International Journal of Pharmaceutical Science Invention
ISSN (Online): 2319-6718, ISSN (Print): 2319- 670X
www.ijpsi.org Volume 15 Issue 3 ǁ May. – June., 2026 ǁ PP. 01-05

Pharmaceutical QbD: A Comprehensive Review of Systematic Framework, Emerging Trends and Implementation Strategies in Drug Development

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ABSTRACT*: The pharmaceutical industry is advancing towards Quality by Design (QbD) as a modern, systemic approach to ensuring product quality. Earlier, the industry relied on QbT, which ensured the quality through end product testing with a limited understanding of the manufacturing process and critical parameters. QbD was one of the designs of experiments approved by the FDA to maintain the quality of the product.*

This review emphasises the foundational principle that quality cannot be tested into products; it must be built in by design. Grounded in the ICH Guidelines, QbD begins with predefined objectives and emphasises product & process understanding, process control based on sound science and risk management. The implementation of QbD provides significant business and scientific benefits such as eliminating batch failures, reducing manufacturing costs, enhancing regulatory flexibility and ensuring patient safety and therapeutic efficacy.

Ultimately, the implementation of QbD fosters a science-based manufacturing environment that ensures pharmaceutical products consistently deliver their intended therapeutic benefits while promoting efficiency and innovation throughout the product lifecycle.

KEYWORDS: *Quality by design (QbD), Quality by Testing (QbT), Science-based manufacturing, □ Batch failure elimination, Regulatory flexibility.*

Date of Submission: 25-05-2026 Date of acceptance: 05-06-2026

I. INTRODUCTION

The pharmaceutical industry is in a constant state of searching, seeking ways to ensure and enhance the safety, quality and efficacy of the drug products.

Historically, the industry relied on quality by testing (QbT) which is testing of the product after it's manufacture. Which lead to drug recalls, unpredictable scale-up issues and high manufacturing failure costa due to limited understanding of underlying manufacturing processes and critical parameters.

Quality Scientist Dr. Joseph M. Juran pioneered the modern alternative QbD, based on the principle that quality must be built in to the product starting from its design. The US FDA encourage risk-based approach like QbD in drug product development, manufacturing and regulation that quality must be built in to the product.

As defined by ICH Q8 (R2) guideline- Quality by design is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management (QSM).

The foundational philosophy of this approach is that *quality cannot be tested in to products, rather it must be built in by design.* This paradigm shift was catalysed by regulatory initiatives such as US FDA's Process analytical technology (PAT) guidance and the 21st century modernization of current GMP.

QbD Framework is built upon the ICH guidelines Q8 (pharmaceutical development), Q9 (Quality risk management), Q10 (pharmaceutical quality system). Unlike empirical trial & error methods, this systematic approach utilizes design of experiments (DoE) & Multivariate analysis to establish a design space, a Mult personal combination of material attributes and process parameters that ensure quality. Key elements of this process include defining the quality target product profile (QTPP), identifying critical quality attributes (CQAS) & monitoring critical process parameters (CPP's).

QbD serves as a vital bridge between industry and regulatory authorities fostering a proactive environment that aims to eliminate batches failure, reduce costs and ensure patients receive medicines that consistently deliver their intended therapeutic performance.

II. DEFINITIONS

QbD Is defined by the ICH (Q8 (R2)) Guidelines as a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding, process control based on sound science and quality risk management.

QUALITY : the features or characteristics of a product that bear on its ability to satisfy stated and implied needs.

For example :– in pharmaceuticals a high-quality drug is one that is free from contamination and reliably delivers the therapeutic response promised on the label.

DESIGN : the plan or the sequence for the construction of an object or process.

III. CHARECTERISTICS

Characteristics describes the important features of the QbD Approach in pharmaceutical development.

SYSTEMIC AND DYNAMIC PROCESS : it relies on the principle that quality cannot be tested in to a product instead it must be built in to it from the start.

BROAD APPLICABILITY: the approach is applicable to drug substance development, drug product development and analytical methods.

LIFE CYCLE USE : QbD can be implemented at any stage of a drugs life cycle and is actively encouraged by global regulatory bodies.

IV. BENEFITS

Implementing QbD offers significant advantages to manufacturers, regulations and patients. These are :

ENHANCED PATIENT SAFETY AND EFFICACY: The process directly links product quality to clinical safety and therapeutic effectiveness.

