Ind. J. Pharm. Edu. Res., 2024; 58(4s):s1145-s1155.
https://www.ijper.org

Review Article

Critical Review of Risk Assessment Tools in Pharmaceutical Quality by Design

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ABSTRACT

Pharmaceutical Quality by Design is a systematic approach to product development that starts with specified objectives and emphasizes product knowledge, methodologies, and operational procedures. It is based on trustworthy science and excellent risk reduction. Risk analysis is a beneficial science-based approach that may assist in discovering the material properties and production variables that may have an impact on the critical quality attributes of the finished product when it comes to high-quality risk management. An active pharmaceutical quality system comprises quality risk management nineteen. It can offer a pro-active strategy for identifying, objectively assessing, and managing possible quality issues. Throughout the course of the product's lifetime, it enables ongoing better performance results and product quality enhancement. This review article discusses various Quality by Design methodologies for risk assessment during research and development.

Keywords: Quality by design, Risk assessment, Risk management, Pharmaceutical, Risk control, Failure mode.

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Received: 11-12-2023;
Revised: 22-03-2024;
Accepted: 22-08-2024.

INTRODUCTION

Quality means suitability for planned use.[1] Pharmaceutical consistency is the term used to describe a product that is free of contaminants and consistently delivers the therapeutic benefit promised to the consumer on the container.[1] Performance testing can assess the pharmaceutical product's consistency (*in vivo* or *in vitro*). *In vitro* product efficiency is ensured by development consistency (Quality by Design), and *in vitro* product output provides evidence of *in vivo* quality performance. Thus, product efficiency is related to quality by design. Pharmaceutical consistency refers to a contamination-free product that reproducibly provides the therapeutic benefit offered to the customer in the bottle. The consistency of the pharmaceutical product can be determined by performance tests (*in vivo* or *in vitro)*. Development consistency (Quality by Design) guarantees *In vitro* product efficiency and *in vitro* product output offers confirmation of *in vivo* product performance.[2] "Therefore, Quality by design also has to do with product efficiency."

Quality by Design (QbD)-The Concept

Pharmaceutical Quality by Design (QbD) is a systematic approach to product development that starts with specified goals and emphasizes product knowledge, methodologies, and continuous improvements that are founded on trustworthy science and excellent risk management.[3,4] To increase consumer confidence in the consistent supply of medications and to significantly improve manufacturing quality, Quality by Design (QbD) is being developed.[5] Figure 1 provides a quick summary of QbD applied to product development and analytical method development.

Phases of Quality by Design method

The phases in the Quality by Design method for product development are as follows:[6-8]

Quality Target Product Profile (QTPP) and Critical Quality Attribute (CQA) Development: Define the drug's purpose, effectiveness, and safety. Identify key quality characteristics for clinical considerations.

Past Information Gathering: Collect relevant information on the drug substance.

Risk Analysis for Knowledge Gaps: Use risk analysis to identify and address knowledge gaps.

Design and Critical Material Attribute (CMA) Specification: Design the product, focusing on critical material attributes. Specify characteristics crucial for achieving product quality.

DOI: 10.5530/ijper.58.4s.113

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Raw Material and Critical Process Parameters (CPP) Determination: Identify critical raw material characteristics. Determine critical process parameters for manufacturing.

Risk Assessment for Testing Procedures: Employ risk assessment to define testing procedure requirements. Use experiments and past knowledge to establish effective procedures.

Control Procedures Definition: Establish control procedures for input materials, manufacturing, and finished product processing. Include measures for site setup and potential scale changes.

Continuous Monitoring and Review: Implement ongoing monitoring of the entire process. Regularly review processes for effectiveness and make necessary adjustments.

Quality Risk Management

The pharmaceutical industry, like numerous other corporate sectors and industries, frequently involves the use of high-risk management systems, albeit this is not always the case. The pharmaceutical sector recognizes the significance of quality control, and it is evident that quality risk management is an integral component of a successful quality system.[9,10] Every stage of a pharmaceutical product's development and use, as well as all of its component elements, unavoidably carries some risk. A small portion of the overall risk is related to the effectiveness risk. It is crucial to realize that item uniformity needs to be maintained over the duration of the product's lifespan in order to maintain the qualities of the medicinal product. With a meticulous effort to detect and address possible quality issues during development and manufacturing, an effective strategy to quality risk management may further assure the excellent performance of the pharmaceutical product to the user. When there is a performance issue, tracking the quality dangers may improve decision-making. Effective compliance risk management may encourage wiser, better-informed decisions, increase the capacity of regulators to handle possible hazards, and increase the scope and intensity of direct regulatory oversight. The following guidelines guide effective risk management:[11,12]

The determination of safety threats should be based on scientific experience and directly relevant to patient security and

The degree of commitment, formality and reporting of the method of handling safety threats should be in accordance with risk levels.

