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QUALITY BY DESIGN AND RISK MANAGEMENT IN PHARMACEUTICAL QUALITY ASSURANCE: A REVIEW ARTICLE

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ABSTRACT

Quality by Design (QbD) and Quality Risk Management (QRM) have emerged as essential approaches in modern pharmaceutical quality assurance for ensuring consistent product quality, safety, and efficacy. QbD is a systematic, science- and risk-based approach that emphasizes building quality into pharmaceutical products during development rather than relying solely on final product testing. QRM supports this approach by identifying, assessing, controlling, communicating, and reviewing risks throughout the product lifecycle. This review highlights the principles, elements, and implementation of QbD and QRM in the pharmaceutical industry, including concepts such as Quality Target Product Profile (QTPP), Critical Quality Attributes (CQAs), Critical Material Attributes (CMAs), Critical Process Parameters (CPPs), design space, and control strategies. The article also discusses major risk assessment tools such as Failure Mode and Effects Analysis (FMEA), HACCP, and Fault Tree Analysis (FTA), along with important regulatory guidelines including International Council for Harmonisation Q8, Q9, Q10, Q11, and Q14. Furthermore, the review addresses applications, challenges, future perspectives, and emerging technologies associated with QbD and QRM. Overall, the integration of QbD and QRM strengthens pharmaceutical quality systems, enhances regulatory compliance, and improves patient safety.

KEYWORDS: QbD, QRM, QTPP, CQAs, CMAs, CPPs, Design space, FMEA.

INTRODUCTION

QbD stands for quality by design which means that quality should be designed into the product at first rather than inspecting later. QbD was first introduced by Dr. Joseph M. Juran in the 1970's.[1]

USFDA defines the QbD as a systemic approach to development that begins with predefined objectives and emphasises product and process understanding and process control, based on sound science and risk management.[2]

Dr. Janet Woodcock emphasises the Quality by design (QbD) as "process and product performance are scientifically designed to meet specific objectives, not merely empirically derived from the test batches''.[3]

QbD does not necessarily imply reducing analytical testing; instead, it highlights performing appropriate analysis at the correct stage, guided by scientific principles and risk assessment.[5]

Quality is an important concern for any manufacturing process because it has a direct impact on patient's and customer's health. In pharmaceutical products, the quality of any drug substances, excipient, packaging and labelling and manufacturing is indispensable. Any product development fundamentally aims to deliver a quality product capable of meeting patient needs. Accordingly, in pharmaceutical development, the final product must be designed to address patient's requirements and achieve the desired intended performance. Nowadays, the FDA announced that every product development file must have a QbD approach (7). QbD covers a better scientific understanding of critical process and product qualities, designing controls and tests based on the scientific limits of understanding during the development phase and using the knowledge obtained during the life-cycle of the product to work on a constant improvement environment. Mathematical models and guidelines are used to check the establishment and leveraging expertise on the subject in an autonomous and combined way.[6]

Pharmaceutical QbD goals include the following[4]

1. To achieve meaningful quality products with clinical performance.
2. To reduce process and product variability
3. To maximise the product efficiencies
4. To boost product development

5. Root cause analysis and post approval changes management.
6. To raise process and product capability
7. Reducing product defects by enhancing product and process design, understanding and control.

Flow of QbD process

1. Define TPP (target product profile) and QTPP (quality target product profile)
2. Identify CQA (critical quality attributes)
3. Carry out risk assessment to establish the relationship between material attributes, process parameters and CQA
4. Make design space and explain design strategy
5. Life cycle management and continuous improvement

Elements of quality by design[8]

In the pharmaceutical QbD method of product development, an applicant first identifies quality characteristics that matter to patients, then translates these into the drug product's critical quality attributes (CQAs). The applicant also establishes formulation and manufacturing variables related to CQAs to ensure consistent delivery of a drug product possessing those CQAs to patients. QbD includes the following elements:

1. QTPP stands for quality target product profile that distinguishes the CQAs of the drug product.
2. Understanding the product and product design including the identification of CMAs i.e., critical material attributes.
3. Understanding the process and design including the identification of CPPs (critical process parameters) and linking CMAs and CPPs to CQAs.
4. A control strategy that includes specification for the drug substance(s), excipient(s), and drug product as well as controls for each step of the manufacturing process.
5. Process capability and continual improvements.

