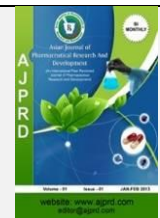


Available online on 15.06.2026 at <http://ajprd.com>

Asian Journal of Pharmaceutical Research and Development

Open Access to Pharmaceutical and Medical Research

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Review Article

Quality by Design Approach in Pharmaceutical

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ABSTRACT

This review aims to clarify the concept of Pharmaceutical Quality by Design and delineate its foundational objectives within the context of drug development and manufacturing. It traces the evolution from traditional quality control, which relied heavily on post-production testing, to the proactive and integrated approach of QbD, emphasizing quality built in at every stage. This systematic approach begins with predefined objectives and prioritizes comprehensive product and process understanding, coupled with robust process control strategies, all underpinned by sound scientific principles and rigorous quality risk management. This transformative methodology ensures that quality is not merely tested into the product but is systematically designed and built-in from the outset, leading to enhanced product quality and reduced batch-to-batch variability. This review will delve into the seven vital elements of QbD, as outlined by the International Council for Harmonization guidelines Q8, Q9, and Q10, examining their interplay in achieving a robust control strategy and ultimately a Quality Target Product Profile. Furthermore, this article will explore the practical implementation of QbD, addressing its complexities and showcasing its applications across various pharmaceutical development stages. By moving beyond traditional trial-and-error methods, QbD fosters a science-based and risk-oriented strategy that optimizes drug product formulation and manufacturing processes. This methodical approach mandates the initial establishment of a Quality Target Product Profile and the subsequent identification of Critical Quality Attributes derived directly from these objectives, thereby guiding the entire development process.

Keywords: Critical Quality Attributes, Design Space, Control Strategy, Quality Risk Management, Process Analytical Technology**ARTICLE INFO:** Received 29 Dec.2025; Review Complete 21 Feb, 2026; Accepted 25 March. 2026; Available online 15 June. 2026**Cite this article as:**Waghmare R, Bharatee C, Quality by Design Approach in Pharmaceutical, Asian Journal of Pharmaceutical Research and Development. 2026; 14(3):00-00, DOI: <http://dx.doi.org/10.22270/ajprd.v14i3.1784>

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INTRODUCTION

The pharmaceutical industry's paradigm shift towards Quality by Design represents a significant evolution from traditional quality control, which primarily focused on end-product testing, to a comprehensive, proactive, and risk-based approach to drug development and manufacturing. The pharmaceutical industry is undergoing a significant paradigm shift with the adoption of Quality by Design, moving away from traditional quality control methods that primarily focused on end-product testing [1]. This evolution emphasizes a comprehensive, proactive, and risk-based approach to drug development and manufacturing, integrating quality into all phases of the product lifecycle, rather than assessing it post-production. This proactive strategy ensures that quality is systematically designed and built in from the outset, leading to enhanced product quality and reduced batch-to-batch variability. At its core, QbD is a systematic methodology that begins with predefined objectives, prioritizing a comprehensive understanding of both the product and the manufacturing process [2]. This

approach is underpinned by sound scientific principles and rigorous quality risk management, facilitating robust process-control strategies. The shift to QbD moves beyond conventional trial-and-error methods,,, fostering a science-based and risk-oriented strategy that optimize drug product formulation and manufacturing processes. A key aspect of this methodical approach is the initial establishment of a Quality Target Product Profile and the subsequent identification of Critical Quality Attributes directly derived from these objectives, thereby guiding the entire development process. [3].

The International Council for Harmonization guidelines Q8, Q9, and Q10 serve as foundational frameworks for QbD, outlining its vital elements. These elements, in combination with enablers, constitute the fundamental basis for the QbD approach, involving the identification of a Quality Target Product Profile, Critical Quality Attributes, risk analysis, Critical Process Parameters, Design Space, and a Control Strategy [4]. Adherence to these elements is crucial for

achieving a robust control strategy and ultimately ensuring the desired Quality Target Product Profile.