Quality Risk Management Process

Making rational and useful judgments is simpler by effective risk management. It provides established reliable and consistent procedures for carrying out actions of quality risk management procedure based on current data on probability assessment, seriousness, and occasional danger detection.[13]

Risks have historically been recognized, examined, rated, and managed in a number of informal methods. These techniques frequently offer helpful data that might assist with issues like report management, product failures, inconsistencies, and strategic planning.[14] Using proven techniques and/or organizational procedures for risk management, the pharmaceutical sector and regulators may also assess and manage risk. An organized method for measuring, tracking, coordinating, and analyzing risks over the course of a product's entire life cycle is the qualitative process for risk management.[15] Different components may place a different priority than others. However, a rigorous approach should pay attention to each aspect to an amount of detail commensurate to the specific risk.[16] A typical quality risk management process is described as follows:[17-20]

Commencing the Quality Risk Management Process

Identify the problem by considering the key assumptions that influence the risk's potential. Collect background information and/or details on potential risks, damages, or impacts on human health that are relevant to risk evaluation. Identify the leader and resources that are required. For making judgments, establish a timeline, goals, and a reasonable risk management criterion.

Risk Assessment

Risk assessment comprises identifying hazards, analyzing risks, and evaluating the potential risks associated with exposure to those hazards.

Risk Identification

Risk identification involves intentionally utilizing data to identify hazards associated with a specific question or problem statement. The statistics are based on past information, facts, patterns, characteristics, theoretical models, commercial agency interests, viewpoints, expertise, inspections, and many other factors. Risks come in numerous different forms and are often caused by the active pharmaceutical components, excipients, procedure, personnel, environment, and machinery. The Quality Risk Management (QRM) team conducts hazard evaluation to identify risks that need to be eliminated or minimized. Risks are identified using a variety of methodologies, including data collection techniques like the Delphi method, interviews, documentation reviews, checklists, and modeling methods. (Cause impact diagram, system mapping, flow charts and influence diagrams). Table 1 describes several tools and strategies that can be used in the process.

Risk Analysis

Evaluating the risk presented by the risks outlined is done through risk analysis. The theoretical framework that connects the size of an object to its likelihood of harm, whether it be qualitative or quantitative. The actual risk is calculated using risk analysis. The quality risk analysis team chooses a method for

doing risk analysis when hazards are discovered. It is evaluated if a risk will materialize and how it will impact quality, cost, patient health, compliance, and timing. The need for trustworthy, understandable, and strong information is emphasized by the fact that likelihood of occurrence is often obtained from facts and history and expertise. Prioritizing risks involves assigning them a score and creating a probability-impact matrix. The data is now illustrated graphically, providing a helpful summary of the risks.[21] Risk prioritizing is thus used as a chance control technique to choose the best hazard mitigation measures. International norms for determining severity and likelihood criteria are not set in stone. It is possible to evaluate a risk's possibility in both a qualitative and a quantitative approach. The same applies to magnitude, which may be qualitatively classified as extremely high, high, medium, or low. Additionally, when appropriate, the capability of monitoring could be added as an extra risk measure. The effects of the surgery are recorded in a register and frequently reviewed to keep it current.[21]

Some of the recognized/ established risk analysis tools are:[22]

Basic risk management facilitation methods (flowcharts, check sheets etc.): Utilized for the collection and organization of data, structuring risk management processes, and facilitating decision-making.

Advantages: Collection of data from various sources, simple technique.

Disadvantages: Cannot be used alone.

Failure Mode Effects Analysis (FMEA)-Determines potential hazards and their impact on performance. RPN (Risk Priority Number) is calculated by multiplying severity, probability, and detection range ratings. Techniques for risk reduction are employed to maintain RPN at a desirable level.

Advantages: Identifies failure modes, allows for corrective actions, uniform risk quantification.

Disadvantages: Costly, time-consuming, demands extensive knowledge, complex, and may lead to misinterpretation.

Failure Mode, Effects and Criticality Analysis (FMECA)-Involves studying different odds of findings, their sensitivity, and seriousness. Assigns a relative risk "score" to each mode of failure for ordering them according to risk.

Advantages: Corrective actions for hazards, improved reliability, better quality, higher safety margins.

Disadvantages: Time-intensive, costly, and demands substantial information.

Fault Tree Analysis (FTA)-Graphically represents hazards, uses logic gates to find hazards, and evaluates machine disasters one at a time. Developed top-down, relies on process understanding.

Advantages: Visual representation of failure modes, logical analysis of root causes, handles complex processes.

Disadvantages: Time-consuming, costly, demands extensive knowledge, may miss some events.

