INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

Review Paper

Quality By Design (QBD)

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ARTICLE INFO

Published: 30 Nov 2025

Keywords:
Quality by Design (QbD); Critical Quality Attributes; Design of Experiments; Risk management; Pharmaceutical development; Regulatory guidelines

DOI:
10.5281/zenodo.17768871

ABSTRACT

Quality by Design (QbD) is a systematic, science-based approach to pharmaceutical development that emphasizes understanding the product and process, and controlling variability to ensure predefined quality outcomes. Unlike traditional quality control methods, QbD integrates quality into the design of processes and products from the early stages of development. This approach involves identifying Critical Quality Attributes (CQAs), Critical Process Parameters (CPPs), and employing risk management tools alongside Design of Experiments (DoE) to establish a robust design space. Regulatory agencies such as the FDA and ICH have strongly endorsed QbD principles through guidelines like ICH Q8(R2), Q9, and Q10. Implementation of QbD results in more consistent product quality, reduced risk of failure, improved regulatory compliance, and increased process efficiency. This paper provides an overview of QbD principles, tools, and their applications in pharmaceutical formulation and manufacturing, highlighting its importance in ensuring product efficacy, safety, and patient-centric quality.

INTRODUCTION

The pharmaceutical industry has undergone a paradigm shift from traditional quality assurance methods toward a more proactive and science-based approach known as Quality by Design (QbD). Introduced and endorsed by regulatory bodies such as the U.S. Food and Drug Administration (FDA) and the International Council for Harmonisation (ICH), QbD represents a modern framework for designing and developing pharmaceutical products and processes that consistently meet predefined quality requirements.

Central to the QbD approach are key concepts such as:

- **Quality Target Product Profile (QTPP)**: A prospective summary of the quality characteristics that the final product should possess.[12]
- **Critical Quality Attributes (CQAs)**: Physical, chemical, biological, or

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

microbiological properties that must be maintained within limits to ensure product quality.

- **Critical Process Parameters (CPPs)** and **Critical Material Attributes (CMAs)**: Factors that can affect CQAs and must be tightly controlled.
- **Design Space**: The multidimensional combination of input variables and process parameters that ensure product quality.

Principles of Quality by Design (QbD)

Quality by Design (QbD) is a strategic, structured, and risk-based approach to pharmaceutical development that ensures product quality through a deep understanding of processes and proactive control of variability. The foundational principles of QbD are rooted in scientific knowledge, risk management, and regulatory compliance. Below are the core principles that guide QbD implementation:

1. Quality Target Product Profile (QTPP)
2. Identification of Critical Quality Attributes (CQAs)
3. Risk Assessment and Management
4. Design of Experiments (DoE)
5. Establishment of Design Space
6. Control Strategy

Key Elements of Quality by Design (QbD)

Quality by Design (QbD) is a comprehensive approach that integrates quality into pharmaceutical product and process development from the outset. Its implementation is based on a framework of key elements that collectively ensure a well-understood, robust, and controlled manufacturing process. These elements are outlined and supported by international regulatory guidelines such as ICH Q8(R2), Q9, and Q10.

1. Quality Target Product Profile (QTPP)

- A prospective summary of the quality characteristics (such as dosage form, strength, route of administration, stability, release profile) that a drug product must meet to ensure safety and efficacy.[13]
- It guides the entire development process and serves as a foundation for identifying Critical Quality Attributes (CQAs).

2. Critical Quality Attributes (CQAs)

- CQAs are physical, chemical, biological, or microbiological properties of the product that should be within an appropriate limit, range, or distribution to ensure product quality.
- Examples include: drug content, dissolution rate, particle size, pH, sterility, etc.
- Identified through risk assessment based on the QTPP.

3. Risk Assessment and Management

- Involves systematically identifying and evaluating potential risks to product quality during development.
- Tools used include:

  - Failure Mode and Effects Analysis (FMEA)
  - Ishikawa diagrams (Fishbone)
  - Risk ranking and filtering

- Helps prioritize variables that could impact CQAs.

