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Review Article

Quality by Design: A Strategic Approach to Pharmaceutical Development

Mahavir M. Sharma[1,*], Harshkumar Brahmbhatt[1], Priyanka Shah[2], Ujjval P. Vaghela[1]

[1]Department of Pharmacy, Sumandeep Vidyapeeth (Deemed to be University), Piparia, Vadodara, Gujarat, INDIA.
[2]Department of Pharmaceutical Chemistry and Quality Assurance, Krishna School of Pharmacy and Research, KPGU, Vadodara, Gujarat, INDIA.

ABSTRACT

This review delineates the primary objectives of Quality by Design (QbD) and provides an in-depth exposition of its foundational concepts. The core components of QbD include: (1) the establishment of a comprehensive control strategy that defines quality requirements for drug substances, excipients, and final pharmaceutical products, while incorporating controls at each stage of the manufacturing process; (2) product design and understanding, encompassing the identification and characterization of Critical Material Attributes (CMAs); (3) process design and understanding, which involves the identification of Critical Process Parameters (CPPs) and their interactions with CMAs and Critical Quality Attributes (CQAs); (4) the formulation of a Quality Target Product Profile (QTPP), outlining the desired CQAs of the final drug product; and (5) the evaluation of process capability and the implementation of continuous improvement strategies. The practical application of QbD is facilitated by a range of scientific methodologies, including prior knowledge, risk assessments, mechanistic modeling, Design of Experiments (DoE), data analytics, and Process Analytical Technology (PAT). As the pharmaceutical industry increasingly adopts QbD principles, the standardization of terminology and a unified conceptual framework are critical. Such alignment will enhance communication and collaboration among stakeholders, thereby supporting risk-based drug development and regulatory evaluation processes.

Keywords: Process Analytical Technology, Critical Quality Attributes, QBD.

Correspondence:
Mr. Mahavir M. Sharma
Assistant Professor, Department of Pharmacy, Sumandeep Vidyapeeth (Deemed to be University), Piparia, Vadodara-391760, Gujarat, INDIA.
Email: mahavir.svp@gmail.com

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INTRODUCTION

The well-known quality specialist Dr. Joseph M. Juran was the first to conceptualise the fundamental quality management idea known as Quality by Design (QbD). Dr. Juran stated that the majority of quality-related problems arise from flaws in the original design process, underscoring the importance of quality being inherently ingrained in a product's design. This idea was further developed by Woodcock, who defined a high-quality pharmaceutical product as one that is free from impurities and continuously provides the therapeutic effect listed on the label (Juran *et al*., 1992).

The Food and Drug Administration (FDA) of the United States is a strong supporter of risk-based approaches and the incorporation of QbD concepts into the manufacturing, regulatory, and drug development processes. Realising that thorough testing by itself does not always improve product quality led the agency to concentrate on QbD. To ensure dependability, safety, and effectiveness, quality must instead be methodically incorporated into the product at every stage of its existence (Woodcock, 2004).

With the advent of important regulatory standards such as ICH Q8 (R2) (Pharmaceutical Development), ICH Q9 (Quality Risk Management), and ICH Q10 (Pharmaceutical Quality System), the pharmaceutical Quality by Design (QbD) framework has changed throughout time. Supplementary papers have also been released, including ICH Q11 (Development and Manufacture of Drug Substance), the ICH Q1WG guideline on Q8, Q9, and Q10 Questions and Answers, and the ICH Q8/Q9/Q10 Points to Consider document. The regulatory environment has been further influenced by the findings of the FDA-EMA parallel evaluation of QbD components in marketing applications (U.S, 2006).

Regarding the definition and application of QbD in the pharmaceutical industry, these recommendations provide general strategic guidance. Nevertheless, despite the availability of contemporary research, they do not fully cover all elements of implementation, which results in continued ambiguity among academicians, industry experts, and regulatory agencies (U.S FDA, 2011). Clarifying the goals of pharmaceutical QbD, offering a thorough analysis of its core ideas and elements, and outlining

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the instruments and procedures utilised for its actual application are the objectives of this study.

