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Implementing Quality by Design (QbD): Strategies, Challenges, and Best Practices Across Industries

Patil Divyashree K.[1,*], Mahale Devendra S.[1], Amit Kumar R. Dhankani[2], Mansi A. Dhankani[3], S.P. Pawar[4]

Abstract

The present comprehensive review investigated the dynamic landscape of quality standards within the pharmaceutical sector, with a primary focus on the implementation and impact of Quality by Design principles. It illuminated the multifaceted challenges encountered by pharmaceutical companies in upholding stringent quality standards amidst evolving regulatory requirements and complex manufacturing processes. By embracing Quality by Design principles, the industry aims to foster a proactive and systematic approach to product development and manufacturing, thereby enhancing product quality, safety, and efficacy while mitigating risks. Central to the Quality by Design framework is the concept of critical quality attributes, which are vital characteristics of a drug product that ensure its desired performance and therapeutic effectiveness. Through a thorough understanding of critical quality attributes, pharmaceutical companies can design robust control strategies and implement risk-based approaches to ensure consistent product quality throughout the product lifecycle. Moreover, the adoption of Quality by Design principles necessitates a paradigm shift in regulatory expectations, with agencies such as the International Conference on Harmonization and the United States Food and Drug Administration advocating for a more science-based and integrated approach to quality management. The use of cutting-edge techniques and technologies, such as Process Analytical Technology and Design of Experiments, is essential to the effective application of Quality by Design. Pharmaceutical producers may now methodically identify and adjust key process parameters, improving process robustness, process comprehension, and product quality control; thanks to these cutting-edge methodologies. Furthermore, the present review underscored the importance of integrating Quality by Design principles into the broader product development lifecycle, from early-stage formulation development to commercial manufacturing. By embedding Quality by Design principles into every stage of the development process, pharmaceutical companies can streamline operations, accelerate time-to-market, and ultimately deliver safer and more effective medicines to patients worldwide. Overall, the present review offered valuable insights into the transformative role of Quality by Design in shaping the future of pharmaceutical quality assurance and regulatory compliance.

***Author for Correspondence**
Patil Divyashree K.
E-mail: divyashree2609@gmail.com

[1]Student, M Pharm, Department of Pharmaceutical Quality Assurance, P.S.G.V.P. Mandal's College of Pharmacy, Shahada, Maharashtra, India
[2]Assistant Professor, Department of Pharmaceutical Quality Assurance, P.S.G.V.P. Mandal's College of Pharmacy, Shahada, Maharashtra, India.
[3]Assistant Professor, Department of Pharmaceutics, P.S.G.V.P. Mandal's College of Pharmacy, Shahada, Maharashtra, India
[4]Principal, P.S.G.V.P. Mandal's College of Pharmacy, Shahada, Maharashtra, India

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INTRODUCTION

As one of the industries with the strictest regulations, the pharmaceutical industry has a long history of producing high-quality pharmaceuticals that have the required pharmacotherapeutic effects when used to treat a wide range of illnesses in people. The pharmaceutical business has, however, been dealing with ongoing difficulties in producing

high-quality pharmaceutical products over the last few decades. As stated in the September 2002 Wall Street Journal article, "The pharmaceutical industry has a little secret as it invents futuristic new drugs, yet its manufacturing standards lag far behind the makers of potato chips and laundry soap." The main problems with the low quality of pharmaceutical products can be traced to a number of factors, including inconsistent raw materials, a lack of automation and control in the manufacturing process, and a lack of knowledge about the parameters of the product and the process. The primary sources of variability linked to the creation of pharmaceutical products are depicted in Figure 1, and they play a significant role in product recalls. The United States Food and Drug Administration (USFDA) took the initial move toward incorporating quality standards into pharmaceutical development and regulatory practice as a result of the low quality of pharmaceutical products. Regarding this, a concept paper titled "Pharmaceutical GMP for the 21st century" was issued in 2004 and presented the agency's vision for changing the quality paradigm. Following this initiative, the quality by design (QbD) idea was introduced by the International Conference on Harmonization (ICH), which established several regulatory guidelines (Q8, Q9, and Q10) as well as a comprehensive methodology that yields resilient, high-quality drug products [1].