4. Design of Experiments (DoE)

- A statistical tool used to study the effects of multiple variables (formulation or process parameters) on CQAs.

- Helps in:
  - Identifying Critical Process Parameters (CPPs)
  - Understanding interactions between variables
  - Optimizing the formulation and process[17]

5. Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs)

- **CMAs**: Properties of raw materials (e.g., particle size, moisture content) that can impact product quality.
- **CPPs**: Process variables (e.g., temperature, mixing speed, compression force) that have a direct impact on CQAs.
- Controlling these ensures the process produces consistent quality.

6. Establishment of Design Space

- A design space is the multidimensional range of input variables and process parameters that have been proven to result in a product meeting all quality requirements.
- Operating within the design space is considered within regulatory compliance.

7. Control Strategy[21]

- A planned set of controls, derived from product and process understanding, to ensure consistent product quality.
- May include:
  - In-process controls
  - Real-time release testing
  - Monitoring of CMAs and CPPs
  - Final product testing

Tools and Methodologies in Quality by Design (QbD)

Quality by Design (QbD) relies on a variety of scientific, statistical, and risk-management tools to ensure product quality is built into the process from the start. These tools aid in understanding how formulation and process variables affect product performance, identifying risks, and developing robust manufacturing strategies.

The main tools and methodologies used in QbD are categorized as follows:[22]

1. Risk Assessment Tools

Risk assessment is fundamental in identifying and prioritizing the factors that could affect product quality.

Common Tools:

- **Ishikawa (Fishbone) Diagram**: Visual tool to systematically identify potential causes of variation in quality.
- **Failure Mode and Effects Analysis (FMEA)**:
  - Analyzes possible failure points in a process or formulation.
  - Assesses severity, occurrence, and detectability of risks to prioritize control strategies.

Risk Ranking and Filtering: Used to qualitatively or semi-quantitatively evaluate and rank risks based on predefined criteria.

2. Design of Experiments (DoE)

DoE is a powerful statistical methodology used to study the effects of multiple variables on one or more quality attributes.[3]

Purpose:

- To identify Critical Process Parameters (CPPs) and Critical Material Attributes (CMAs).
- To evaluate interactions between variables.
- To optimize formulation or process conditions.
- To define the Design Space.

Types of DoE Designs:

- Full Factorial Design
- Fractional Factorial Design
- Central Composite Design (CCD)
- Box-Behnken Design
- Taguchi Methods

3. Process Analytical Technology (PAT)

PAT is a system for designing, analyzing, and controlling manufacturing processes through real-time measurements.

Applications:

- Monitoring and controlling CPPs and CQAs in real time.
- Reducing variability and improving product consistency.
- Enhancing process understanding and enabling real-time release testing (RTRT).[8]

Examples of PAT Tools:

- Near-infrared (NIR) spectroscopy
- Raman spectroscopy
- Particle size analyzers
- UV-Vis spectroscopy
- Mass spectrometry

4. Statistical Process Control (SPC)

SPC involves the use of statistical tools to monitor and control a process to ensure consistent quality over time.

Techniques Include:

- Control charts (X-bar, R-chart)
- Process capability analysis (Cp, Cpk)
- Histograms

SPC is essential in the lifecycle phase of QbD, especially in continued process verification (CPV).[13]

5. Knowledge Management Systems

Effective QbD implementation requires systematic collection, organization, and analysis of data throughout the product lifecycle.

Methods:

- Electronic lab notebooks (ELNs)
- Databases for material and process tracking
- Data visualization and mining software
- Historical batch data analysis

6. Modelling and Simulation Tools

- **Mechanistic Models**: Based on scientific principles to predict how systems behave under different conditions.

- **Empirical Models**: Derived from experimental data (e.g., regression models from DoE).

- **Computational Fluid Dynamics (CFD)** and **Finite Element Analysis (FEA)**: For simulating complex processes like mixing, heat transfer, etc.

7. Control Strategy Development Tools

Tools for defining and verifying the control strategy based on process understanding and risk analysis.