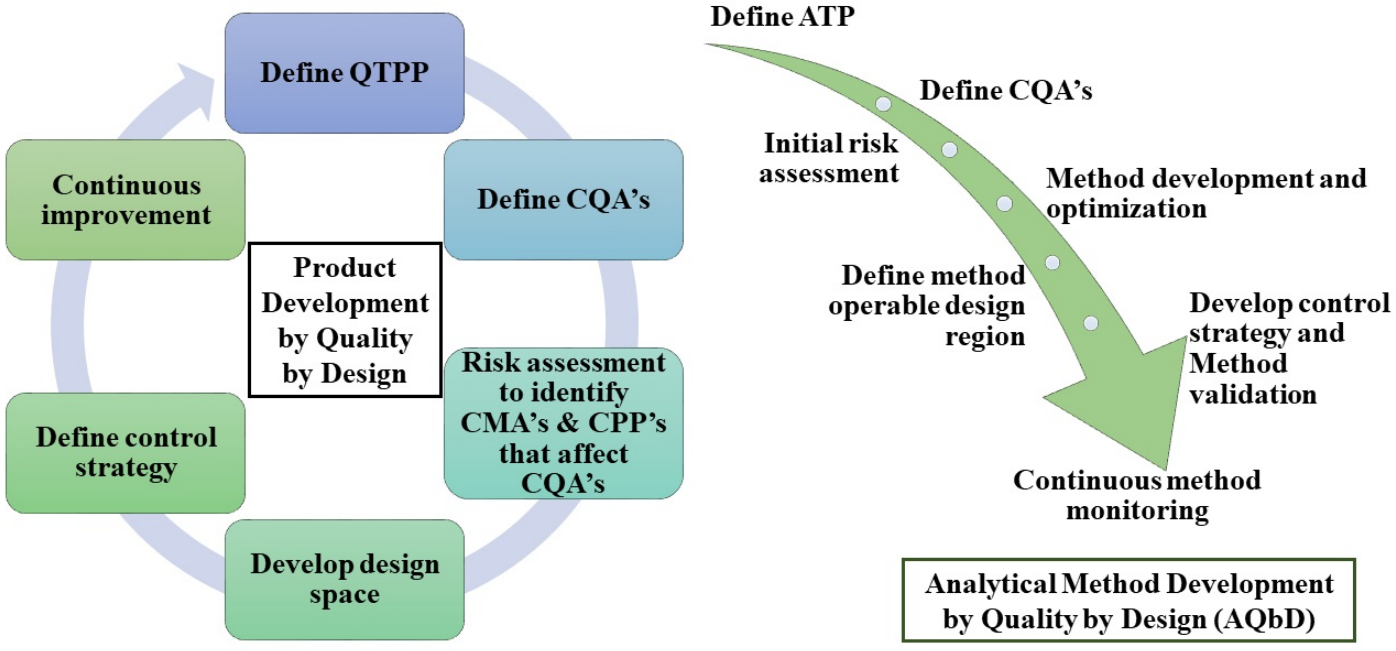

Figure 1: Process flow for Quality by design.[6-8,46]

Table 1: Description of risk identification tools/ techniques.[21]

Sr. no.	Risk identification tools/ techniques	Description
1.	Brainstorming	Risks are identified by suggestions and ideas given by groups from different scientific backgrounds.
2.	Delphi technique	Risks are identified by the responses provided by the participants after filling the feedback anonymously.
3.	Interviews	Risks are addressed after interviewing experienced professionals and experts.
4.	Checklists	Risks associated with the project are identified with the help of a checklist prepared with the help of prior knowledge gained from similar projects; however unknown risks should also be investigated.
5.	Prompt list	Risks are identified with the help of question-based tools.
6.	Mapping	It is a hazard identification tool which helps in visualizing the extent of dangers in relation to one another.
7.	Flow charts	Flow charts show the link between the stages and the elements influencing the method steps as they are carried out each step by step.
8.	Cause and effect diagram	A visual risk identification tool that visually represents the causes of a particular issue or consequence in increasing levels of detail and suggests causal connections between ideas.

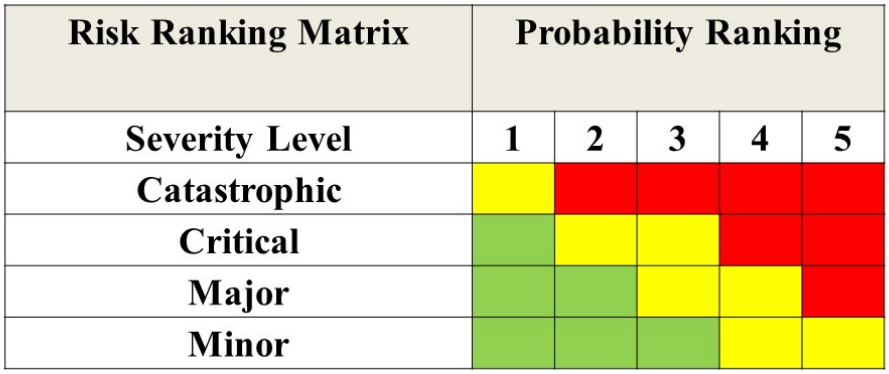

Figure 2: Risk ranking matrix for Risk ranking and filtering.[21]

Hazard Analysis and Critical Control Points (HACCP)-A methodical approach to recognize, assess, and manage risks arising from biological, chemical, or physical factors.

