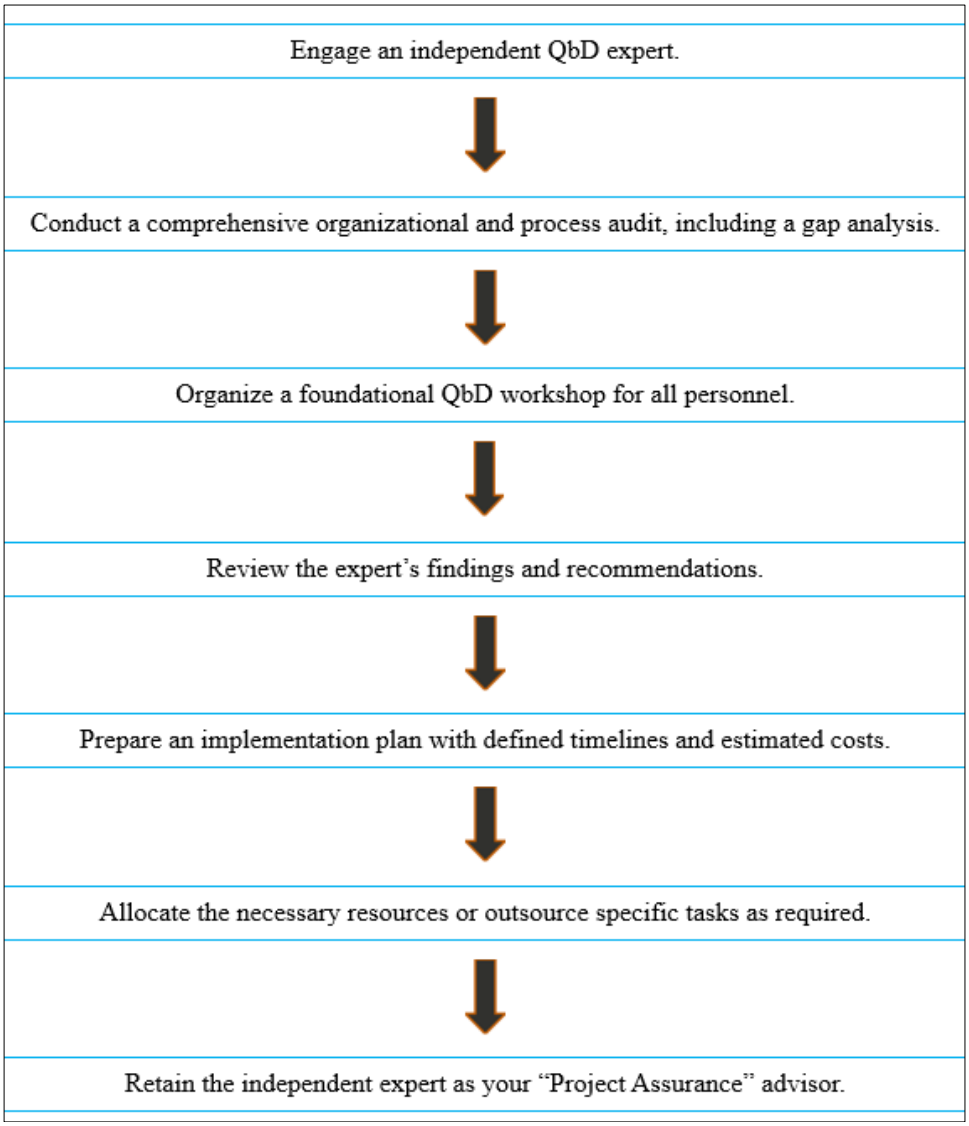


1. Development of a New Molecular Entity
- Conduct preclinical evaluations.
- Perform nonclinical investigations.
- Undertake clinical trials to establish safety and efficacy.
- Scale up the manufacturing process.
- Submit the complete dossier for marketing authorizatin

2. Manufacturing Stage
- Establish the design space.
- Implement Process Analytical Technology (PAT).
- Apply real-time quality control strategies to ensure consistent product performance.

3. Control Strategy
- Utilize risk-based decision-making to manage critical factors.
- Emphasize continuous improvement throughout the product lifecycle.
- Monitor and ensure consistent product performance.

Seven steps of quality by design start up plan



Conclusion

Quality by Design (QbD) has become a foundational element of modern pharmaceutical quality management, gradually replacing traditional, less predictive approaches. It is increasingly embedded within the industry as a forward-looking strategy that drives continuous improvement, innovation, and enhanced process understanding. This paper highlights the significance of the Quality Target Product Profile (QTPP) in establishing clear, quantitative performance objectives within the QbD framework. A key outcome of a well-defined method development process is the creation of an analytical method that consistently generates reliable data and meets predetermined criteria when operated within established limits. Applying QbD principles to analytical method development and evaluation provides a more robust alternative to conventional technology transfer and standard ICH validation practices. By integrating risk assessment and structured change-control procedures, each method modification can be scientifically justified and effectively managed. Overall, the QbD approach offers the potential for greater regulatory flexibility, improved product and process performance, and a more science-driven pathway for pharmaceutical development in the future.