ICH Q10 describes a model for the institution of a good quality management system which will be utilized by makers implementing the QbD system and might value and improve the quality of product throughout the merchandise lifecycle.[10]

TPP[11]

The target product profile (TPP) describes the essential characteristics of a drug product that

direct labelling and drug development efforts. It states the proposed use, target population, administration rate, and additional critical product attributes, as well as quality design aspects for the drug product.

TQPP[12]

Target quality product profile is a vital document that allows the rationalisation and tracing the evolution of the data not inheritable throughout the lifecycle of the drug. It embraces indefinite -quantity, type, strength, instrumentation closure system, identity, as say, indefinite-quantity type, purity, and stability.

CQAs[13]

Critical quality attributes (CQAs) are physical, biological, microbiological and chemical characteristics that ensure the resulting product achieves the required quality, safety, efficacy and stability. They can be defined, quantified and continuously monitored to keep final product outputs within acceptable quality limits. Quality attributes encompass clinical safety and efficacy, manufacturing- related attributes, and parameter boundaries nearing the edge of failure. The level of criticality may vary for the manufacturing process, and higher criticality increases risk.

CMAs[15]

Critical material attributes. A parameter is considered critical if a real change in that parameter causes the product to not meet the QTPP. Therefore, whether a parameter is critical depends on the magnitude of the change being considered as well as the various properties or characteristics of the associated input material. CMAs must be kept within an appropriate limit, range or distribution to ensure the required quality of the drug substance, excipient or in-process material.

CPPs[16]

Critical process parameter is defined as any measurable input, such as input material attributes or operational parameters, or output, such as process state variables or output material attributes, of a process step that must be controlled to achieve the required product quality and process consistency. In this context, each item would be a process parameter. Parameters that significantly affect the appearance, impurity profile and yield of the final product are monitored before or during processing.

Control strategy[17]

A planned set of controls, based on current product and process understanding, to ensure process performance and product quality (FDA, 2009). It covers drug substances/ product attributes, materials, equipment, in-process controls, specifications and monitoring methods.

It is developed by studying material attributes and process parameters that pose high or medium risk to CQAs. This identifies CMAs and CPPs and sets acceptable ranges. All high-risk variables are included due to complex multivariate effects. The strategy reflects current knowledge and may be updated during the product lifecycle.

The control strategy includes CMAs of the drug substances and excipients, in-process controls, high risk process parameters from development, commercial operating ranges, and release specifications.

Design space

1. The product is designed to meet patient needs and performance requirements.
2. The process is designed to consistently meet product quality attributes.
3. The process is continually monitored and updated to allow for consistent quality over time.
4. Influence of starting raw material and process parameters on product quality is understood.

Product lifecycle management and continual improvement

Product quality can be enhanced throughout its lifecycle, giving firms opportunities to use innovative approaches for improvement. Process performance is monitored to ensure consistent quality. Additional knowledge gained during routine manufacturing supports process development. While companies perform periodic maintenance under their internal quality systems, the design space should remain unchanged. The QbD approach enables continual improvement across the product lifecycle, unlike traditional approaches that rely on a fixed method.