Advantages: Proactive tool for risk assessment and management, identifies key control points, capable of managing complex problems.

Disadvantages: Time-consuming, expensive, requires external training, ideal for specific applications.

Hazard Operability Analysis (HAZOP)-Based on the premise that hazard incidents result from deviations from operational or design objectives. A rigorous brainstorming method that uses "guidewords" to identify existing threats.

Advantages: Used in the pharmaceutical sector, systematic methodology, helpful in addressing difficult risks.

Disadvantages: Costly, time-consuming, requires outside training, needs to be used with other techniques.

Preliminary Hazard Analysis (PHA)-Severity and probability are scored, and the risk score is calculated as the product of probability and severity.

Advantages: Can be used early in projects, systematic risk recognition, graphical risk depiction.

Disadvantages: Limited information, potential bias in filter selection, identifies major risks only.

Risk ranking and filtering-Technique for examining and assessing hazards by breaking down a risk question into components. Variables are added to provide a single relative risk score used to rank hazards.

Advantages: Helpful for grading complex risks.

Disadvantages: Lacks quantitative values, challenging to measure impacts and frequencies.

Supporting statistical tools-Analyzes and graphically ranks sources of problems. The Pareto principle is applied, stating that most causes lead to consequences. These tools are useful for examining hazards associated with a process.

Advantages: Simple and resource-efficient, can use tools like MS Excel, visually illustrates trends.

Disadvantages: Requires a risk assessment tool, results may be skewed, needs a significant quantity of data.

Each tool has specific principles, strengths and weaknesses and approaches tailored to its objectives, providing a diverse set of methods for risk analysis and management. The choice of tool depends on the specific context and requirements of the risk analysis. The application and uses of risk analysis tools is described in Table 2.

Applications of risk analysis tools in Quality risk management

FMEA

"Steps for performing FMEA.[23-26]

Clearly explain the item or process.

Review a flowchart or representation of the product.

Fill in the FMEA table with relevant headings.

Break down the product or process into components or stages.

List every possible failure mode for each component or process step.

Describe the repercussions of each failure mode and rate their severity.

Quantify the likelihood of each cause of a failure mode using Table 3.

Identify existing controls preventing the incidence of each cause.

Evaluate the effectiveness of each control in preventing or detecting failure modes.

Calculate RPN (Risk priority number) using the formula RPN=(Severity x Occurrence x Detectability).

Identify and address failure modes with high RPN values.

Assign responsibilities for implementing corrective actions with target completion dates.

Reassess the overall effect of implemented actions and calculate a new RPN.

Use the new RPN to determine if additional corrective action is needed.

Regularly update the FMEA table, especially after significant changes in design or process."

FMECA

"Steps for performing FMECA.[27-30]

Define system, rules, and assumptions for design enhancement.

Formulate System Boundary and Parameter Diagrams.

Recognize and evaluate failure modes and their impacts.

Ascertain the causes of failure modes.

Integrate outcomes into the design process.

Transmit information from FMEA to FMECA.

Categorize the severity of failure effects.

Perform criticality calculations.

Rank criticality of failure modes and confirm highest risks.

Implement mitigation actions and document remaining risks.

Follow up on effectiveness of corrective action."

Criticality is calculated in two ways

Modal Criticality (attributed to each failure mode)=Cm=Part Failure Rate (lambda) * Effect Failure Rate (Beta)*Failure Mode Ratio (alpha)*Operating Time (in units of time or cycles)

Item Criticality (aggregate of all failure modes)=Cr=the sum of all Cm

Severity level

Catastrophic (Rank 10): A failure that could cause death or complete loss of the system.

Critical (Rank 7-9): A failure that can cause serious injury, significant damage to property, major damage to the system or major production losses.

Major (Rank 4-6): A failure that may cause minor injury, minor damage to property, minor damage to the system, or delay or minor output loss.

Minor (Rank 1-3): A failure that is not severe enough to cause harm, damage to property or damage to the system, but that results in unplanned maintenance or repair."

FTA

"Steps to perform FTA.[31]

Initiate the process by identifying potential hazards.

Gain a thorough understanding of the system involved.

Create a Fault Tree to visually represent potential failure pathways.

Identify critical contributors in the form of Cut Sets.