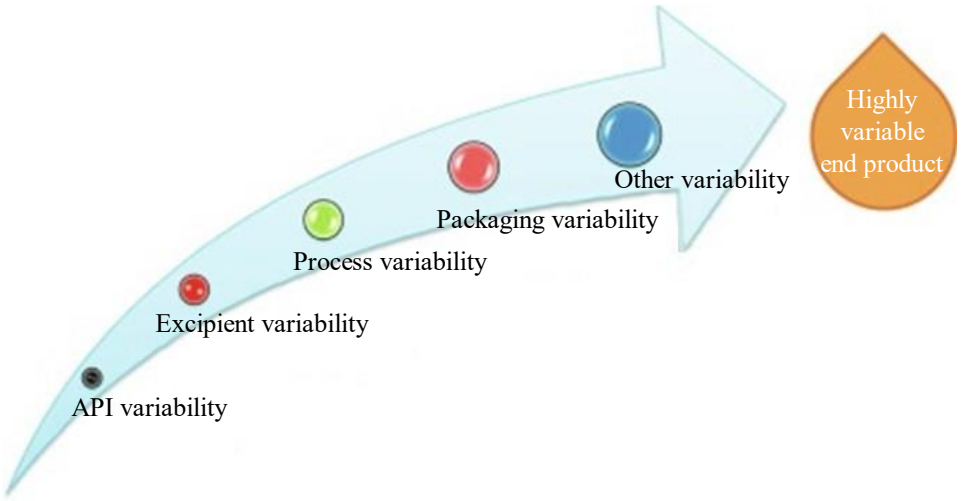

Figure 1. Sources of variability in drug product quality [1].

The goal of pharmaceutical development is to provide high-quality goods and manufacturing techniques that consistently deliver the intended level of performance. Design space, specifications, and manufacturing controls are established with the use of scientific understanding provided by data and expertise gathered from pharmaceutical development research and manufacturing experience. Quality risk management may be based on data from pharmaceutical development research. It is critical to understand that items cannot be tested for quality; rather, quality should be included in design. Modifications to the formulation and manufacturing processes during the lifecycle management and development stages should be viewed as chances to learn more and help create the design space. Compiling pertinent information from tests that produce unexpected findings can also be helpful in this regard. The applicant proposes the design space, which must be approved and evaluated by the regulatory body. It is not deemed a change to work within the design space. Departure from the design space is deemed a modification and typically triggers a regulatory post-approval change procedure. Products should always be made with the needs of the patient and the intended use of the product in mind. Approaches to product development differ between businesses and between products. An explanation of the strategy—which may vary—should be included in the submission.

An application may decide to design a product using an empirical technique, a more methodical approach, or a combination of the two. A more methodical approach to development, often known as QbD, can involve, among other things, applying knowledge management (ICH Q10) across the product's lifespan, including prior knowledge and the findings of studies conducted using the design of

experiments. It can also involve implementing quality risk management. Such a methodical approach can improve attaining the intended product quality and assist regulators in comprehending a company's business plan. Knowledge acquired during the course of the product lifecycle can be used to refresh understanding of the product and process [2].

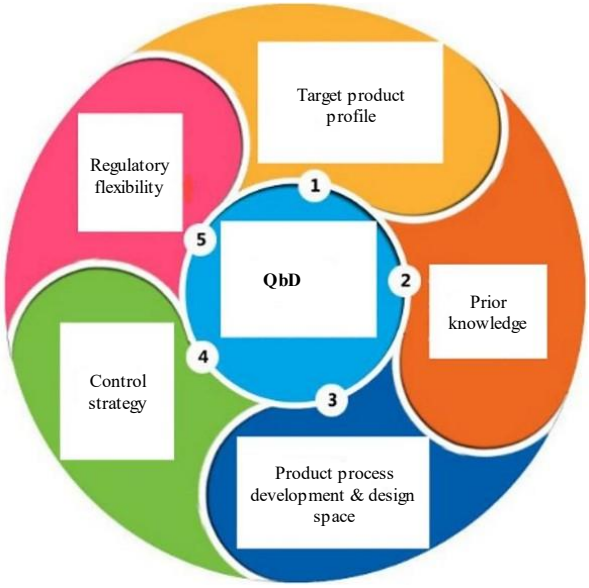

Figure 2. Flow diagram for Quality by design [3].