OBJECTIVES

QbD

Pharmaceutical Quality by Design (QbD) is a methodical, scientifically based approach to drug development that starts with clearly defined goals and places a high value on a thorough comprehension of the product and the process. To provide strong control over industrial processes, this technique combines scientific reasoning with quality risk management concepts.

The following are the main goals of pharmaceutical QbD:

- Developing quality standards for products that are clinically relevant and in line with therapeutic outcomes.
- Improving design, understanding, and control of both product and process characteristics to increase process capability while reducing product variability and errors.
- Improving production and product development efficiency to create more economical and efficient processes.
- Improving the capacity for root cause analysis and enabling better change management after approval.

By putting these ideas into practice, QbD hopes to create a framework for pharmaceutical development that is more dependable, effective, and compliant with regulations. Designing a reliable formulation and manufacturing process that reliably guarantees the required product quality is made possible by connecting product quality to its intended clinical performance, which is a crucial component of QbD (ICH Quality International Working Group, 2011).

The FDA has made significant strides in accomplishing one of its main goals, performance-based quality requirements, since the beginning of pharmaceutical QbD. Guidelines for tablet scoring and bead sizes in capsules used for sprinkling are two examples of FDA standards that demonstrate this advancement. This dedication to performance-driven quality standards is further demonstrated by the FDA's continuous debates on the physical characteristics of generic medicine products and tested potency limitations for narrow therapeutic index medications. It is crucial to remember that although clinical performance-based criteria are not specifically defined as a QbD aim in the ICH guidelines, contemporary scientific literature has recognised this idea. This changing viewpoint emphasises the necessity of ongoing discussion and improvement of regulatory requirements in order to completely match QbD principles with clinical performance results (U.S FDA, 2012).

Enhancing process capability while reducing product variability-which frequently results in faults, rejections, and recalls-is the second major goal of pharmaceutical QbD. The creation of a reliable product formulation and manufacturing process is necessary to accomplish this aim. It is possible to identify and regulate the variables that affect the quality of medicinal products by having a better grasp of both product and process parameters. Crucially, in order to further enhance processes and lower variability, faults, and recalls, continuous improvement initiatives should continue after regulatory clearance.

To improve formulation design, development efficiency, and overall speed, QbD uses a methodical, science-driven approach to product design and development. QbD improves a manufacturer's capacity to identify and solve the underlying causes of production failures by refocusing resources from a reactive, corrective approach to a proactive, preventative strategy. The third QbD goal, which is to increase production and product development efficiency, is supported by this proactive strategy (U.S FDA, 2013).

Improving post-approval change management and root cause analysis is the ultimate goal of QbD. It becomes difficult to scale up production and carry out efficient root cause analysis without a solid grasp of product and process dynamics, frequently necessitating the creation of large amounts of extra data. The FDA has created regulatory guidelines that offer an organised framework for revisions to authorised medicinal items in order to facilitate post-approval alterations. The FDA recently released recommendations to streamline the implementation of enhancements while preserving product quality and compliance by lowering the regulatory filing requirements for low-risk Chemical, Manufacturing, and Control (CMC) post-approval manufacturing adjustments (Yu, 2008).

Pharmaceutical QbD Element

The applicant determines quality-critical attributes from the viewpoint of the patient, converts them into the drug product's Critical Quality Attributes (CQAs) (Lionberge *et al*., 2008), and uses CQAs to establish the relationship between formulation and manufacturing variables in a pharmaceutical Quality by Design (QbD) approach to product development. A high-quality medication product that satisfies patient demands is consistently delivered thanks to this methodical process.

The key elements of QbD include (Rathore *et al*., 2009):

1. **Quality Target Product Profile (QTPP):** Describes the Critical Quality Attributes (CQAs) that the final medicinal product should have.
2. **Product Design and Understanding:** This includes determining and managing the Critical Material Attributes (CMAs) that affect the quality of the product. Identifying Critical Process Parameters (CPPs),

comprehending scale-up concepts, and creating connections between CMAs, CPPs, and CQAs are the main objectives of Process Design and Understanding.