Table 2: Applications and uses of risk analysis tools.[21,22,26,38]

Sr. no.	Risk analysis tool	Uses
1.	Basic risk management facilitation methods	An easy-to-understand graphic breakdown of the procedures is established. It encourages comprehension, justification, and a methodical examination of dynamic processes and associated hazards.
2.	FMEA	Formulation selection and improvement for pharmaceutical products. Establishing the design space for drug substance and drug product production procedures. Design and manufacture of devices.
3.	FMECA	Potential flaws in the system, design, or procedure are identified, prioritized, and removed before they affect the client. It aids in resolving possible system issues prior to their occurrence.
4.	FTA	It may be used to look into grievances and deviations to determine what went wrong in the first place. It ensures that the measures taken to improve will resolve the issue and does not result in another issue. It helps in evaluating multiple factors that are responsible for a given issue. It can help in developing monitoring programs.
5.	HACCP	Improves issue avoidance and problem resolution through appropriate industry surveillance and record-keeping. Avoids known dangers and lowers the likelihood that they may materialize at particular places in the food chain. It can help to control the hazards occurring due to chemicals used in production or analysis.
6.	HAZOP	Evaluating the capacity of device design to meet user requirements and safety standards. Recognizing defects in systems. Assessing the environment to ensure the right location of the system, prolonged, serviced, featured, etc. Assessing operational and procedural controls.
7.	PHA	It is employed in the early stages of a product's development, when there is less knowledge about the design specifications and operational guidelines. It may be used to assess the many kinds of risks associated with product, process, and facility design.
8.	Risk ranking and filtering	To prioritize production facilities by regulators or industry for assessment. It is beneficial for management to analyze risks using both quantitative and qualitative methods within the same organizational structure.
9.	Supporting statistical tools	Improve the efficiency in analyzing data. Helps in evaluating the importance of the data sets. Promote more reliable decision-making.

Implement risk mitigation measures to enhance the safety and reliability of the system."

HACCP

"Seven principles to conduct HACCP.[32-36]

Perform a hazard analysis and identify preventive measures for each stage of the process.

Recognize Critical control points (CCP's).

Establish critical limits.

Introduce a monitoring system for the CCP's.

Specify corrective actions to rectify deviations when monitoring signals that CCP's are not in control.

Develop a system to confirm the HACCP system's effective operation.

Implement a record-keeping system."

HAZOP

"HAZOP analysis process.[37,38]

Table 3: RPN calculation criteria for FMEA.[21]

"FMEA	Priority				
	1	2	3	4	5
Seriousness	Deviation	Successful Outcome	Rejected Batch	Halt Manufacturing	Withdrawal
Likelihood	Not more than once per 10,000 lots.	Not more than once per 1,000 lots and not less than once per 10,000 lots.	Not more than once per 100 lots and not less than once per 1,000 lots.	Not more than once per 10 lots and not less than once per 100 lots.	Not less than once per 10 lots.
Identifiability	Prior to each unit operation.	Throughout a unit operation.	During a series of unit operations.	Testing of the final product.	Discovered by customers.

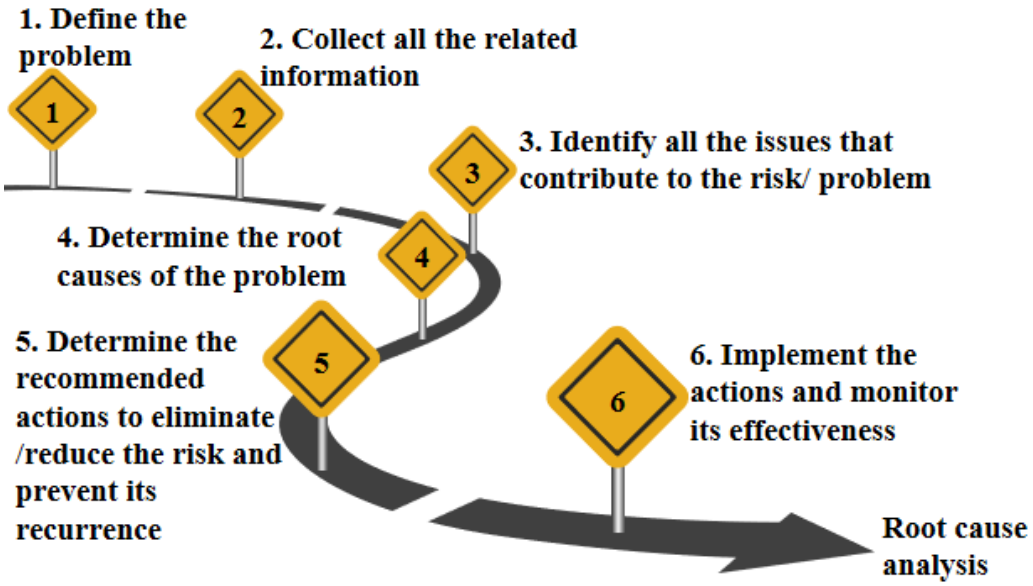

Figure 3: Steps to conduct root cause analysis.21

Project Definition: Outline the scope and objectives of the project, allocate responsibilities, and bring together the project team.