Key Principles of Quality by Design

When developing a pharmaceutical product using a QbD approach, an applicant finds qualities that are important to the patient, converts those qualities into critical quality attributes (CQAs) for the drug product, and determines how formulation and manufacturing variables relate to CQAs in order to consistently provide the patient with a drug product that meets those criteria. The following components make up QbD:

a. A quality target product profile (QTPP) that lists the CQAs of medication product.
b. Product design and comprehension, which includes determining the crucial material attributes (CMAs).
c. Process design and comprehension, which includes determining important process parameters (CPPs) and having a solid grasp of the principles of scale-up, which connect CMAs, CPPs, and CQAs.
d. A control plan that comprises controls for every stage of the manufacturing process in addition to specifications for the drug substance(s), excipient(s), and drug product.
e. Process efficiency and ongoing development (Figures 2 and 3) [4].

The fundamental tenet of QbD is that things should be designed with quality in mind rather than having quality tested into them. Thus, QbD evaluates the factors that could affect the product's quality in order to guarantee the intended level of quality (Table 1) [5].

Regulatory Landscape

"In a QbD concept, the regulatory burden is less because there are wider ranges and limits based on product and process understanding," claim Lolas and Rathore. Modifications made within these bounds and ranges do not need prior consent [6].

The FDA system-based methodology and CDER's Compliance Program, "Inspection of Licensed Biological Therapeutic Drug Products," have historically been followed while conducting inspections. But considering that QbD is now necessary, the question of how the inspection will go forward now

emerges. Pre-license or preapproval inspections under a QbD concept will assess the application's process design, implementation, and efficacy, as well as if knowledge and risk management have been successfully transferred from development to production by the FDA inspection team. Throughout the product's lifetime, the inspection will assess the quality system's efficacy in managing knowledge and risks, implementing modifications to control procedures, streamlining processes, managing deviations, and maintaining consistent product quality.

Table 1. Principles and definitions of Quality by Design (QbD).

QbD principles [5]	Definition [5]
Control strategies	A carefully thought-out control system, using the most recent knowledge of the product and process, ensures both process performance and product quality.
Critical process parameters (CPP)	A process parameter whose unpredictability affects a crucial quality feature and needs to be watched over or managed to guarantee the process generates the required quality
Critical quality attributes (CQA)	A physical, chemical, biological, or microbiological characteristic or trait that must lie within a specific range, limit, or distribution in order to ensure the desired degree of product quality.
Design space	Combining and interacting in several dimensions with input variables (such as material qualities) and process parameters that have been shown to guarantee quality.
Proven acceptable range (PAR)	A defined range of a process parameter for which operating within it will produce a material that satisfies pertinent quality standards while maintaining the same values for other parameters.
Quality risk management	A methodical procedure for identifying, managing, sharing, and reviewing risks to the medication's quality during the course of its lifecycle.
Quality target product profile (QTPP)	An anticipated synopsis of a medication's quality attributes that, with the safety and effectiveness of the product taken into consideration, should be attained to guarantee the intended quality.