The practical implementation of QbD offers substantial benefits, including maximizing time and cost savings by demanding an in-depth understanding of the formulation and manufacturing process to optimize the safety, efficacy, and quality of a drug. This innovative approach streamlines pharmaceutical research and development, provides greater manufacturing flexibility, and can reduce the regulatory burden. This review aims to clarify the concept of Pharmaceutical Quality by Design, delineate its foundational objectives, explore its seven vital elements, and discuss its applications across various pharmaceutical development stages,[5].

Definition

The USFDA formally defines Quality by Design as a systematic approach to pharmaceutical development that commences with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management [1]

Key elements of Quality by Design

This systematic methodology is underpinned by six fundamental components that must be considered prior to implementation.

Quality Target Product Profile (QTPP): defines the desired quality characteristics. Critical Quality Attributes (CQAs): attributes that must be maintained within certain limits to ensure product quality.

Risk Assessment: to identify how materials and process parameters affect CQAs.

Design Space: as described above.

Control Strategy: a planned set of controls to manage variability and ensure quality.

Lifecycle Management – ongoing monitoring and optimization of the process [5]

Critical Quality Attributes:

Critical Quality Attributes are defined as physical, chemical, biological, or microbiological properties or characteristics that must be maintained within appropriate limits, ranges, or distributions to ensure the desired product quality [6]. Their criticality is primarily determined by the potential severity of harm to the patient if the product falls outside acceptable ranges for that attribute [5]. Within the Quality by Design framework, CQAs are essential for addressing patient demands, encompassing aspects such as safety, effectiveness, and performance criteria. The identification and control of CQAs represent a critical stage in the QbD methodology, guiding the entire development process by deriving directly from predefined objectives. Examples of CQAs include drug potency, stability, dissolution rates, and impurity levels. These attributes are intricately linked to Critical Material Attributes and Critical Process Parameters, and they are meticulously monitored and controlled throughout the development and manufacturing processes to ensure that the finished product consistently meets its quality requirements

and stays within predetermined limits, thereby reducing variability and ensuring reliability[2].

Critical Material Attributes:

CQAs are intrinsically interconnected with Critical Material Attributes and Critical Process Parameters, which are manipulated to maintain CQA specifications. Through Design of Experiments, developers map these relationships, establishing multivariate interactions that inform the design space. A robust control strategy, incorporating Process Analytical Technology, provides real-time monitoring and adjustments to uphold CQAs, reducing reliance on end-product testing[2].

Design Space

The Critical Quality Attributes of a product are intrinsically linked with the Critical Material Attributes and Critical Process Parameters, forming the basis for establishing a robust design space. This design space delineates the multivariate relationships between material attributes and process parameters that have been demonstrated to provide assurance of quality Design Space[1].

The Design Space represents a cornerstone of the Quality by Design paradigm in pharmaceutical development, defined as the multidimensional combination and interaction ranges of input variables (e.g., material attributes and process parameters) that have been demonstrated to provide assurance of quality with respect to the Critical Quality Attributes[5]. Unlike traditional fixed-point specifications, the DS delineates the established range of parameters within which the product quality is assured, accounting for multivariate relationships between Critical Material Attributes, Critical Process Parameters, and CQAs(Aziz-Andersen, 2020; Bastogne, 2021). This concept, rooted in ICH Q8 guidelines, shifts the focus from rigid process controls to a flexible operational envelope where variations within the DS do not compromise quality, thereby enhancing process robustness and regulatory flexibility[1].

Establishing the DS begins with a thorough risk assessment linking CMAs and CPPs to CQAs, often through Design of Experiments and multivariate statistical modeling. Critical Quality Attributes of a product are intrinsically connected to CMAs and CPPs, forming the foundational basis for DS delineation. For instance, risk mapping identifies regions such as the Normal Operating Region, where CQA requirements are reliably met, distinguishing it from areas of potential failure. This systematic mapping ensures that the DS is not merely a statistical boundary but a scientifically justified space that mitigates variability sources, aligning process performance with the Quality Target Product Profile[4].