Preparation for Analysis: Create a study plan, gather pertinent data, define a recording style, and outline time estimates to establish a schedule.

Thorough Examination: Analyze system components, specify design purposes, employ guidewords for detecting deviations, evaluate impacts and factors, assess the significance of problems, review current mechanisms, optionally explore remedial measures, and establish agreed-upon actions—repeat for each element and part.

Documentation and Follow-up: Systematically document examination findings, secure required signoffs on documentation, compile a comprehensive report summarizing the study, ensure the implementation of agreed-upon actions, revisit specific system parts if necessary, and generate the final output report."

PHA

"Steps to carry out PHA.[39]

PHA Pre-requisites: Forming a PHA team, providing a system description for analysis, and Collecting risk information from the previous system.

Identify Hazards.

Estimate Consequences and Frequency.

Risk Ranking and Follow-up Actions."

Risk ranking and filtering

Steps to perform risk ranking and filtering.[40]

Specify the Risk Query and Scope.

Recognize and Enumerate All Risk Factors.

Organize Risk Factors in Logical and Administrative Categories.

Assess the Risk for Each Item in the Inventory.

Rank the risks as given in Figure 2.

Filter the ranked lists.

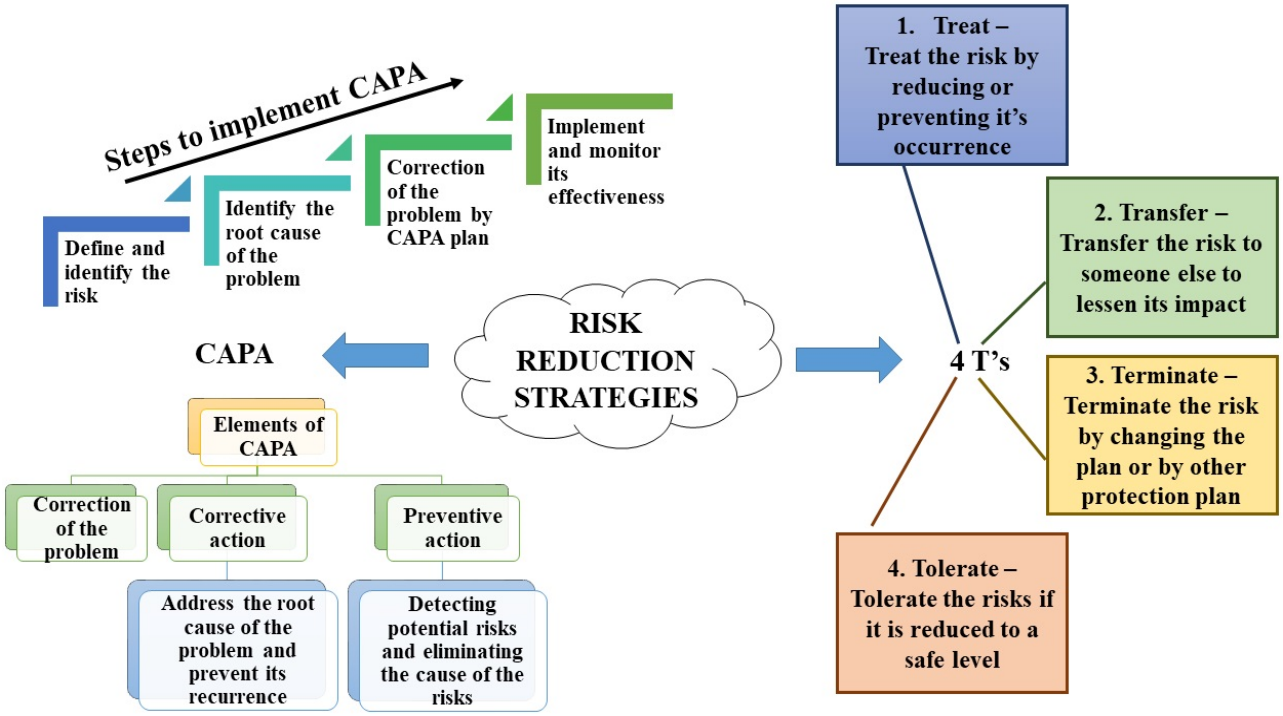

Figure 4: Risk reduction strategies based on 4T's.[21,32]