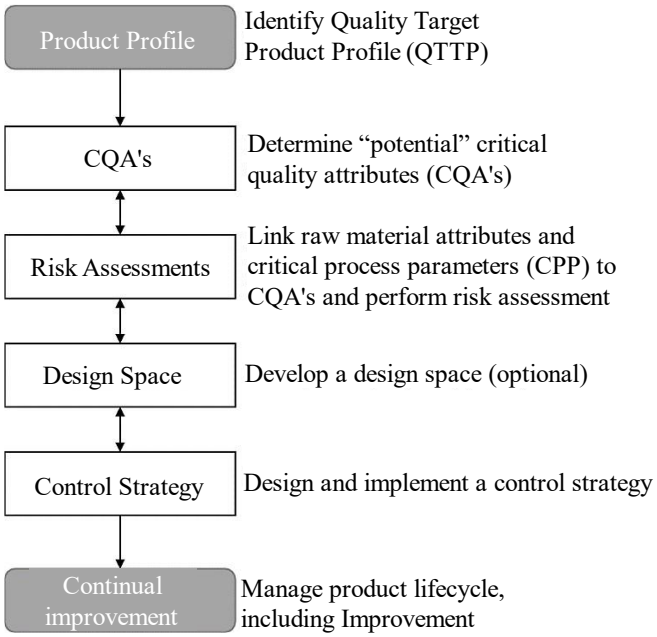

Figure 3. QbD scheme with QbD elements [5].

The same inspection procedures will be used for supplier management, raw material screening, and equipment qualification and maintenance as they were in the past. However, emphasis would be placed on designing, testing, and monitoring programmes that show consistency and robustness [7].

a. *Expectations and Requirements Related to QbD:* Pharmaceutical regulations now place more of an emphasis on guaranteeing the efficacy, safety, and quality of the products. QBD is becoming

more and more well-known as a methodical way to satisfy regulatory requirements. The following are important facets of the QbD regulatory environment.

b. *International Conference on Harmonization (ICH):* The QbD concepts are outlined in the ICH Q8, Q9, and Q10 recommendations, which stress the significance of comprehending the product and process in order to attain and maintain the target quality. ICH recommendations are aligned with the requirements of regulatory authorities worldwide, such as the FDA, EMA, and others. The creation and production of pharmaceuticals are thought to require adherence to QbD principles.
c. *FDA's Quality Systems Approach:* This guidance is intended to help manufacturers implementing modern quality systems and risk management approaches to meet the requirements of the Agency's current good manufacturing practice (CGMP) regulations (2l CFR parts 210 and 211).
d. *Development and Manufacture of Drug Substances:* ICH Q11 offers recommendations for the creation and production of medicinal compounds, with a focus on a QbD methodology. Drug substance development is urged to apply QbD concepts, with a focus on comprehending and managing the production process.
e. *Risk-Based Approach:* To find and manage possible hazards to product quality, regulatory bodies require a comprehensive risk assessment (RA). ICH Q9 promotes the application of risk management techniques. It is essential that risk identification and mitigation be included in regulatory filings.
f. *Post-Approval Changes:* Regulatory bodies support innovation and ongoing development in the pharmaceutical manufacturing process. As long as they stay inside the defined design space and do not jeopardize the quality or safety of the product, modifications to processes or formulations based on QbD principles might be simpler to adopt.
g. *Global Harmonization:* Attempts to harmonize regulatory standards worldwide and align them with QbD principles. Global regulatory expectations that are consistent could help manufacturers and facilitate more seamless international product launches [8].

Integration into Product Development

The essential characteristics for pharmaceutical development are determined by the physico-chemical and pharmacological characteristics of the active pharmaceutical ingredient (API). Achieving desirable patient requirements and identifying characteristics that a pharmacological product should have in order to exert the anticipated therapeutic response are the goals of the QbD-based product development programme. To achieve these predetermined goals, product development must always be systematic, scientific, and risk-based. The experience component adds value to this holistic approach at different phases. It is easier to identify CQA, which needs to be managed in order to consistently deliver the desired output, when one has a solid grasp of the product and its production process. A successful and knowledge-based product development process can result from the use of appropriate statistical approaches, such as experiment design, appropriate RA, and management tools. Establishing relevant and adaptable regulatory product requirements is another benefit of understanding CQA. QbD is facilitated, and enhanced manufacturing capability can be achieved using development expertise [9].