3. **Control Strategy:** This plan lays out requirements for medication ingredients, excipients, and finished pharmaceuticals. It also includes controls at every production stage to guarantee consistency in quality.
4. **Process Capability and Continuous Improvement:** This guarantees continuous process optimisation, lowering variability and gradually raising quality and efficiency.

By combining these components, the QbD framework creates a proactive, science-based approach to pharmaceutical development that fosters innovation, improves manufacturing dependability, and guarantees that pharmaceutical products continuously satisfy patient-centered quality standards as well as regulatory requirements (U.S FDA., 2013).

Identification of Critical Quality Attributes and Quality Target Product Profile

(U.S FDA, 2011) A drug product's key quality attributes are compiled in the Quality Target Product Profile (QTPP), which is intended to guarantee the required degree of performance, safety, and effectiveness. The QTPP serves as the cornerstone for product development, directing formulation and manufacturing choices to satisfy predetermined quality standards.

Key considerations for inclusion in the QTPP include:

- Clinical application and intended usage, including dosage form, delivery system(s), and administration route.
- The dosage strength or strengths needed to provide the desired therapeutic outcome.
- A mechanism for closing containers to guarantee the integrity, stability, and sterility of the product.
- The release and delivery of therapeutic moiety, taking into account characteristics that affect pharmacokinetic performance (such as dissolution rate and aerodynamic qualities), customised for the particular dose form.
- Sterility, purity, stability, and controlled drug release are examples of drug product quality criteria that are in line with legal requirements for the planned commercial product.
- Pharmaceutical developers may successfully connect product characteristics to clinical performance by establishing and methodically putting the QTPP into practice. This ensures consistency, quality, and compliance throughout the drug development lifecycle.

Finding CQAs in the Development of Drug Products

Finding the Critical Quality Attributes (CQAs) is the next stage in the development of medicinal products once the Quality Target Product Profile (QTPP) has been established (U.S FDA, 1995). To guarantee the intended product quality and therapeutic efficacy, a CQA is a physical, chemical, biological, or microbiological property of an output material-such as a completed pharmacological product-that must stay within a given limit, range, or distribution.

Typical CQAs for pharmaceutical products might include:

- **Identification and assay:** making sure the right medication ingredient is present at the right amount.
- Consistency in medication distribution across dosage units is known as content uniformity.
- Degradation products and leftover solvents: keeping an eye out for contaminants that can compromise efficacy and safety.
- Profiles of drug release and dissolution, which provide steady bioavailability.
- Moisture content: it keeps things stable and stops deterioration.
- Microbial limits: guaranteeing sterility or a manageable amount of bioburden.
- Physical characteristics that might affect patient adherence and product use include colour, shape, size, odour, scoring arrangement, and friability.

Criticality of CQAs is based only on the possible danger to patient safety and efficacy in the event that the characteristic is outside of the allowed range. CQAs can be classified as either critical or non-critical. The designation of an attribute as crucial is independent of factors like detectability, controllability, or probability of occurrence.

Although it would seem obvious that a new pharmaceutical product should have clear target qualities before research starts, this is sometimes overlooked. In the past, skipping this stage has resulted in inefficiencies, resource loss, and extended development schedules. The importance of accurately defining the QTPP before to development is emphasised by a recent study by Raw *et al.*, which also confirms that a structured QbD strategy improves productivity and product success. The significance of locating and utilising QTPPs to promote product development and regulatory alignment is further illustrated by QbD case studies (U.S FDA., 1997).

Product Design and Knowledge

According to the ICH Q8 (R2) advice, Quality by Design (QbD) has mostly focused on process design, comprehension, and control

over the years. Recognising the significance of product design, comprehension, and control in guaranteeing pharmaceutical quality is as important, though (U.S FDA, 2014).

A drug's ability to satisfy patient demands is largely determined by its product design, which is then confirmed by clinical research. Furthermore, stability studies verify if the product can continue to function as planned for the duration of its shelf life. In addition to optimising medication efficacy and patient safety, a thorough grasp of product design also reduces the possibility of stability-related failures, which have in the past resulted in recalls, difficulties with regulations, and poor patient outcomes (U.S FDA, 2013).