Steps of QbD[14]

1. Identification of CQAs
2. Define product design space
3. Define process design space

4. Refine product design space
5. Define control strategy
6. Process validation
7. Process monitoring

Advantages of QbD

1. Avoid regulatory compliance problem
2. Better technological decision
3. Reduce batch failure
4. Reduce deviation and minimize costly investigation
5. It is a good business
6. Increase the process understanding
7. Avoids post approval variation
8. Provide space for future invention of the latest techniques
9. Continuous improvement
10. Robust method and greater level of confidence

Risk management[18]

Risk management has been an important tool for the pharmaceutical industry. QRM is a systematic process of reducing the risks to product quality throughout its life-cycle in order to optimise its benefit and balance the risk. QRM principles are efficiently utilized in many areas including business, insurance, work related safety, public health, pharmacovigilance, etc.[19-20]

ICH Q9 defines risk as the combination of the probability of harm occurring and the severity of the harm. Manufacturing and use of a drug product, including its components, inherently involve some risk. QRM approach ensures high product quality for patients by identifying and controlling potential quality issues during development and manufacturing.

QRM also improves decision-making when quality problems arise. Effective QRM implementation enables better, informed decisions and gives regulators greater confidence in a company's ability to manage potential risk.[21-22]

Definitions[23]

1. **Risk**

Combination of both probability of occurrence of harm and severity of that harm.

2. **Harm**

Damage of health due to the loss of product safety, efficacy and quality or availability.

3. **Quality**

Degree to which a set of an inherent characteristics of product, system or process fulfils the requirements.

4. **Requirements**

Needs or expectations that is stated.

Principle of QRM

According to ICH Q9 guidelines, the 2 primary principles are:

1. **Science-Based decision making**

Risk evaluation is based on scientific knowledge, experience, and eventually linked to the protection of the patient.

2. **Proportionality (risk-based effort):** the level of effort, formality and documentation in the QRM process should be commensurate with the level of risk.
3. **Continual improvement**
4. QRM should be **dynamic, iterative** and **responsive to change**

Importance of QRM in QA[24]

1. Ensuring patient safety and product quality
2. Proactive rather than reactive
3. Regulatory compliance and consistency
4. Optimal resources allocation
5. Improved decision making

Steps in risk management process[25]

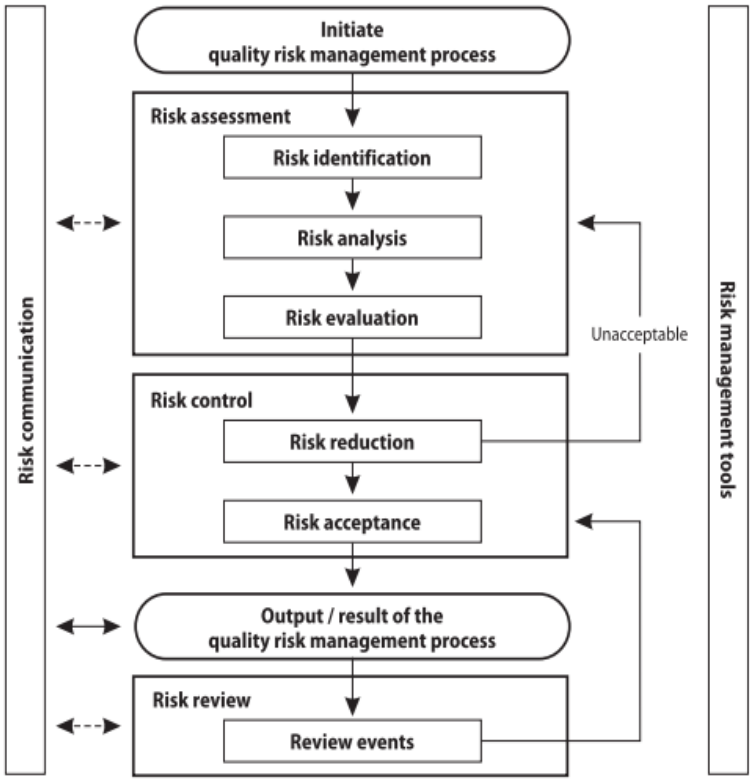

Figure 1: Steps in risk management process.