Includes:

- Control trees or decision matrices
- Real-time control systems
- Feedback and feedforward control mechanisms[22]

Application Areas of Quality by Design (QbD)

Quality by Design (QbD) is widely applicable across various stages of pharmaceutical product development and manufacturing. Its systematic and science-driven approach can be integrated into formulation design, process development, analytical method validation, and even regulatory submissions. With the goal of building quality into the product rather than testing it afterward, QbD has become a cornerstone in modern pharmaceutical science and technology.

Below are the major application areas of QbD:

1. Formulation Development

QbD is used to develop robust and effective drug formulations with predefined quality.

Applications:

- Selection and optimization of excipients
- Identification of Critical Material Attributes (CMAs)
- Optimization of drug

2. Process Development and Optimization

QbD enables a deep understanding of manufacturing processes and helps establish control strategies.

Applications:

- Identification and control of Critical Process Parameters (CPPs)
- Design Space development
- Process scale-up and technology transfer

3. Analytical Method Development

QbD principles are increasingly applied to develop reliable, and regulatory-compliant analytical methods.

Applications:

- Establishment of Analytical Target Profile (ATP)
- Method optimization using Design of Experiments
- Lifecycle management of analytical methods
- Enhancing method transferability and reproducibility

4. Biopharmaceutical Development

QbD is critical in developing biologics due to their complexity and sensitivity to manufacturing conditions.

Applications:

- Cell line selection and media optimization
- Upstream and downstream process control
- Glycosylation and post-translational modification control
- Stability studies for proteins, antibodies, vaccines, etc.

5. Generic Drug Development

For generic drugs, QbD helps meet regulatory expectations and ensures equivalency with the reference product.[10]

Applications:

- Bioequivalence study design

- Optimization of formulation variables
- Control of variability to match reference listed drug (RLD)
- Faster and more successful ANDA approvals (Abbreviated New Drug Applications)

6. Regulatory Submissions

QbD data supports more flexible and science-based regulatory submissions.

Applications:

- Submission of a risk-based control strategy
- Defining and operating within a regulatory-approved design space
- Facilitating Post-Approval Change Management Protocols (PACMP)
- Enhancing communication with regulatory agencies (FDA)

7. **Technology Transfer and Scale-Up**

QbD ensures seamless transfer of processes from R&D to manufacturing scale by maintaining quality and performance.

Applications:

- Reducing scale-up risks
- Defining critical process conditions for commercial batches
- Improving efficiency during site transfers

8. Medical Devices and Combination Products

QbD is also being applied to the development of drug–device combination products. (e.g., inhalers, transdermal patches)

Applications:

- Device design optimization
- Interface control between drug and device
- Risk assessment of delivery performance

Regulatory Perspective of Quality by Design (QbD)

Quality by Design (QbD) has gained significant support and endorsement from global regulatory authorities. It is not only encouraged but is becoming an essential component of pharmaceutical development and manufacturing submissions. The regulatory perspective emphasizes science- and risk- based approaches that ensure product quality, patient safety, and process efficiency throughout the product lifecycle.

1. International Harmonization (ICH Guidelines)

The **International Council for Harmonisation (ICH)** has provided a series of guidelines that form the foundation for QbD in pharmaceuticals:[1]

ICH Guideline	Title	Role in QbD
ICH Q8(R2)	Pharmaceutical Development	Introduces QTPP, CQAs, Design Space, and Control Strategy
ICH Q9	Quality Risk Management	Describes tools and principles for risk identification, analysis, and control
ICH Q10	Pharmaceutical Quality System	Integrates QbD into the lifecycle approach and continuous improvement
ICH Q11	Development and Manufacture of Drug Substances	Extends QbD concepts to active pharmaceutical ingredient (API) development

These guidelines emphasize enhanced product understanding, regulatory flexibility, and a lifecycle approach to quality.

2. U.S. FDA (Food and Drug Administration)

The FDA strongly supports the adoption of QbD to improve product quality and reduce regulatory burden. Key initiatives include:

- **FDA's QbD Pilot Programs**: To support QbD submissions in New Drug Applications (NDAs), Abbreviated NDAs (ANDAs), and Biologics License Applications (BLAs).
- **Office of Pharmaceutical Quality (OPQ)**: Promotes integration of QbD into review and inspection processes.
- **Guidance Documents**:
  - "PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance"
  - "Q8(R2), Q9, Q10" — Endorsed and used in FDA evaluations.[12]
- **Encourages the use of Design Space and PAT** for increased manufacturing flexibility.