Benefits and Opportunities of Quality by Design

Quality by Design offers key benefits for drug development. It saves time and costs by building deep knowledge of the product and process. This leads to safer, more effective drugs with improved quality. Unlike traditional trial-and-error methods, QbD uses science and risk assessments to reduce defects and ensure consistent results. QbD creates opportunities for flexible manufacturing. It sets a "design space" where small changes do not harm quality, easing

production tweaks without full reapprovals. It also lowers regulatory work and speeds reviews. Tools like real-time monitoring spot issues early, reduce waste, shorten production times, and boost output [2,5].

Over the product lifecycle, QbD drives ongoing gains. It fights drug shortages and recalls by removing process flaws. Companies gain trust from regulators, make smarter choices, and protect patients more effectively. This approach helps innovate faster and meet needs reliably [7].

Conceptual Shift and Proactive Quality Assurance

Quality by Design represents a fundamental conceptual shift from traditional empirical manufacturing to a proactive, science-based approach that builds quality into the product from the outset. Unlike reactive methods reliant on end-product testing, QbD emphasizes predefined quality targets, risk assessments, and systematic process design to ensure consistent safety and efficacy[1]. This paradigm, endorsed by ICH Q8-11 guidelines, fosters a culture of prevention over correction, integrating tools like the Quality Target Product Profile to align development with patient needs throughout the lifecycle[4].

Enhanced Process Understanding through Risk Management and DoE

QbD enhances process understanding by employing Quality Risk Management and Design of Experiments to systematically identify Critical Material Attributes, Critical Process Parameters, and their impacts on Critical Quality Attributes(Baker, 2018). Risk assessments evaluate severity, occurrence, and detectability, while DoE maps multivariate interactions, delineating the design space where quality is assured. This rigorous methodology, supported by ICH principles, minimizes variability and provides a knowledge foundation for robust scaleup and control[7].

Cost and Time Efficiency

By front-loading scientific knowledge and risk mitigation, QbD delivers substantial cost and time efficiencies in drug development and manufacturing. It reduces trial-and-error iterations, defects, rework, and waste through predictive modeling and real-time Process Analytical Technology, shortening timelines from lab to market[5]. Studies highlight decreased batch failures and optimized resource allocation, enabling faster approvals and lower lifecycle costs while maintaining high standards[2].

Regulatory Benefits and Flexibility

QbD offers significant regulatory advantages, including greater flexibility for post-approval changes within the established design space, which exempts operations from additional oversight[1]. Agencies like the US FDA and EMA reward QbD submissions with streamlined reviews, recognizing justified risk-based controls that harmonize with ICH guidelines. This facilitates global harmonization, particularly for generics and biosimilars, reducing submission burdens and accelerating access to therapies[7].

Improved Product Quality and Patient Safety

At its core, QbD ensures superior product quality and patient safety by linking inputs (CMAs/CPs) to outputs via the

QTPP, mitigating risks that could compromise efficacy or introduce impurities[6]. Continuous verification and PAT enable real-time deviations detection, thereby preventing shortages and recalls associated with legacy processes[7]. This patient-centric focus yields more consistent, reproducible drugs, enhancing therapeutic outcomes and public health confidence.

Opportunities for Innovation and Continuous Improvement

QbD unlocks innovation by encouraging knowledge-driven experimentation within the design space, supporting novel formulations, PAT integrations, and lifecycle enhancements[5]. It promotes continuous improvement through data accumulation, process capability indices (Cp/Cpk), and adaptive controls, addressing variability in raw materials and operations[9]. This dynamic framework fosters breakthroughs in complex biologics and personalized medicines, positioning industry leaders for competitive advantage.