Pharmaceutical developers may reduce risks and ensure long-term quality compliance while producing more robust, dependable, and patient-centric medicinal products by incorporating both product and process design into the QbD framework.

Important Goals for Product Design and Knowledge

In the QbD framework, the main objective of product design and comprehension is to create a pharmaceutical product that is reliable and continuously satisfies the Quality Target Product Profile (QTPP) during the course of its shelf life. A systematic method is necessary to guarantee product performance, stability, and manufacturability since product design is an open-ended process with several viable paths (CMC Biotech working group, 2013).

Crucial Components of Product Design and Knowledge

Detailed Description of Drug Substance(s)

- Assessing the substance's physical, chemical, and biological characteristics to make sure it is suitable for formulation.
- Excipient Selection and Understanding: Determining the kind and quality of excipients while taking into account their inherent variability and how it affects the effectiveness of drugs (USP 34-NF29, 2011).
- Evaluation of possible incompatibilities or synergistic effects that might impact stability, solubility, or bioavailability is known as drug-excipient interactions (USP 34-NF29, 2011).
- Critical Material Attributes (CMAs) and Formulation Optimisation: Identifying and defining CMAs for the drug substance and excipients helps regulate their impact on the final product's Critical Quality Attributes (CQAs) (U.S FDA, 2013).

Important Things to Think About When Developing New Products

Pharmaceutical scientists must carefully assess the drug substance's physical, chemical, and biological characteristics to make that the drug product retains its intended CQAs: (Nazzal *et al.*, 2002).

- Physical characteristics include the distribution of particle sizes, shape, polymorphism, solubility (as a function of pH), hygroscopicity, intrinsic dissolving rate, and melting point or points.
- Because polymorphism affects solubility, dissolution, stability, and manufacturability, it has drawn a lot of attention.
- Chemical Properties: oxidative stability, photolytic stability, solid-state and solution stability, and pKa.
- Biological Properties: Bioavailability, membrane permeability, and partition coefficient all have a direct impact on medication absorption and therapeutic effectiveness (Awotwe-Otoo *et al.*, 2012).

In addition to ensuring the creation of a stable and therapeutically effective medication, a well-defined product design approach reduces formulation failure risks, improves regulatory compliance, and expedites manufacturing and scale-up procedures.

The Function and Categorisation of Pharmaceutical Excipients

Pharmaceutical excipients are inert ingredients that have different functions than the Active Pharmaceutical Ingredient (API) in a medicinal formulation. For formulations to be stable, manufacturable, and patient-compliant, they must be included (Glodek *et al.*, 2006; NIST/SEMATECH, 2013).

Functions of Excipients

Pharmaceutical formulations benefit from excipients in the following ways (ASTM E2281, 2013):

- Facilitating Manufacturing: Improving processing effectiveness and guaranteeing consistency when producing drugs.
- Protecting and Stabilising: extending the drug product's shelf life, stability, and bioavailability.
- Improving Taste, Texture, and Administration Ease to Increase Patient Acceptability.
- Supporting Aesthetic Appeal and Identification: Assisting with branding, colour, and form.
- Improving Safety and Effectiveness: Changing the release patterns of drugs, making them more soluble, or making sure they are delivered correctly.

Classification of Excipients

The purpose of excipients in pharmacological dosage forms determines their classification (De Feo *et al.*, 2005). The following are examples of frequently used excipients from the 42 excipient groups specified in USP/NF:

- Binders: These, including hydroxypropyl cellulose, provide tablets cohesion.
- Disintegrants, such as croscarmellose sodium, help break down tablets so that drugs may be released.
- Diluents, or fillers, give formulas more volume (lactose, microcrystalline cellulose, etc.).
- Lubricants: These, such as magnesium stearate, stop tablets from adhering when compressed.
- Glidants (Flow Enhancers): These include colloidal silicon dioxide, which improves the flow characteristics of powders.
- Compression aids, such as starch derivatives, help form tablets.
- Colours and sweeteners, such as aspartame and titanium dioxide, improve both look and flavour.
- Preservatives, such as benzalkonium chloride, stop microorganisms from growing.
- Suspending/dispersing agents, such as xanthan gum, preserve a consistent dispersion in liquids.
- pH buffers and modifiers: These help to stabilise and adjust pH (e.g., citric acid).
- Tonality agents, such as sodium chloride, help injectable formulations maintain osmotic equilibrium.
- Film formers and coatings, such as hydroxypropyl methylcellulose, protect tablets and alter medication release.
- Printing inks and flavours: Enhance product palatability.