Risk assessment

Its systematic, science-based process used in identifying, analysing and evaluating hazards to patient safety and product quality. It is a methodical process of organizing information to support a risk decision to be made within a risk management process.[26]

Three essential questions are frequently helpful

1. What may go wrong?
2. What is the possibility that it will go wrong?
3. What are the consequences?

Risk identification[25]

Its systematic, proactive process of identifying potential hazards (what could go wrong?) , potential consequences and sources of harm to product quality or patient safety. It initiates the QRM cycle, utilizing data, expert knowledge, and techniques like brainstorming or failure mode analysis to assess risk throughout the product lifecycle.

Risk analysis[27]

It's a systematic, science-based process used, particularly in pharmaceuticals (ICH Q9), to identify hazards and evaluate the risk to product quality and patient safety. It involves estimating the severity, probability and detectability of risks to prioritize actions and make informed decisions, often using tools like FMEA, FTA, or HACCP.

Risk Evaluation[28]

In this step, identified hazards are analysed for severity, probability and detectability. It compares analyzed risks against predefined criteria to determine the need for control, often using tools like RPN (S*L*D) or risk matrices.

This formula shows the risk priority number

RPN = (severity / consequences) x (probability of occurrence) x (chances of detection)

A high RPN indicates that the risk is high and a low RPN indicates that the risk is low.

Risk control[29]

It is a systematic process of reducing or accepting risks to product quality. It involves implementing measures to mitigate risks to an acceptable level–or eliminating them entirely–based on previous risk assessment, proportionality.

Risk acceptance[30]

It is a formal decision to accept the residual risk– or the risk remaining after mitigation–because it falls within predefined acceptable levels or because further mitigation is not feasible. It is a critical component of risk control (ICH Q9), requiring documented, evidence-based justification that patient safety is not compromised.

Risk communication[31]

It’s essential, bi-directional exchange of information regarding product quality risks between stakeholders–such as management, regulators and consumers–throughout the product lifecycle. It ensures transparency regarding the risk severity, controls and decision facilitating informed, proactive and timely decisions to protect patient safety.

Risk review[32]

It is the final and crucial step in the QRM lifecycle, serving as an ongoing, systematic evaluation of risk control effectiveness, often triggered by new information, audits or product

changes. It ensures that decisions remain valid and that the process improves, often integrated into annual product review or management reviews to maintain a state of control.

Risk assessment tools used in pharmaceuticals

Tools that are used in risk assessment in pharmaceuticals are:

1. Failure Mode and Effects Analysis (FMEA)
2. Failure Mode, Effects and Criticality Analysis (FMECA)
3. Hazard Analysis and Critical Control Points (HACCP)
4. Fishbone Diagram
5. Fault Tree Analysis (FTA)
6. Pareto Analysis
7. Risk Ranking and Filtering
8. Basic risk management methods (flowcharts, check sheets, etc)
9. Hazard operability analysis (HAZOP)
10. Supporting statistical tools

Failure Mode and Effects Analysis (FMEA)[33][38]

It is a structured, proactive QRM tool used to identify, evaluate and mitigate potential failures in processes or products. It prioritizes risks based on severity (S), occurrence (O), and detection (D), calculating a risk priority number

(RPN= S X O X D) to guide mitigation, particularly in pharmaceutical manufacturing and design.

Potential use of areas is

1. It can be used to prioritize risks and monitor the efficiency of risk control activities.
2. It applied to equipment and facilities and used to analyse a manufacturing process and its effect on the product or method.
3. Output of FMEA can be used as a basis for design or additional analysis or to guide resource deployment.[34]

Failure mode, effects and criticality analysis (FMECA)[35]

It is a systematic, data-driven, and inductive method used to identify, evaluate and prioritize potential failure modes in processes or products. It extends FMEA by incorporating criticality analysis to rank risks based on severity, occurrence and detection, helping teams mitigate risks early, improve reliability and minimize costs.