Adoption Challenges as Opportunities

While QbD adoption faces hurdles like expertise demands, resource intensity, and high-dimensional modeling complexities, these challenges present opportunities for growth (Baker, 2018). Over-designation risks can be mitigated via focused DoE and simplified tools, transforming initial investments into long-term gains in efficiency and compliance. By viewing barriers as catalysts for training, interdisciplinary collaboration, and simplified QRM, organizations convert obstacles into strategic advantages, advancing QbD maturity across the pharmaceutical sector[3].

Total Quality Management

principles deeply intertwined with the QbD framework, which further augment these benefits by fostering a culture of continuous improvement and defect prevention throughout the pharmaceutical product lifecycle. This holistic approach integrates quality into every stage of development and manufacturing, from initial design to commercial production, ensuring consistent product quality and patient safety [1]. Total Quality Management is a simple approach to running a business where everyone works together to improve quality. It focuses on achieving customer satisfaction by delivering the best products and services every time. TQM means monitoring and rectifying every step of the work process, from planning to delivery. Its origins can be traced to Japan after World War II and spread to other countries like the US. The core principle is "do it right the first time" to avoid mistakes and waste. The process of TQM follows clear steps. First, leaders commit to quality and set ambitious goals. They train all personnel and create teams to solve problems. Second, understanding customer needs through feedback and surveys is crucial. Third, all work processes are mapped out to identify weaknesses, utilizing simple tools such as charts and checklists

In pharmaceuticals, TQM fits well with modern methods like Quality by Design. It ensures drugs are safe, effective, and consistent. By focusing on processes and people, TQM lowers risks of recalls or shortages. It builds trust with regulators and patients, thereby strengthening the industry [7]

Target drug profile

The Target Product Profile, also called Quality Target Product Profile in Quality by Design, is a clear roadmap for a new drug. It lists the key features the drug must have to work well and be safe for patients. This includes features such as the drug's form (tablet, liquid, etc.), strength, its sensory attributes, its stability or shelf life, and how it helps treat the disease. TPP serves as a guiding document that guides everyone from scientists to regulators [4].

Teams use TPP early in drug development to set clear targets. It helps select the right ingredients and processes. During tests, it verifies whether the drug matches the profile. In QbD, TPP links to quality attributes, such as potency or purity. It also guides packaging and storage requirements to ensure drug safety until patient use.

Quality Risk Management

Quality Risk Management is an integral component of QbD, offering a structured approach to identifying, assessing, controlling, communicating, and reviewing risks to product quality throughout its lifecycle [1]. This systematic process serves as a fundamental tool within QbD, allowing for a thorough evaluation of all possible sources of variation that could impact a drug's quality. By proactively addressing these potential issues during development and manufacturing, QRM helps ensure the consistent high quality of the drug product, ultimately prioritizing patient protection. The Quality Risk Management process typically involves several key steps. It begins with risk assessment, where potential hazards are identified, analyzed, and evaluated (Baker, 2018). This stage involves linking Critical Quality Attributes with process input variables to understand and control manufacturing risks [1]. Next, risk control focuses on reducing or accepting these identified risks. This is followed by risk communication, which involves sharing information about the risks. Finally, risk review is an ongoing process of monitoring and evaluating operations and risk management strategies as new information becomes available, ensuring their continued effectiveness throughout the product's life. The implementation of Quality Risk Management is guided by two main principles: first, that the assessment of risk to quality should be based on scientific knowledge and ultimately aim to protect the patient; and second, that the effort and formality of the QRM process should be proportionate to the level of risk involved.

An effective QRM approach not only helps manufacturers confidently manage threats and ensure product safety, but also improves decision-making, offers greater assurance to regulators, and can lead to more efficient regulatory oversight. This iterative process fosters continuous learning and optimization of production, helping to reduce quality deviations and safety concerns from the earliest stages of product development [2].