Regulatory Aspects

Safety limits for excipients are provided by the FDA's Inactive Ingredients Database (IID) according to their previous usage in pharmaceutical products that have received FDA approval. This improves the safety and efficacy of pharmaceutical formulations by guaranteeing that excipients satisfy toxicological, regulatory, and functional criteria. Quality by Design (QbD) principles provide stable medication formulations that balance stability, patient adherence, regulatory compliance, and manufacturability by carefully choosing and optimising excipients (Wu H *et al.*, 2009).

Excipients are known to have a major impact on the variability of pharmaceutical formulations. Excipient selection is usually done ad hoc, without thorough drug-excipient compatibility testing, and lacks a systematic strategy, despite their significant influence on stability, manufacturability, and bioavailability.

ICH Q8 (R2) advises early drug-excipient compatibility studies to proactively evaluate possible interactions and reduce risks related to material waste and development delays. There are several significant benefits to doing a methodical compatibility examination, including:

- Reducing unanticipated stability issues, which can lengthen development schedules and raise expenses (Rahman *et al.*, 2013).
- Improving formulation stability to extend the medicinal product's shelf life.
- Improving knowledge of interactions between drugs and excipients, making it easier to identify the underlying causes of stability issues.

Pharmaceutical scientists can secure the manufacturing of stable and reliable therapeutic products, minimise formulation risks, and expedite development by including compatibility testing into the Quality by Design (QbD) framework.

Formulation Optimisation Studies' Significance in QbD

The development of a strong pharmaceutical formulation that is impervious to failure depends heavily on formulation optimisation research (Zidan *et al.*, 2007). Recent case studies have shown that formulations that are not well optimised are more vulnerable since it is unclear how changes in formulation composition or raw material qualities would affect the quality and performance of medicinal products (United States Food and Drug Administration, 2012; United States Food and Drug Administration, 2014).

This research offers crucial information about:

- Robustness of the formulation, including the development of functional connections between Critical Material Attributes (CMAs) and Critical Quality Attributes (CQAs).
- The drug substance, excipients, and in-process materials' CMAs are identified.
- The creation of control plans to guarantee the uniformity of the drug's ingredients and excipients.

The value of optimisation studies in a Quality by Design (QbD) approach is not found in their quantity but rather in the significance of the data they provide and how they aid in the creation of high-quality pharmaceutical products. Although

Design of Experiments (DoE) is a useful technique in QbD, it is not the same as QbD.

Knowing the Difference Between Critical Quality Attributes (CQAs) and Critical Material Attributes (CMAs)

CMAs are the physical, chemical, biological, or microbiological characteristics of input materials (such excipients and drug ingredients) that need to stay within a certain range in order to guarantee the quality of the final product (Xu *et al.*, 2012).

Contrarily, CQAs are quality characteristics of output materials, such as product intermediates and final pharmaceutical products. It is noteworthy that a CQA of an intermediate might turn into a CMA for a later downstream production stage.

Pharmaceutical scientists may improve product dependability, lower development risks, and guarantee regulatory compliance by including formulation optimisation into the QbD framework. This will ultimately result in safer and more effective medicinal products.

It is impractical for formulation scientists to look into every attribute during formulation optimisation due to the large number of characteristics linked to drug substances and excipients that could affect the Critical Quality Attributes (CQAs) of intermediates and the finished drug product. To prioritise which material properties need more research, a risk assessment is essential.

The formulation scientist's experience and accepted scientific concepts should serve as the foundation for this evaluation. If a reasonable fluctuation in a material property has a substantial effect on the end product's quality, that attribute is deemed essential. Establishing a clear connection between Critical Material Attributes (CMAs) and CQAs is essential to comprehending product behaviour.