Potential Areas of Use: It is utilized to analyse potential failures in design, processes, and systems, ranking them by severity, occurrence, and detection to calculate a risk priority number (RPN).[32]

Fault Tree Analysis (FTA)[36]

It is a deductive, top-down tool used to identify the root causes of a specific, undesired system failure. It visually maps potential failures– including hardware, software and human errors–using logic gates to analyse complex failure interaction. It is primarily used to identify root causes during investigations, assess risks of complex systems and evaluate the effect of multiple, simultaneous faults.

Methodology

1. Define the top events
2. Construct the tree
3. Use logical gates
4. Identify cut sets

Hazard analysis and critical control points (HACCP)[37]

It is a methodical, practical and preventive tool for assuring product quality, reliability and safety. It's a structured approach that applies scientific and technical principles to analyse, evaluate, prevent and control the risk or adverse consequences of hazards due to the design, development, production and use of products.

***HACCP consists of the following seven steps*[39]**

1. Conduct a hazard analysis and identify preventative measures for each step of the process.
2. Determine the CCP
3. Establish critical limits
4. Establish a system to monitor the CCP
5. Establish the corrective action to be taken when monitoring indicates that the CCP are not in a state of control
6. Establish system to verify that the HACCP system is working effectively
7. Establish a record-keeping system

Risk ranking and filtering[40]

It's a tool for comparing and ranking risks. It requires evaluation of multiple diverse

quantitative and qualitative factors for each risk. It involves breaking down a basic risk question into as many components as needed to capture factors involved in the risk. These factors are combined into a single relative risk score that can then be used for ranking risks. "Filters" in the form of weighting factors or cut-off for risk scores, can be used to scale or fit the risk ranking to management or policy objectives.

Potential areas of use: It can be used to prioritize manufacturing sites for inspection/audit by regulators or industry. Risk ranking methods are particularly helpful in situations in which the portfolio of risks and the underlying consequences to be managed are diverse and difficult to compare using a single tool. It is useful when management needs to evaluate both quantitatively-assessed and qualitatively-assessed risks within the same organizational framework.

Regulatory guidelines related to QbD and QRM

1. *ICH Q8*
2. *ICH Q9*
3. *ICH Q10*
4. *ICH Q11*
5. *ICH Q14*
6. *WHO guidelines*
7. *FDA guidance*

ICH Q8

International Council for Harmonisation guideline **ICH Q8** focuses on **Pharmaceutical Development** and forms the foundation of the **Quality by Design (QbD)** approach in the pharmaceutical industry. It encourages manufacturers to develop products and processes based on scientific understanding and risk management rather than relying only on final product testing. The guideline emphasizes identifying:

- Critical Quality Attributes (CQAs)
- Critical Material Attributes (CMAs)
- Critical Process Parameters (CPPs)

Overall, ICH Q8 promotes a systematic, science-based, and risk-based approach to pharmaceutical development, supporting continuous improvement and regulatory flexibility.

ICH Q9

International Council for Harmonisation guideline ICH Q9 provides principles and tools for Quality Risk Management (QRM) in the pharmaceutical industry. It supports a systematic approach for identifying, assessing, controlling, communicating, and reviewing risks related to product quality throughout the product lifecycle.

The guideline emphasizes that risk evaluation should be: Science-based and Proportional to the level of risk.

ICH Q9 helps manufacturers make informed decisions regarding development, manufacturing, testing, and distribution processes while ensuring patient safety and product quality. Common risk assessment tools suggested in the guideline include:

- Failure Mode and Effects Analysis (FMEA)
- Hazard Analysis and Critical Control Points (HACCP)
- Risk ranking and filtering

Overall, ICH Q9 strengthens the implementation of **Quality by Design (QbD)** by integrating risk management into pharmaceutical development and quality assurance systems.