Risk Assessment and Management

CQA and input process variables are linked through RA. The following instruments are included in RA:

1. Analysis of failure mode and effect (FMEA) Pareto analysis;
2. The fishbone or Ishikawa diagram;
3. Pareto analysis.

After that, an FMEA may be used to rank the variables according to risk and identify the process parameters that carry a higher risk so that additional research can be done to better understand how

those factors affect critical quality attributes. The raw materials, instrumental factors, and environmental factors that can affect a certain CQA are the variables that are identified using an Ishikawa or fishbone diagram. To quantitatively separate the effects of each issue on the selected CAAs, Pareto charts were employed. The main goals of chromatographic technique development are identification and chemical separation. Through RA, the QbD methodology places a strong emphasis on a solid and durable process [10].

A certain amount of risk is inherently involved in the production and use of pharmaceutical products, including their component parts, according to ICH Q9 quality risk management. A degree of formality, paperwork, and effort proportional to the risk level should be used in the quality risk management process. The evaluation of the risk to quality must be based on scientific data and ultimately connected to patient safety. Although RA in product development is not directly covered by ICH Q9, it does provide a methodical approach to quality risk management. But product development RA can also use the RA instruments listed in ICH Q9.

Finding potentially high-risk formulations and process variables that could affect the drug product's quality is the goal of RA conducted before development studies. It is frequently motivated by information gaps or uncertainty and aids in prioritizing which investigations should be carried out. The results of the study help identify the variables that are and are not critical, which makes it easier to design a control approach. Finding the factors to be studied experimentally is the result of the RA.

ICH Q9 offers the following non-exhaustive list of typical RA instruments:

- Simple techniques for facilitating risk management (check sheets, flowcharts, etc.).
- Hazard analysis and crucial control points;
- Hazard tree analysis;
- Risk rating and filtering;
- Analyzing failure mode impacts;
- Hazard operability analysis; failure mode, effects, and criticality analysis;
- Providing assistance with statistical instruments [11].

Design of Experiments

DoE is a systematic and structured way of determining the relationships between input items (xi, independent variables) that affect one or more output responses (y, dependent variables) by building mathematical models ($y = f(xi)$). By methodically varying the controlled input factors, the DoE approach reveals how these factors affect the output responses. This information helps identify the most crucial input factors, pinpoint the settings of those input factors that produce the best output responses, and clarify how different input factors interact.

Choice of the Experimental Layout: A number of factors should be considered in order to determine the best experimental design, such as specific goals, the number of input components and interactions that need to be investigated, and the effectiveness and statistical validity of each design. According to Belzarr et al. (2008), Candioti et al. (2014), and Politis et al. (2017), there are two types of experimental designs that can be categorized to aid in the comprehension of DoE applications—screening designs and optimization designs—an explanation of the characteristics of screening and optimization designs, such as the number of factors to be studied, the number of levels of input factors, and the number of experiments required [12].

In order to gain a better understanding of product performance across a broader range of material qualities, processing alternatives, and process parameters, the applicant may elect to conduct pharmaceutical development studies. It is possible to show a deeper level of comprehension of manufacturing processes and process controls by including this extra information in this area. This

knowledge from science creates the design space. These circumstances present opportunities to create more flexible regulatory frameworks, such as those that support risk-based regulatory decisions (reviews and inspections); manufacturing process improvements that fall within the approved design space specified in the dossier and do not require additional regulatory review; and real-time quality control that reduces the need for end-product release testing.

The applicant must exhibit an improved understanding of product performance across a variety of material qualities (such as flow properties, moisture content, and particle size distribution), processing alternatives, and process parameters in order to actualize this flexibility. Applying Process Analytical Technology (PAT), or formal experimental designs, for instance, can help acquire this knowledge. Prioritizing the additional pharmaceutical development studies needed to gather this information can be aided by the appropriate application of risk management principles [13].

Process Analytical Technology

The FDA's Center for Drug Evaluation and Research (CDER) has made PAT and QbD top priorities. The goal of several recent CDER and FDA initiatives has been to encourage the pharmaceutical sector to use PAT and QbD in their production and product development processes. Even though sterile goods may not be as common as non-sterile dosage forms (such as solid orals), their full sterility makes manufacturing process design and control crucial. With their focus on the manufacturing process, QbD and PAT readily identify the sterile medicine product as a target. While QbD submissions are encouraged by the FDA, there is still little use of QbD and PAT for sterile items. The current status of QbD and PAT for sterile products, along with a look at a few instances that are being used, we will also talk about other possible uses of QbD and PAT for sterile product development and production [14].