How to Improve Product Knowledge

- Determine possible characteristics of input materials that can influence the performance of pharmaceutical products (Yerlikaya *et al.*, 2012).
- To identify high-risk characteristics, apply scientific knowledge and risk assessment methods.
- Establish acceptable ranges or values for these high-risk characteristics.
- Perform focused experiments, use Design of Experiments (DoE) as necessary.
- Examine experimental data and, if practical, use first-principle models to determine an attribute's criticality.

Create a strong control plan

- Define clear acceptable boundaries for crucial material properties. Establish the permissible range for noncritical material characteristics according to the study's parameters.
- A formulation design space may be formed by the combined established acceptable ranges when many excipients are used.

Pharmaceutical scientists may expedite formulation optimisation, improve product dependability, and guarantee a consistent, high-quality medicinal product that satisfies regulatory and therapeutic requirements by using a methodical, risk-based strategy.

Design and Understanding of Processes

A number of unit activities are used in pharmaceutical manufacturing to guarantee the creation of a high-quality medication product. Continuous production or batch mode can be used for these unit processes (Rahman *et al.*, 2013). Mixing, milling, granulation, drying, compression, and coating are examples of unit operations that each reflect a unique physical or chemical reaction.

A production procedure is deemed adequately described when

- Every important source of variability has been located and comprehended.
- Consistent output is ensured by properly controlling process variability.
- Based on process inputs, it is possible to anticipate product quality features with reliability.

The Function of Critical Process Parameters (CPPs)

The input operating conditions (such as speed or flow rate) or process state variables (such as temperature or pressure) that affect unit operations are referred to as process parameters. If changes in a process parameter have a direct effect on a Critical Quality Attribute (CQA), the parameter is considered critical. To preserve the consistency and quality of the final output, these characteristics need to be tracked and managed (Yu *et al.*, 2004).

A manufacturing process's general condition is established by:

- The Critical Process Parameters (CPPs) that control the operation of every unit.
- The input materials' Critical Material Attributes (CMAs).

Manufacturing of solid oral dosage forms usually entails a number of unit processes, each with unique material properties, process variables, and quality attributes that need to be optimised in order to meet therapeutic and regulatory requirements.

CONCLUSION

The systematic identification and integration of the Quality Target Product Profile (QTPP) and Critical Quality Attributes (CQAs) are central to the Quality by Design (QbD) paradigm, facilitating the development of robust, efficacious, and regulatory-compliant pharmaceutical products. Establishing a well-defined QTPP ensures alignment with clinical objectives, while the identification of CQAs, CMAs, and CPPs enables a risk-based approach to formulation and process design. Integrating formulation optimization, excipient selection, and compatibility studies within the QbD framework enhances product performance, minimizes development risks, and supports lifecycle management. Furthermore, understanding the interrelationships among material attributes, process parameters, and product quality allows for the development of a well-controlled, predictive manufacturing process. As QbD principles continue to evolve, their adoption ensures consistent product quality, improved patient outcomes, and regulatory alignment. A science- and risk-based development strategy thus serves as a cornerstone for innovation and quality assurance in modern pharmaceutical development.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

QbD: Quality by Design; **CMAs:** Critical Material Attributes; **CPPs:** Critical Process Parameters; **CQAs:** Critical Quality Attributes; **QTPP:** Quality Target Product Profile; **PAT**: Process Analytical Technology; **DoE:** Design of Experiments; **FDA:** Food and Drug Administration; **ICH:** International Conference of harmonization; **CMC:** Chemical, manufacturing, and control; **CQAs:** Critical Quality Attributes; **QTPP:** Quality Target Product Profile; **CMAs:** Critical Material Attributes; **IID:** Inactive Ingredients Database; **FDA:** Food and Drug administration.

ETHICAL STATEMENT

This review article is based on the analysis and synthesis of existing published literature and does not involve any studies with human participants or animals performed by the author. All sources of information have been properly cited to acknowledge the original authors and avoid plagiarism. The author declares that there are no conflicts of interest related to the content of this article.

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