ICH Q10

International Council for Harmonisation guideline ICH Q10 describes a comprehensive Pharmaceutical Quality System (PQS) that integrates Quality by Design (QbD), Quality Risk Management (QRM), and Good Manufacturing Practices (GMP) throughout the product lifecycle.

The guideline aims to establish a systematic approach for achieving and maintaining product quality by promoting:

- Process performance and product quality monitoring
- Corrective and preventive actions (CAPA)
- Change management systems
- Continuous improvement

ICH Q10 applies from pharmaceutical development to product discontinuation and encourages management responsibility and continual enhancement of manufacturing processes.

Overall, ICH Q10 supports consistent product quality, improves process understanding, and

enhances regulatory compliance through an effective and science-based quality management system.

ICH Q11

International Council for Harmonisation guideline **ICH Q11** provides guidance on the development and manufacture of **drug substances** used in pharmaceutical products. It extends the principles of Quality by Design (QbD) and Quality Risk Management (QRM) to the manufacturing process of active pharmaceutical ingredients (APIs). The guideline emphasizes:

- Understanding the manufacturing process and material attributes
- Identification of critical process parameters (CPPs) and critical quality attributes (CQAs)
- Use of risk assessment and scientific knowledge during process development
- Establishment of an appropriate control strategy to ensure consistent product quality

Overall, ICH Q11 helps ensure the safety, quality, and consistency of drug substances through a science-based and risk-based development approach.

ICH Q14

International Council for Harmonisation guideline ICH Q14 provides a scientific and risk-based approach for the development of analytical procedures used in pharmaceutical quality control. It complements the International Council for Harmonisation by emphasizing enhanced understanding of analytical methods throughout their lifecycle.

The guideline encourages the application of Quality by Design (QbD) and Quality Risk Management (QRM) principles in analytical method development by identifying:

- Analytical Target Profile (ATP)
- Critical method parameters
- Method performance characteristics
- Control strategies for reliable analytical performance

Overall, ICH Q14 enhances method robustness, reliability, and regulatory flexibility through a science-based and risk-oriented analytical development approach.

WHO guidelines

World Health Organization guidelines support the implementation of Quality by Design (QbD) and Quality Risk Management (QRM) in pharmaceutical manufacturing to ensure the safety, efficacy, and quality of medicines. These guidelines emphasize a science-based and

risk-based approach throughout the product lifecycle.

WHO encourages

- Systematic pharmaceutical development
- Risk assessment and risk control
- Process validation and continuous improvement
- Good Manufacturing Practices (GMP)
- Effective quality management systems

The WHO guidelines align closely with International Council for Harmonisation recommendations such as ICH Q8, Q9, and Q10, promoting global harmonization in pharmaceutical quality assurance.

Overall, WHO guidelines help pharmaceutical industries strengthen product quality, regulatory compliance, and patient safety through robust quality and risk management practices.

FDA guidance

United States Food and Drug Administration guidance promotes the implementation of **Quality by Design (QbD)** and **Quality Risk Management (QRM)** in pharmaceutical development and manufacturing. The FDA encourages a science-based and risk-based approach to ensure consistent product quality, safety, and efficacy.

The FDA guidance emphasizes

- Building quality into the product during development rather than relying only on end-product testing
- Identification of Critical Quality Attributes (CQAs) and Critical Process Parameters (CPPs)
- Use of risk assessment tools for process understanding and control
- Process Analytical Technology (PAT) and continuous improvement
- Lifecycle management and effective pharmaceutical quality systems

Overall, FDA guidance strengthens pharmaceutical quality assurance by integrating QbD and QRM principles into product development, manufacturing, and quality management systems.