3. World Health Organization (WHO)

WHO promotes QbD to improve product quality, especially in low- and middle-income countries, ensuring safe, effective, and affordable medicines.

WHO's guidelines for prequalification include elements of QbD such as risk-based development, lifecycle management, and control strategies.

4. European Medicines Agency (EMA)

The EMA aligns closely with ICH and FDA in its QbD approach. It supports submissions incorporating:

- Enhanced process understanding
- Real-time release testing (RTRT)
- Defined Design Space
- Lifecycle data management

5. Japan's Pharmaceuticals and Medical Devices Agency (PMDA)

- Strongly aligns with ICH Q8-Q11.
- Accepts QbD-based submissions with a focus on continuous improvement and robust product design.

6. Regulatory Submissions Incorporating QbD

QbD can be incorporated into various submission types:

Submission Type	QbD Application
IND/NDA/BLA (USA)	QTPP, Design Space, Risk Assessments, Control Strategies
ANDA (USA)	Equivalence with reference product, DoE, process robustness
MAA (EU)	Enhanced understanding, RTRT, lifecycle approach
DMF (Drug Master File)	QbD for API development and manufacturing

Below are the key benefits of QbD:

1. Enhanced Product and Process Understanding

- QbD encourages a thorough understanding of how formulation components, material attributes, and process parameters affect product quality.
- Enables early identification of Critical Quality Attributes (CQAs).

2. Improved Product Quality and Consistency

- By controlling variability at its source, QbD ensures consistent batch-to-batch quality.

- Reduces the risk of product recalls, deviations, and out-of-specification (OOS) results.
- Enhances patient safety and therapeutic efficacy.

3. Reduced Product Development Time and Cost

- Systematic tools like Design of Experiments (DoE) reduce the number of trials required to optimize formulations and processes.
- Early identification of potential failures avoids costly and time-consuming rework.
- Faster scale-up and technology transfer due to well-defined design space and process understanding.

4. Greater Regulatory Flexibility

- Regulatory agencies (FDA, EMA, ICH) support QbD approaches, which:
  - Allow operating within a design space without requiring a post-approval change.
  - Lead to faster regulatory reviews due to more transparent and science-based submissions.
  - Facilitate better communication with regulators via risk-based documentation.

5. Cost-Effective Manufacturing

- QbD enables the design of robust processes that minimize waste, rework, and downtime.
- Improves process efficiency and resource utilization.
- Supports lean manufacturing principles and real-time monitoring (via PAT tools).

6. Supports Real-Time Release Testing (RTRT)

- Real-time monitoring of CQAs and CPPs (e.g., via Process Analytical Technology) can eliminate the need for traditional end-product testing.
- Enables faster product release, reduces inventory, and improves supply chain efficiency.

7. Stronger Risk Management

- QbD uses structured risk assessment tools (e.g., FMEA, Fishbone Diagram) to prioritize and mitigate risks.
- Focuses resources on high-risk areas, improving overall process reliability.

8. Competitive Advantage

- Companies adopting QbD often experience:
  - Faster time to market
  - Stronger regulatory relationships
  - Higher product reliability
  - Better reputation and brand trust

Challenges and Limitations of Quality by Design (QbD)

While Quality by Design (QbD) offers significant advantages in pharmaceutical development and manufacturing, its successful implementation is not without challenges. These arise from technical, organizational, financial, and regulatory complexities, especially for companies transitioning from traditional quality systems to QbD-based approaches.[17]

1. High Initial Investment

- Infrastructure and tools (e.g., DoE software, PAT instruments, data analytics platforms) can be costly.

- Requires investment in training, qualified personnel, and interdisciplinary collaboration.
- Smaller companies or those with limited resources may find the initial costs a significant barrier.