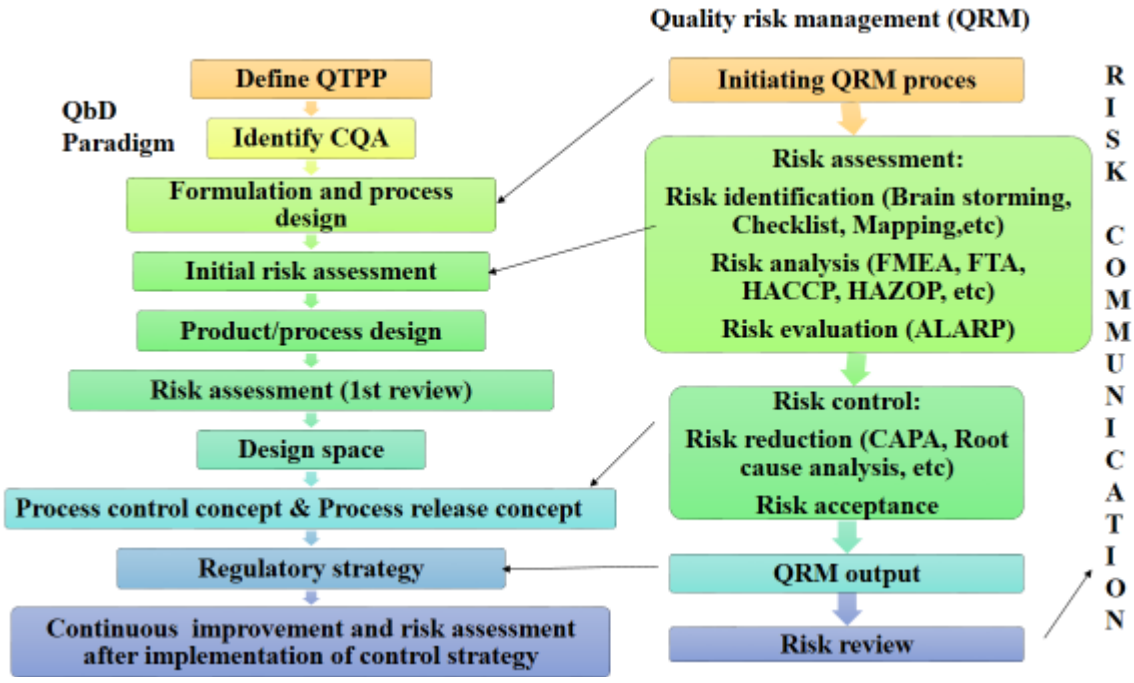

Figure 5: Inter-connection between Quality by Design and Quality risk management.[21]

Using various risk analysis tools in risk management is summarized in Table 4.

Risk Evaluation

Risk assessment compares known risk with assessed risk against risk criteria.

ALARP (As low as reasonably practicable) is an assessment approach where all the risk-reducing attempts are undertaken which takes profit to cost ratio into consideration.[21,41] Multivariate experimental design is used to establish the link between the selected CQA's from the initial risk assessment and the properties of materials or processing parameters. The most often employed

Table 4: Summary of using various risk analysis tools in quality risk management.

Risk analysis tools	Summary of Steps to perform the analysis
FMEA	Conduct FMEA to identify failure modes, assess severity, likelihood, and effectiveness of controls, prioritize corrective actions, and regularly update the analysis for continual improvement.[47,48]
FMECA	Establish system parameters, evaluate failure modes, prioritize risks, implement mitigation strategies, and monitor effectiveness for design enhancement.[49]
HACCP	Perform hazard analysis with preventive measures, identify CCPs, set critical limits, introduce monitoring for CCPs, specify corrective actions for deviations, confirm HACCP system effectiveness, and implement record-keeping.
HAZOP	Define project scope, prepare analysis plan, conduct thorough examination, document findings, and ensure implementation for comprehensive project management.[50]
PHA	Prepare PHA team, identify hazards, estimate consequences, rank risks, and implement follow-up actions for comprehensive risk management.[50,51]
FTA	Identify hazards, understand the system, create Fault Tree/Cut Sets, and implement risk mitigation for system safety and reliability.[52]
Risk ranking and filtering	Specify risk query and scope, enumerate risk factors, organize into categories, assess risk for each item, rank risks, and filter ranked lists for prioritization and management.[53]

designs to close the knowledge gap during the creation of new products and procedures are:[39]

Factorial Design: It assesses the effect of factors and their interactions. Factors vary independently at different levels. It allows for the efficient assessment of the effects without confounding them with other experimental factors.

Plackett and Burman Design: Saturated screening design for testing many factors which is used early in development for screening purposes. It primarily focuses on the main effects. Main effects can be confounded with interaction effects in this design.

Central Composite Design: Factorial or fractional factorial design which includes center points and star points. It is used for estimating curvature in response surface designs. It is helpful for understanding the relationship between factors and responses in a comprehensive manner.