Designing, evaluating, and managing the important quality and performance characteristics of the materials and processes in the process using real-time measurements to guarantee the quality of the finished product is what the FDA (2004) defines as PAT. The utilization of this method as integrated application of chemical, physical, mathematical, microbiological, and risk analysis is commonly referred to as analytical. Understanding and managing the production process in a way that complies with our existing drug quality standards is PAT's main goal. Regarding this, the pharmaceutical industry's quality idea should be stated as follows: “The pharmaceutical products' quality should be designed and built in this direction, and the quality tests applied to the final product should not reflect the actual quality.”

Tools for process analysis, process control, highly variable data capture, continuous improvement, and information management are all included in PAT. The pharmaceutical industry uses Raman spectroscopy (RAMAN), near infrared spectroscopy (NIRS), ultraviolet-visible-spectrum (UV-VIS) region spectroscopy, and nuclear magnetic resonance spectroscopy (NMR) commonly for PAR applications. NIRS is very useful for determining process parameters, limit compliance, optimal values, and process termination points. It is utilized in several units, including mixing, granulation, drying, and coating, during the production of solid oral dosage forms. Yet, viscosity measurements and online chromatographic techniques are additional crucial analytical instruments utilized in process development. Chemometric methods are helpful in determining mathematical correlation and can be applied to real-time monitoring and control to achieve the characterization of raw and intermediate products when evaluating the performance of the production process [3].

Three primary steps comprising PAT are design, analysis, and control. These steps are linked as shown in Figure 4. When assessing the quality of the finished product in the design stage, it is essential to ascertain the degree of impact of every process step and the initial material. During the analysis step, real-time, direct, or indirect analytical techniques are employed to ascertain the quality attributes of the process materials and raw materials. Ultimately, in the last phase, the balance between all the outcomes acquired from process control is assessed [6].

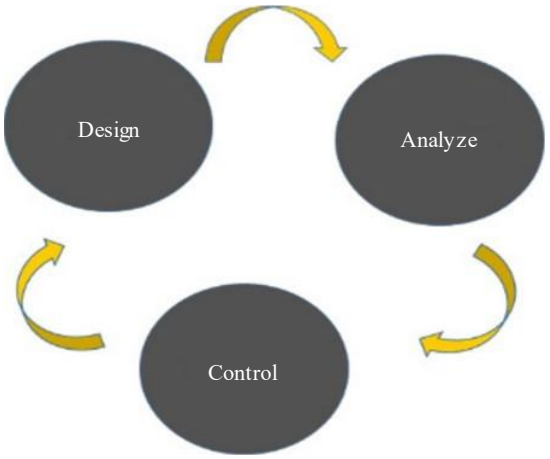

Figure 4. Steps of Process Analytical Technology [13].

CONCLUSION

In conclusion, the implementation of QbD principles represents a significant paradigm shift in the pharmaceutical industry towards ensuring consistent product quality, safety, and efficacy. The present review has highlighted the evolution of quality standards and the challenges faced by the industry, prompting regulatory initiatives to promote the adoption of QbD. Key principles of QbD, such as understanding CQAs and implementing control strategies, have been discussed, along with their integration into product development processes. In addition, the regulatory environment related to QbD has been studied, including the standards and specifications set by agencies such as the FDA and the ICH. Along with the use of PAT and DoE, the function of RA and management in QbD has also been investigated. All things considered, QbD provides a methodical and scientific approach to drug development, highlighting the significance of building quality into goods from the beginning. Pharmaceutical firms can guarantee regulatory compliance, improve product quality, and lower variability by incorporating QbD principles into their manufacturing operations. As the industry continues to evolve, QbD will play a crucial role in shaping the future of pharmaceutical manufacturing, ultimately benefiting patients worldwide with safer and more effective medications.

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