2. Complexity of Implementation

- QbD involves a systematic approach requiring deep understanding of formulation science, process engineering, and statistical analysis.
- Managing multiple variables and large data sets can be overwhelming, especially in early-stage development.
- Integration of QbD into legacy systems is often complex and time-consuming.

3. Lack of In-House Expertise

- Successful QbD requires skilled personnel in areas such as:[9]
  - Design of Experiments (DoE)
  - Risk assessment tools (FMEA, fishbone diagrams)
  - Process Analytical Technology (PAT)
  - Regulatory compliance and lifecycle management

4. Data Management Challenges

- QbD generates a large volume of data from formulation trials, process development, risk assessments, and analytical testing.
- Storing, analyzing, and interpreting this data efficiently requires robust data systems, often integrated with knowledge management platforms.
- Inadequate data infrastructure can undermine the effectiveness of QbD.

5. Difficulties in Defining and Managing Design Space

- Establishing a validated design space requires:
  - Extensive DoE studies
  - Risk-based justifications

Future Perspectives of Quality by Design (QbD)

As the pharmaceutical industry continues to evolve, Quality by Design (QbD) is set to play an even more pivotal role in shaping the future of drug development, manufacturing, and regulatory science. With advances in digital technologies, artificial intelligence, continuous manufacturing, and increasing regulatory alignment, QbD is expected to move beyond a best practice to become a global standard for ensuring quality, innovation, and efficiency.

1. Integration with Digital Technologies

The rise of Pharma 4.0 and Industry 4.0 is transforming how QbD is applied:[24]

- **Big Data Analytics**: Allows for real-time monitoring and analysis of large datasets generated from manufacturing and development.
- **Machine Learning & AI**: Will enhance prediction of process outcomes, anomaly detection, and risk-based decision-making.
- **Digital Twins**: Virtual modeling of processes for simulation, optimization, and lifecycle monitoring.

Future Impact: QbD will become more dynamic and predictive, enabling continuous learning and improvement based on real-time data.

2. QbD in Continuous Manufacturing

Continuous manufacturing (CM) aligns perfectly with QbD principles:

- Requires a deep understanding of process variables and control strategies.
- Relies heavily on Process Analytical Technology (PAT) and real-time monitoring.
- Offers faster, flexible, and more efficient production with less waste.

Future Impact: QbD will serve as a foundation for the widespread adoption of CM, particularly for solid oral dosage forms and biologics.[15]

3. Enhanced Regulatory Harmonization and Support

Regulatory bodies are increasingly aligning around QbD:

- Global harmonization of expectations across FDA, EMA, PMDA, WHO, and others.
- Greater support for:
  - Real-Time Release Testing (RTRT)
  - Design Space Flexibility
  - Adaptive post-approval changes
- Regulatory submissions are expected to become more modular, digital, and science-driven.

Future Impact: More companies will be encouraged to adopt QbD without fear of regulatory uncertainty or inconsistency.

4. Lifecycle and Knowledge Management Platforms

With ongoing digital transformation, the industry will increasingly rely on integrated platforms for:

- Lifecycle data tracking
- Real-time control strategy updates

Future Impact: Automated systems will support real-time decision-making, deviation management, and process optimization in alignment with QbD principles.

CONCLUSION

Quality by Design (QbD) represents a paradigm shift in pharmaceutical development and manufacturing—moving from a traditional quality-by-testing approach to a proactive, systematic, and science-driven methodology. By emphasizing product and process understanding, risk management, and lifecycle thinking, QbD ensures that quality is built into the product from the very beginning, rather than being tested at the end. Through the integration of tools such as Design of Experiments (DoE), Process Analytical Technology (PAT), and risk assessment frameworks, QbD enhances decision-making, reduces variability, and improves regulatory transparency. Its application spans all areas of pharmaceutical development—from formulation and process design to analytical method development and continuous improvement.

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HOW TO CITE: Shubham Gunjal, Quality By Design (QBD), Int. J. of Pharm. Sci., 2025, Vol 3, Issue 11, 4918-4928. https://doi.org/10.5281/zenodo.17768871