Control Strategy

Control strategy within the Quality by Design framework refers to a comprehensive, planned set of controls derived from in-depth product and process understanding. It ensures consistent manufacturing performance and desired product quality by managing variability in critical process parameters and critical material attributes. This strategy integrates

elements such as input material controls, process monitoring, equipment specifications, and personnel training, forming a holistic approach that links directly to critical quality attributes [5].

Key advantages of implementing a well-defined control strategy include enhanced process robustness, minimized quality risks, and improved regulatory compliance. By emphasizing science-based controls over rigid testing, it promotes efficiency, shortens release times, and fosters innovation through data-driven optimizations. Ultimately, it assures patient safety by maintaining product consistency, lowers manufacturing costs via waste reduction, and builds greater assurance with regulators (Kumari et al., 2024).

Continuous improvement & Lifecycle Management:

Continuous improvement, in the context of pharmaceutical manufacturing, is defined as a recurring activity aimed at enhancing the ability to fulfill requirements, quantifiable through process capability. Its primary objective is to eliminate inherent variability stemming from process operations and raw material quality, thereby achieving higher process capability. The need for continuous improvement arises from the persistent challenges of drug shortages and product recalls, particularly for older products, emphasizing the ongoing necessity to enhance overall product quality. Regulatory bodies are encouraged to foster an environment that incentivizes manufacturers to consistently improve their processes [7].

The advantages of implementing continuous improvement are multifaceted. It cultivates a culture of innovation and efficiency within an organization, ensuring that each iteration of product development builds upon previous successes. Furthermore, it bolsters proactive risk management by enabling the identification of potential problems and the implementation of preventive measures, thereby mitigating unanticipated quality issues and safeguarding patient safety [2]. This systematic approach frequently involves five key phases: problem definition and goal setting, measurement of critical process aspects and data collection, data analysis to identify cause-and-effect relationships, process optimization, and control of the refined process to manage deviations. Tools such as prior knowledge, risk assessment, Design of Experiments, and Process Analytical Technology are instrumental in facilitating these continuous improvement efforts [5].

Lifecycle Management

Pharmaceutical product lifecycle management involves maintaining product quality consistently throughout its entire lifespan, ensuring that critical attributes remain aligned with those established during clinical studies. This comprehensive approach spans from the initial development phases through to the eventual discontinuation of the product. The essence of lifecycle management is to integrate quality directly into the product's design from its inception, rather than merely relying on end-product testing to confirm quality [1].

The product lifecycle encompasses several distinct stages. It begins with pharmaceutical development, focusing on designing a quality product and its manufacturing process for consistent performance. This is followed by technology transfer, which involves sharing product and process

knowledge between developmental stages and large-scale manufacturing to enable product realization and continuous improvement. Commercial manufacturing then focuses on efficient control strategies and ongoing refinement. Finally, product discontinuation involves effectively managing the product's terminal stage [1]. Throughout these stages, product and process capabilities are regularly assessed and continuously improved to ensure sustained quality [5].

CONCLUSION

This iterative process, deeply embedded within the QbD framework, ensures that the product consistently meets its Quality Target Product Profile and critical quality attributes throughout its market presence. Process Analytical Technology, continuous improvement, and robust lifecycle management are integral to modern pharmaceutical manufacturing, collectively ensuring product quality, efficiency, and patient safety. PAT provides real-time monitoring and proactive deviation correction, thereby reducing defects and streamlining production. This is complemented by continuous improvement efforts aimed at minimizing process variability and enhancing overall product quality, particularly for existing products, fostering a culture of innovation and proactive risk management. Lifecycle management, which integrates quality by design from inception through discontinuation, further solidifies product integrity by maintaining critical attributes and employing effective quality risk management strategies. Together, these approaches facilitate evidence-based decision-making, optimize processes, and ensure that pharmaceutical products

consistently meet stringent quality requirements throughout their entire lifespan.

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