MANUFACTURING FLEXIBILITY: Establishing a design space allows manufacturers to make process changes within predefined ranges without requiring new regulatory approvals.

EFFICIENCY AND COST REDUCTION: By using real-time releasing testing (RTRT) companies can make immediate decisions during manufacturing, reducing the need for time-consuming end-product testing and lowering production costs.

REDUCED PRODUCT VARIABILITY: QbD enhances process capability and ensures more consistent product quality.

V. OBJECTIVES

The primary goals of pharmaceutical QbD include :

ACHIEVING QUALITY SPECIFICATIONS:

to develop meaningful product quality specifications that are based on actual clinical performance.

PROCESS ENHANCEMENT:

to reduce product variability and defects by improving process design understanding and control.

INCREASED EFFICIENCY:

to streamline pharmaceutical development and increase manufacturing productivity.

IMPROVE MANAGEMENT OF CHARGE:

to enhance root cause analysis and management of post-approval changes.

CONSISTENT QUALITY: to ensure that the drug product is free from contamination and reliably delivers the promised therapeutic response.

VI. STEPS INVOLVED IN QbD

The implementation of QbD follows a structure of steps:

1) Define quality target product profile (QTPP)
   This involves identifying the quality characteristics the drug product should possess (e.g., dosage form, route of administration, strength and stability) to ensure safety and efficacy.

2) Identify critical quality attributes
   Determine the physical, chemical, biological or microbiological properties that must be within specific limits to ensure desired product quality.

3) Perform risk assessment
   Use specific knowledge to link material attributes and process parameters to CQAS prioritizing those that pose the highest risk to product quality.

4) Determine critical process parameters (CPP's)
   Identify measurable process inputs (e.g. mixing time, temperature or pressure) that must be controlled to achieve the desired quality and process uniformly.

5) Establish design space:
   Define the multidimensional combination and interaction of input variables and process parameters that have been demonstrated to assure quality.

6) Develop a control strategy :

   Create a planned set of controls, including material controls, in-process controls and finished product specifications to ensure the process remains within the design space.

7) Continuous monitoring and improvement:

Regularly monitor the process and update it as needed based on manufacturing data to ensure consistent quality and foster a culture of innovation.

VII. APPLICATIONS

Drug development :

it is used for both drug substance and drug product development to ensure quality is built into the design from the start.

Formulation optimisation:

case studies show its success in optimising tablet formulations by identifying critical Quality attributes (CQA'S) like hardness, dissolution rate and content uniformity.

Biopharmaceutical processes:

QbD is applied to optimise complex processes such as monoclonal antibody production, focusing on cell culture conditions and purification steps.

Analytical methods**:**

the principles are also used to develop and refine analytical methods to ensure they are robust and reliable.

Generic drug development:

it helps in developing generic oral solid dosage forms that are bioequivalent to reference listed drugs(RLDs).

VIII. ADVANTAGES

The shift from traditional quality by test to QbD offers several strategic and operational benefits. These are :

Enhanced patient safety: by focusing on clinical activity and ensuring on clinical activity and a reliable therapeutic response, it directly protects the consumers.

Manufacturing efficiency: reduces production costs by streamlining processes and decreasing the rate of batch failures.

Regulatory flexibility**:** defines a design space where manufacturers can make process changes without needing new regulatory approvals, provided they stay within predefined ranges.

Patient safety: focuses on clinical safety and efficacy by linking material attributes and process parameters to patient needs.

Improved process understanding: provides a deep scientific understanding of how various factories interact to affect the final product.

IX. ADVERSE EFFECTS

Resistance to change:

Shifting from traditional quality by testing to a science-driven QbD Approach requires a cultural change within the organisation.

Complexity and cost of implementation**:**

Establishing a design space requires extensive experimentation, such as design of experiments (DoE), which can be resource-intensive initially.

Knowledge Gaps:

The need for deep scientific knowledge and risk assessment tools can be a barrier for companies used to empirical methods.

Regulatory alignment:

while global harmonization efforts like ICH are ongoing, aligning varying regulatory expectations across different regions remains a challenge.

X. CONCLUSION

QbD Represent a fundamental paradigm shift in pharmaceutical development, moving away from empirical trial and error methods towards a systemic risk-based approach by integrating science and quality risk management. It fosters a culture of continuous improvement and innovation. Ultimately, the adoption of QbD Principles leads to more robust manufacturing, processes, increased regulatory confidence and most importantly, safer and more effective medications for patients

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