Integration of QbD and risk management in QA

The integration of Quality by Design (QbD) and Quality Risk Management (QRM) in

Quality Assurance (QA) establishes a proactive, science- and risk-based approach in which quality is built into pharmaceutical products from development through the entire product lifecycle rather than being tested only in the final product. Supported by International Council for Harmonisation, International Council for Harmonisation, and International Council for Harmonisation, this integration enables the identification of Critical Quality Attributes (CQAs), Critical Process Parameters (CPPs), and potential risks, leading to the establishment of design space, robust control strategies, continuous improvement, enhanced regulatory flexibility, and consistent product quality.

In this integrated framework, QRM tools such as Failure Mode and Effects Analysis (FMEA) and Design of Experiments (DoE) are widely applied to assess, prioritize, and control risks associated with material attributes and process variability. The combined implementation of QbD and QRM improves process understanding, reduces batch failures and manufacturing deviations, supports efficient decision-making, and ultimately ensures product quality, patient safety, and regulatory compliance.

Applications of QbD and Quality Risk Management (QRM) in Pharmaceutical Industry:

- Development of robust pharmaceutical formulations and manufacturing processes
- Identification and control of Critical Quality Attributes (CQAs) and Critical Process Parameters (CPPs)
- Establishment of design space for consistent product quality
- Application of risk assessment tools such as Failure Mode and Effects Analysis (FMEA) for risk identification and control
- Development of effective control strategies and Process Analytical Technology (PAT) systems
- Improvement of process understanding and process validation
- Reduction in batch failures, deviations, and product recalls
- Enhancement of product quality, safety, and efficacy throughout the product lifecycle
- Support for continuous monitoring and continuous improvement
- Facilitation of regulatory compliance and regulatory flexibility according to International Council for Harmonisation guidelines
- Reduction in manufacturing costs and efficient utilization of resources
- Strengthening of overall pharmaceutical quality assurance systems and patient safety

Challenges and Limitations of QbD and Quality Risk Management (QRM)

- High initial implementation cost for advanced technologies, equipment, and training
- Requirement of extensive scientific knowledge and process understanding
- Complexity in identifying Critical Quality Attributes (CQAs) and Critical Process Parameters (CPPs)
- Large amount of experimental data and documentation required
- Time-consuming risk assessment and process optimization studies
- Difficulty in establishing and validating design space
- Need for skilled personnel and cross-functional collaboration
- Challenges in integrating QbD and QRM into traditional manufacturing systems
- Variability in raw materials and manufacturing processes may affect consistency
- Continuous monitoring and lifecycle management increase operational workload
- Regulatory expectations may differ across countries and regions
- Resistance to organizational and technological changes during implementation

Future Perspectives and Emerging Technologies in QbD and QRM

- Increasing adoption of Artificial Intelligence (AI) and Machine Learning (ML) for predictive risk assessment and process optimization
- Wider implementation of Process Analytical Technology (PAT) and real-time monitoring systems
- Application of big data analytics for enhanced process understanding and decision-making
- Integration of continuous manufacturing with QbD and QRM approaches
- Use of automation and digital technologies to improve quality control and reduce human error
- Development of advanced analytical techniques for better identification of Critical Quality Attributes (CQAs)
- Enhanced regulatory harmonization and global acceptance of science- and risk-based approaches
- Increased focus on lifecycle management and continuous improvement strategies
- Expansion of personalized medicine and complex drug delivery systems requiring advanced QbD applications
- Adoption of cloud-based systems and digital documentation for efficient quality management
- Improved patient safety and product reliability through smart manufacturing technologies

CONCLUSION

The integration of Quality by Design (QbD) and Quality Risk Management (QRM) has revolutionized pharmaceutical quality assurance by shifting quality from a reactive concept to a proactive, science- and risk-based approach. Supported by International Council for Harmonisation guidelines, these approaches enhance process understanding, strengthen control strategies, reduce variability and manufacturing failures, and ensure consistent product quality, safety, and regulatory compliance throughout the product lifecycle.

With the advancement of automation, artificial intelligence, and continuous manufacturing, QbD and QRM will continue to play a critical role in the future of pharmaceutical quality systems and patient safety.

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