Risk Control

"Risk control requires risk mitigation and/or acceptance decision-making. Risk control aims at reducing the risk to a degree acceptable. The effort used to mitigate the risk should be proportional to the risk level. Risk management focuses on quality risk mitigation processes or avoidance when it reaches the (acceptable) amount specified. Actions to minimize severity and probability of the risk might be included in the risk reduction program. A strategy for risk control may also include processes that improve risk detectability and quality risks. In order to incorporate risk management strategies, new risks can be added, or other existing risks may increase. Therefore, it may be necessary to review the risk assessment process after the implementation of a risk management procedure to detect and analyze any future changes to the risk. Acceptance of risk may take the form of a formal decision, acknowledging the residual risk, or it can be a passive decision that overlooks the residual risk. The level of acceptance is contingent on various factors and should be determined on a case-by-case basis".[21,22] Risk reduction can be done by root cause analysis, CAPA (corrective action and preventive action) and 4T's which are described in Figure 3 and Figure 4.[21]

Risk Communication

"Risk communication is the sharing between decision-makers and others of risk education regarding risk management. The execution of the quality risk management process should be communicated and reported in an appropriate manner. The information included could relate to life, design, shape, likelihood, intensity, acceptability, control, care, detectability, and other aspects of quality risks".[22]

Risk Review

Quality assurance must always include risk management. A system must be put up in order to track or control events. It's critical to assess the outcomes and recommendations of the risk management plan periodically in order to account for recent knowledge and expertise. Irrespective of whether

these occurrences were intended (such as product review findings, inspections, audits, or change control) or unforeseen, a high-quality risk management method should be used for situations that might alter the initial risk management choice (e.g., root cause of failure inquiries, reminder). The degree of risk must be used to decide each test's duration. The risk review procedure could involve reevaluating risk management choices.

Implementing Quality Risk Management in Product Development through Quality by Design

Quality risk management is applied in a variety of settings, including regulatory operations, product design, inventory control, facility management, equipment management, manufacturing, laboratory control, mechanical stability, packing, and branding.[42,43]

Product development by Quality by Design approach involves many steps. The possible risks involved in each step can be identified, analyzed, and evaluated before the product is formed using risk management tools.[44,45] The application of risk management tools in quality risk management steps as well as in Quality by Design paradigm is described in Figure 5 along with Risk management tools.[21]

CONCLUSION

There is a certain amount of unpredictability involved with the creation of new items. One of the key goals of product development is to reduce this ambiguity. For the development of the new product, sound risk management procedures should be upheld. This review article discusses how risk management is important for the creation of new products. The Quality by Design methodology has identified many methodologies (tools and techniques) for risk assessment and risk control during the process of product development. Assessing crucial quality aspects of raw materials, active pharmaceutical ingredients, excipients, solvents, and packaging materials can facilitate the establishment of acceptable specifications.[21] By assessing and analyzing CPP's, manufacturing controls for managing uncertainty within the technique will be determined, thereby promoting the usage of design space. Product and manufacturing defects are reduced as CQA variability decrease.[21] Risk assessment and management are carried out throughout the product development lifecycle. This could lead to constant product development improvements.

ACKNOWLEDGEMENT

The authors are thankful to Vivekanand Education Society's College of Pharmacy, Chembur, Maharashtra, India for their constant support and encouragement.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

QbD: Quality by Design; **CQA:** Critical Quality Attribute; **QTPP:** Quality Target Product Profile; **CPP:** Critical Process Parameters; **CMA:** Critical Material Attributes; **FMEA:** Failure Mode Effects Analysis; **FMECA:** Failure Mode, Effects and Criticality Analysis; **FTA:** Fault Tree Analysis; **HACCP:** Hazard Analysis and Critical Control Points; **HAZOP:** Hazard Operability Analysis; **PHA:** Preliminary Hazard Analysis; **RPN:** Risk Priority Number.

AUTHOR'S CONTRIBUTION

Each author significantly contributed to the conception and design, data acquisition, and analysis and interpretation of data. They actively participated in drafting or critically revising the article for important intellectual content. All authors agreed to submit the manuscript to the current journal, provided final approval for the published version, and committed to being accountable for all aspects of the work. Additionally, all authors meet the eligibility criteria for authorship outlined by the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

SUMMARY

The article underscores the crucial role of risk management in the pharmaceutical industry, emphasizing its integration into the Quality by Design methodology. It discusses various risk analysis tools and their application steps, highlighting their advantages and disadvantages. The importance of proactive risk identification, periodic review, and informed decision-making based on scientific experience is emphasized. The article concludes by emphasizing the systematic implementation of Quality Risk Management across different aspects of pharmaceutical product development.

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Cite this article: Karia P, Ayre A, Khan A. Critical Review of Risk Assessment Tools in Pharmaceutical Quality by Design. Indian J of Pharmaceutical Education and Research. 2024;58(4s):s1145-s1155.