References

1. US Food and Drug Administration. Guidance for Industry: Q8 Pharmaceutical Development. Rockville (MD): US Department of Health and Human Services; 2006.
2. Lawrence X, Raw A, Lionberger R, Rajagopalan R, Lee L, Holcombe F, *et al*. U.S. FDA question-based review for generic drugs: A new pharmaceutical quality assessment system. J Generic Med. 2007;4:239-248.
3. US Food and Drug Administration (FDA), Department of Health and Human Services. Pharmaceutical Quality for the 21st Century: A Risk-Based Approach Progress Report. 2007.
4. Lawrence X, Raw A, Lionberger R, Rajagopalan R, Lee L, *et al*. U.S. FDA question-based review for generic drugs: A new pharmaceutical quality assessment system. J Generic Med. 2007;4:239-248.
5. Rathore AS, Winkle H. Quality by design for biopharmaceuticals. Nat Biotechnol. 2009;27:27-34.
6. International Council for Harmonisation (ICH). ICH Q8(R2): Pharmaceutical Development. 2009.
7. MasterControl. What is Pharmaceutical Quality by Design? Available from: https://www.mastercontrol.com/gxp-lifeline/what-is-pharmaceutical-quality-by-design/

8. US Food and Drug Administration (FDA), Department of Health and Human Services. Pharmaceutical Quality for the 21st Century: A Risk-Based Approach Progress Report. 2007.
9. Juran JM. Juran on Quality by Design: The New Steps for Planning Quality into Goods and Services. Rev ed. New York: Free Press; 1992. p. 1-2.
10. Purohit PJ, Shah KV. Quality by design (QbD): New parameter for quality improvement & pharmaceutical drug development. Pharma Science Monitor Int J Pharm Sci. 2013;4:1-19.
11. Roy S. Quality by design: A holistic concept of building quality in pharmaceuticals. Int J Pharm Biomed Res. 2012;3:100-108.
12. Glodek M, Liebowitz S, McCarthy R, McNally G, Oksanen C, Schultz T, *et al*. Pharm Eng. 2006;26:1-11.
13. Siegfried A, Suzzia D, Radekea C, Khinasta JG. An integrated Quality by Design (QbD) approach toward design space definition of a blending unit operation by Discrete Element Method (DEM) simulation. Eur J Pharm Sci. 2011;42:106-115.
14. International Council for Harmonisation (ICH). ICH Q8(R2): Pharmaceutical Development. 2009.
15. Gawade A, Chemate S, Kuchekar A. Pharmaceutical Quality by Design: A new approach in product development. Res Rev J Pharm Pharm Sci. 2013;2:5-12.
16. Purohit PJ, Shah KV. Quality by design (QbD): New parameter for quality improvement & pharmaceutical drug development. Pharma Science Monitor Int J Pharm Sci. 2013;4:1-19.
17. Shah RB. Quality by Design in Pharmaceutical Manufacturing. U.S. Food and Drug Administration; 2009.
18. Bhasin R, Ghosh P. Design and development of ondansetron orally disintegrating tablets and its optimization using design of experiment. Int J Pharm Sci Res. 2012;3:840-847.
19. US Food and Drug Administration (FDA). Guidance for Industry: PAT-A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance. Washington (DC): FDA; 2004.
20. House I. Process Understanding for Scale-up and Manufacturing Method of Active Ingredients. 1st ed. Weinheim: Wiley-VCH Verlag GmbH & Co. KGaA; 2011.
21. Woodcock J. The concept of pharmaceutical quality. Am Pharm Rev. 2004;7(6):10-15.
22. International Council for Harmonisation (ICH). Q10: Pharmaceutical Quality System. 2007.
23. US Food and Drug Administration (FDA). Guidance for Industry and Review Staff: Target Product Profile - A Strategic Development Process Tool. Draft Guidance.
24. International Council for Harmonisation (ICH). Q8(R1): Pharmaceutical Development. 2007.
25. Callis JB, Illman DL, Kowalski BR. Process analytical chemistry. Anal Chem. 1987;59:624A-637A.
26. Yu LX. Pharmaceutical quality by design: Product and process development, understanding, and control. Pharm Res. 2008;25:781-791.
27. Callis JB, Illman DL, Kowalski BR. Process analytical chemistry. Anal Chem. 1987;59:624A-637A.
28. Yu LX. Pharmaceutical quality by design: Product and process development, understanding, and control. Pharm Res. 2008;25:781-791.
29. Leuenberger H, Puchkov M, Krausbauer E, Betz G. Manufacturing pharmaceutical granules: Is the granulation end-point a myth? Powder Technol. 2009;189:141-148.
30. Food and Drug Administration. http://www.fda.gov/ohrms/dockets/ac/06/minute
31. Remy B, Glasser BJ, Khinast JG. The effect of mixer properties and fill level on granular flow in a bladed mixer. AIChE J. 2010;56:336-353.
32. Callis JB, Illman DL, Kowalski BR. Process analytical chemistry. Anal Chem. 1987;59:624A-637A.
33. Munson J, Gujral B, Stanfield CF. A review of process analytical technology (PAT) in the U.S. pharmaceutical industry. Curr Pharm Anal. 2006;2:405-414.